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REVIEW

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Inflammation in cancer: therapeutic opportunities from new insights

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Abstract

As one part of the innate immune response to external stimuli, chronic inflammation increases the risk of various cancers, and tumor-promoting inflammation is considered one of the enabling characteristics of cancer development. Recently, there has been growing evidence on the role of anti-inflammation therapy in cancer prevention and treatment. And researchers have already achieved several noteworthy outcomes. In the review, we explored the underlying mechanisms by which inflammation affects the occurrence and development of cancer. The pro- or anti-tumor effects of these inflammatory factors such as interleukin, interferon, chemokine, inflammasome, and extracellular matrix are discussed. Since FDA-approved anti-inflammation drugs like aspirin show obvious anti-tumor effects, these drugs have unique advantages due to their relatively fewer side effects with long-term use compared to chemotherapy drugs. The characteristics make them promising candidates for cancer chemoprevention. Overall, this review discusses the role of these inflammatory molecules in carcinogenesis of cancer and new inflammation molecules-directed therapeutic opportunities, ranging from cytokine inhibitors/agonists, inflammasome inhibitors, some inhibitors that have already been or are expected to be applied in clinical practice, as well as recent discoveries of the anti-tumor effect of non-steroidal anti-inflammatory drugs and steroidal anti-inflammatory drugs. The advantages and disadvantages of their application in cancer chemoprevention are also discussed.

Keywords Inflammation, Cytokine, Inflammasome, Cancer prevention and treatment, FDA-approved drugs

Introduction

German physician Rudolf Virchow first reported the relationship between inflammation and tumors in the nineteenth century [1]. Chronic inflammatory processes are a fundamental innate immune response to perturbed tissue homeostasis and affect multiple stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis [2]. It is estimated that 15–20% of tumor-related deaths are linked to inflammation.

Recently, a growing body of evidence from basic research and clinical data indicates that inflammatory molecules and inflammation pathways can promote the occurrence and progression of various tumors. Pro-inflammatory cytokines, like interleukin (IL)−6, IL-1β, and tumor necrosis factor-α (TNF-α), as well as

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transcription factors, like nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3), are key players in this relationship [3–7]. Encouraged by pro-inflammatory cytokines, NF-κB and STAT3 can control the expression of target genes, the majority of which are carcinogenic, and increase the ability of cancer cells to survive, proliferate, invade, and spread [8–10]. It is now well-acknowledged that chemicals and processes associated with inflammation can be valuable targets for cancer prevention and treatment.

During the past decades, there has been strong epidemiological evidence showing that nonsteroidal anti-inflammatory drugs (NSAIDs), especially aspirin, have been associated with a reduction in the incidence and mortality of a variety of types of cancer with long-term use, especially colorectal cancer (CRC) [11, 12]. In 2016, the US Preventive Services Task Force (USPSTF) recommended low-dose aspirin for primary prevention of CRC for adults aged 50–59 years [13]. Besides, low-dose aspirin or non-aspirin NSAIDs intake is inversely related to gastric cancer risk based on multiple meta-analyses [14–16]. Recent research based on electronic endoscopy [20] and territory-wide healthcare databases [17] also verified these results. Except for CRC and gastric cancer, aspirin use also reduces the incidence and mortality of endometrial cancer [18], breast cancer [19, 20], esophageal cancer [21], liver cancer [22], and more. Besides, other NSAIDs and steroid anti-inflammatory drugs also have obvious anti-tumor effects. For example, the novel indomethacin derivative CZ-212–3 showed antitumor effects in castration-resistant prostate cancer [23]; indomethacin sensitized death receptor 5 (DR5)-deficient tumor cells to adoptive T-cell therapy [24]; indomethacin-loaded nanocapsules treatment reduced glioblastoma growth in a rat model [25]. These suggest that FDA-approved NSAIDs and steroid anti-inflammatory drugs are promising candidate drugs for cancer prevention and treatment.

In this review, the detailed information on cytokines and their function in tumorigenesis are comprehensively analyzed, and their potential as therapeutic targets for cancer treatment and chemoprevention and their inhibitor/agonists applied in preclinical and clinical studies are also clarified. Uncovering the exact mechanisms of inflammation and inflammatory factors enabled the development of novel, tailored, and highly effective cancer prevention and treatment strategies. We also discussed Food and Drug Administration (FDA)-approved non-anti-tumor drugs that may help prevent and treat cancer-related chronic inflammation, such as aspirin, indomethacin, celecoxib, and other NSAIDs and steroidal anti-inflammatory drugs. The effects of these medicines on proinflammatory cytokines and inflammation-related pathways are addressed, and typical clinical study data are presented. According to data from the current review, agents that target chronic inflammation may have a wide range of applications in the future for the prevention and treatment of cancer.

The relationship between inflammation and cancer

The process of inflammation

Infection, tissue injury, tissue stress, and malfunction are the main causes of inflammation, and they can cause different physiological reactions and pathological outcomes [26]. The acute inflammatory response is triggered by infection or tissue injury, and the blood components including plasma and leukocytes will be recruited to the site of infection and injury [27]. A chronic inflammatory state ensues if the acute inflammatory response fails to eliminate the pathogen [28]. Except for consistent noxious stimuli like pathogens, other causes of tissue damage such as autoimmune responses or undegradable foreign bodies, can also lead to chronic inflammation [26].

Specialized sensors elicit the mediators of inflammation, which are activated by inducers of inflammation. The mediators, in turn, alter the functional states of tissues and organs (which are the effectors of inflammation). Based on their biological characteristics, the inflammatory mediators can be classified into seven groups, including vasoactive amines, vasoactive peptides, fragments of complement components, lipid mediators, cytokines, chemokines, and proteolytic enzymes.

The cellular and molecular events during inflammation include a series of complex events, from in situ to systemic inflammation throughout the body. When microbes infect the body, an acute inflammatory response occurs, which will be recognized by the innate immune system, and triggered by Toll-like receptors (TLRs) and NOD-like receptors [29]. The initial recognition of infection is mediated by tissue-resident macrophages and mast cells, causing the production of many inflammatory mediators, including chemokines, cytokines, vasoactive amines, and others [30]. If the acute inflammatory response cannot clear the antigen, the inflammation process persists, and chronic inflammation occurs. The different effector classes of the T cells can lead to different inflammatory states [26].

The crosslink between inflammation, the immune system, metabolism and autophagy in cancer

Among the various inflammatory factors that contribute to cancer susceptibility, infection has come to be recognized as a primary cause of inflammation-induced carcinogenesis [2]. During infection, inflammation is a fundamental innate immune response to perturbed tissues homeostasis, and inflammation associated with tumor development is triggered by many immune cells

[31]. The regulatory influence on the immune system determines whether inflammation exerts anti-tumorigenic or pro-tumorigenic effects. Tumor heterogeneity is shaped immunologically and through immunosurveillance by immunity's anti-tumorigenic role. Simultaneously, pro-tumorigenic inflammation fosters cancer by suppressing anti-tumor immunity, modifying the TME to a more permissive state for tumors, and directly influencing cancer and epithelial cells to promote tumors [32]. The factors that determine whether inflammation promotes or suppresses cancer are various. Currently, there are several directions for cancer prevention and treatment by regulating the immune system, including cancer vaccines and armored anti-tumor immune cells, various forms of immunotherapies, anti-tumor antibodies, and biological therapies.

A growing body of research suggests that immune cell functional changes throughout immunological responses are mediated by metabolic reprogramming [33]. These suggest that immune response and metabolic reprogramming are necessary events during inflammation-induced carcinogenesis. Reprogrammed energy production and biosynthesis and epigenetic metabolic reprogramming occur in inflammation responses [34]. The immune system exerts anti-tumor effects through immunosurveillance and immunological sculpting of tumor heterogeneity, while inflammation promotes tumor development by blocking immunity and reshaping the tumor microenvironment by regulating multiple signaling pathways and cellular functions [32].

Eating a diet that meets energy requirements and provides essential nutrients helps maintain a healthy immune system. Both undernutrition and overnutrition are associated with immune dysfunction [35]. The immune system works in conjunction with the digestive system, where immunomodulatory and inflammatory processes are linked to gut bacteria and micronutrients [36]. On one hand, people at risk for deficiencies of immune-enhancing micronutrients, such as the military population, are more susceptible to infection due to their nutritional status [37]. The immune function of soldiers consuming compound nutritional drinks with vitamins and minerals decreased slightly [38]. On the other hand, overeating can lead to the accumulation of excess body fat and obesity, which creates a chronic inflammatory state and worsens immunological deficiencies [36, 39].

Other biological factors, such as aging, also influence immune competence. The immune system undergoes several changes throughout a person's life, beginning with the developing immune responses seen in newborns and children. This progression continues to an optimal immune function typically observed in teenagers and young adults. However, in older adults, the immune response may decline [40]. Certain lifestyle factors, including age-specific dietary choices, can worsen age-related changes by influencing and modifying immune function, and in some cases, inhibiting it. Supplements designed for different age groups may provide a solid foundation for optimal immune function. Additionally, age significantly affects how the body responds to vaccines [41, 42]. Creating effective vaccine schedules can enhance the advantages of vaccination and increase the immunogenicity of vaccines.

Several transcription factors like NF-κB are central to immune and inflammatory responses [43]. Metabolic reprogramming occurs in immune cells during inflammatory stages, including energy production biosynthesis reprogramming, and epigenetic reprogramming [33].

Recent studies support the idea that autophagy, a fundamental biological process in mammals, is crucial for regulating inflammation and plays a significant role in cancer related to inflammation. Autophagy is generally considered a protective mechanism that helps prevent the hyperactivation of inflammatory mediators and the malignancy caused by chronic inflammation [44]. Defects in canonical autophagy or mitophagy can lead to necrosis and pathogenic responses, which promote cancer and chronic inflammation [45]. Microorganisms, damaged organelles, and crystals are sources of inflammatory signals, making canonical autophagy an anti-inflammatory process [46]. Autophagy influences immune cells by regulating mitochondrial and endoplasmic reticulum composition. These metabolic changes lead to immunometabolic states that affect macrophage and T cell polarization, ultimately impacting inflammation [47, 48]. The non-canonical autophagy, including LC3-associated phagocytosis (LAP) and its variants, such as LC3-associated endocytosis (LANDO), also utilizes some autophagy machinery and influences inflammation [49]. Research shows that LANDO's long-term clearance of beta-amyloid (Ab) aggregates influences the recycling of Ab receptors and reduces inflammation [50]. When autophagy is inactivated, there is an increased production and secretion of TNFα, type I and type II interferon (IFN), and other inflammatory cytokines [51]. Autophagy deficiency causes uncontrolled innate immune activation, leading to inflammatory diseases like Crohn's disease and an increased risk of colon cancer [52].

Four signaling pathways link autophagy and inflammation in cancer progression: the reactive oxygen species (ROS) signaling pathway, the IκB kinase (IKK)/NF-κB signaling axis, the inflammatory cytokine signaling pathway, and the TLR signaling cascade [53]. Autophagy-related molecules like UVRAG, IRGM, ATG7, Pink1, and Park2, as well as several receptors, connect autophagy to inflammation and influence inflammation-induced

tumors. For example, mice with mutated UVRAG show intestinal inflammation and increased risk of colitis-associated cancer through the NLRP3 inflammasome [54]. As a key negative regulator of NLRP3 inflammasome activation [55], immunity-related GTPase M (IRGM) mediates autophagy and enhances cell proliferation in hepatocellular carcinoma with overexpression of AGBL2 [56]. The activation of ATG7 leads to a pro-inflammatory response dependent on NLRP3, which worsens lipotoxicity in insulinoma [57]. Mice lacking Pink1 or Park2 are susceptible to Kras-driven pancreatic cancer due to the accumulation of mitochondrial iron and the subsequent activation of the absent in melanoma 2 (AIM2) inflammasome [58]. FUNDC1 (FUN14 domain-containing 1) is a mitophagy receptor in the mitochondrial membrane that suppresses hepatocellular carcinoma (HCC) initiation by reducing inflammasome activation and inflammation [59].

As our understanding of the relationship between inflammation, the immune system, metabolism and autophagy in cancer deepens, new therapeutic targets that alter inflammation, the immune system, and metabolism are emerging.

Potential therapeutic strategies for cancer prevention and treatment in inflammation-related cancer

Potential inflammatory therapeutic strategies for cancer prevention and treatment

It is becoming evident that the tumor microenvironment, which is mostly controlled by inflammatory cells, plays a crucial role in cancer development by promoting cell division, survival, and migration. Furthermore, certain innate immune system signaling molecules, including chemokines and their receptors for invasion, migration, and metastasis, have been appropriated by tumor cells. This knowledge is fostering new anti-inflammatory therapy approaches to cancer genesis. Blocking antibodies for inflammatory molecules such as TNF-α has shown obvious therapeutic efficacy in some inflammatory diseases and anti-tumor potential. Matrix metalloproteinases (MMPs) inhibitors have been rapidly developed and applied in the clinic, but the outcomes were less than satisfactory, with efficacy reported mainly occurs during early tumor progression [60].

Based on epidemiological data and experimental data, the FDA-approved anti-inflammatory drugs exhibit significant anti-tumor effects, suggesting the potential of these drugs as anti-tumor drugs and the targets of these drugs may act as promising targets for cancer prevention and treatment. The molecular mechanism underlying the anti-tumor effect of aspirin was first discovered in the 1970s, and it was demonstrated that it irreversibly acetylates and inactivates the cyclooxygenase (COX) enzyme [61]. Since the cancer-promoting effect of COX, many COX inhibitors have been synthesized and have the potential as therapeutic drugs in patients with cancer. For example, flurbiprofen suppressed cell proliferation in colorectal cancer [62], non-small cell lung cancer [63], and others. While the other anti-tumor mechanisms of NSAIDs represented by aspirin and steroidal anti-inflammatory drugs were partly known. Understanding these processes and molecular mechanisms will provide new targets for the prevention and treatment of tumors. For instance, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA)/protein kinase B (AKT)/phosphatase and tensin homolog (PTEN), wingless-type MMTV integration site family (Wnt)-β catenin, and NF-κB pathways are signaling pathways that are significantly activated in cancer, patients with mutations of these pathways showed increased survival after using NSAIDs [64]. Besides, as the important parts of the inflammatory pathway, cytokines, chemokines, growth factors, and components of the extracellular matrix-directed therapy have shown certain effects in anti-tumor treatment. These targets will be summarized in Table 2.

Potential immune therapeutic strategies for cancer prevention and treatment

As an innate immune response to the imbalance of tissue homeostasis, inflammation affects all stages of the occurrence and development of tumors, including regulating aberrant tissue repair, genotoxicity, proliferative responses, invasion, and metastasis. At the same time, tumors modulate the inflammatory environment through the secretion of soluble growth factors and chemo-attractants, causing inflammatory cells to inhibit the anti-tumor T-cell response [2]. Moreover, patients with similar illness stages but different racial/ethnic backgrounds or places of residence may exhibit significantly different tumor mutational burdens due to the consequences of exposure to persistent inflammation, which would change the immune system and the biology of tumors [65]. The complicated interplay of host, tumor, and environmental variables determines immunity and controls the magnitude and timing of the anticancer response. Tumors successfully suppress immune responses by activating negative regulatory pathways (also known as checkpoints) linked by acquiring characteristics that allow them to evade detection actively [66–68]. For various malignancies, immunotherapy is proven to be an efficient therapeutic strategy. Although antibodies targeting the immune regulators CTLA4 and programmed cell death ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) have shown promising therapeutic results, only a small percentage of patients show sustained responses, indicating the need for a more

comprehensive understanding of cancer immunity [69]. A recent study found an interleukin-4 fusion protein (Fc–IL-4), improves the anti-tumor efficacy of immune checkpoint blockade therapies and type 1 immunity-centric adoptive T cell transfer by directly acting on CD8 + T cells and enriching functional terminally exhausted CD8 + T (CD8 + TTE) cells in the tumor, mainly via modification of metabolism mediated by STAT6/mTOR [70].

Differences in inflammation and immune response lead to cancer disparities, including breast cancer, prostate cancer, lung cancer, colorectal cancer, and more. Cancer risk factors such as obesity, affect individuals with African American (AA) and Latina breast cancer more than those with European American (EA) breast cancer. It causes an inflammatory tumor microenvironment in breast tumors and the growth of pro-tumorigenic crown-like structures (CLSs), which comprise dead adipocytes and activated macrophages [71]. Increased numbers of tumor-infiltrating macrophages were found in AA patients [72, 73]. Increased density of $CD8^+$ T cells was found in AA women and AA women with invasive breast cancer [74]. Higher immune content score [75] and difference in the abundance of T-regulatory (Tregs) and T-helper type 2 cells [76] in AA patients compares with EA patients. Exhausted CD8 T-cells also predict the response to anti-PD1 therapy in ER-positive breast cancer women [77]. The immune content in breast tumors also relates to the survival of ER-negative breast cancer patients [78, 79]. Low-grade inflammation and associated immune cells promote prostate cancer progression [80]. Several immune cell types such as $CD4^+$ T cells, natural killer cells (NK) cells, and myeloid-derived suppressor cells and elevated release of IL-6 and IL-8 were associated with worse prognosis of prostate cancer patients [81–85]. The increased expression of PD-L2 was linked to poorer distant metastasis-free survival and inferior radiotherapy outcomes either in isolation or in conjunction with radiation therapy, suggesting that it could be a therapeutic target of interest for prostate cancer [81]. Increased expression of inflammatory factors such as IL-6, vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), Tropomyosin receptor kinase B (TrkB), and higher immune content were found in AA men with prostate cancer [86]. Moreover, pre-clinical studies showed that immune cells such as Tregs, neutrophils, macrophages, and platelets promote prostate cancer metastasis [87–90]. In lung cancer, the circulating plasma levels of inflammation markers such as IL-6, IL-8, interferon gamma (IFNγ, IL-12/IL-23P40, and C-reactive protein are positively associated with lung cancer prognosis [91]. Elevated inflammatory mediators were also related to the risk of lung cancer [92]. IL-15, IL-6, and MCP-4 were identified as potential biomarkers for early-stage lung cancer [65]. AA CRC has a more immunosuppressive environment than EA CRC patients. AA CRC patients had lower densities of cells labeled with TFNg [91]. Fewer macrophages and CD8+ T-cells, but more B-cells were seen in AA tumors compared to EA colon cancer [93]. Therefore, studying how these differences in the immune environment influence tumor biology and exploring the underlying mechanisms may help guide decisions on target therapy. The increased presence of immune-inflammation characteristics in the tumor helps to develop novel treatment therapeutics due to the reason that not every patient can afford the prohibitive expense of immunotherapy.

Although immune checkpoint inhibitors (ICIs) have significant potential, a variety of inflammatory toxicities known as immune-related adverse events (irAEs) have hindered their effectiveness [94]. ICIs are linked to inflammation and tissue damage in various organs [95, 96]. Inflammation also contributes to resistance against ICIs in cases of high microsatellite instability (MSI-H) colorectal cancer [97]. The reports indicate that reducing inflammation may enhance the effectiveness of immunotherapy. A detailed single-cell analysis of immune cell populations in colitis has identified specific cytokines, chemokines, and surface receptors that could be targeted for therapy. These targets could be beneficial not only for colitis but also for addressing other inflammatory side effects associated with checkpoint blockade, including CXCR6 and CXCL16 [98]. ICIs and IL-6 antagonists may enhance the antitumoral effect while also reducing the risk of serious adverse events [99].

Potential metabolic therapeutic strategies for cancer prevention and treatment

Evidence showed that hypercholesterolemia causes cholesterol to build up in immune cells such as macrophages, which in turn triggers inflammatory reactions. These reactions include increased TLR signaling, activation of inflammasomes, and the spleen and bone marrow generation of neutrophils and monocytes. Activation of TLR signaling causes a reduction in cholesterol efflux at the cellular level, which exacerbates inflammatory reactions and causes further cholesterol buildup [100]. As a key factor that regulates the expression of multiple genes implicated in a wide range of lipid and glucose metabolic pathways, peroxisome proliferator-activated receptor alpha (PPARα) exhibits marked anti-inflammatory capacities [101, 102]. It plays an important role in various immune cells such as macrophages [103, 104].

As the relationship between metabolic reprogramming and immune cell activation in cancer becomes clearer, novel therapeutic targets are being identified through modifications to immune cells' intracellular metabolism.

Activation of Toll-like receptor (TLR) 4 is a vital factor that induces pro-inflammatory responses and contributes to metabolic syndrome (MetS) [105]. Therefore, TLRs could be promising targets for the treatment of inflammation-associated diseases as well as cancer.

Studies have shown that PPARα and PPARγ are closely related to carcinogenesis. On the one hand, loss of PPARα promotes the development of colon cancer [106]. Overexpression of PPARα suppressed HCC development [107]. PPARγ plays an anti-tumorigenic role in CRC [108]. On the other hand, PPARα facilitates cell proliferation in prostate cancer [109]. PPARγ acts as an oncogenic role in the development of thyroid carcinoma [110]. Several PPAR-interacting miRNAs, such as miR-506 and miR-27a, have been shown to suppress PPARα and PPARγ in cancer cells [111, 112]. Besides, the upregulation of PPARs or PPAR agonists has been reported to be involved in chemotherapy resistance by metabolic reprogramming. For example, up-regulated PPARs or PPARs agonists foster chemotherapy resistance in cisplatin-resistant ovarian cancer [113], hepatocellular carcinoma [114], colorectal cancer [115], and NSCLC [116]. This suggests the potential of PPARs to act as a promising target for cancer treatment and prevention.

Potential antupohagic therapeutic strategies for cancer prevention and treatment

Dysregulation of autophagy contributes to inflammation and tumor progression. Enhancing autophagy can boost CTLA-4 expression and Tregs, potentially reducing inflammation and cancer [117]. Inhibiting the autophagy pathway encourages the transformation of macrophages into pro-inflammatory M1 cells, which worsens liver inflammation [118]. Research is focused on small molecules and nanomaterials that modulate autophagy for anti-tumor effects. For example, 3-Methyladenine (3-MA) blocks autophagy, reduces ROS, inactivates pro-inflammatory proteins STAT3 and IL-6, and inhibits the survival of HeLa cells [119]. Combining the induction of autophagy by rapamycin with the activation of TLR4 and TLR9 has shown to have a synergistic effect in enhancing anticancer effectiveness.

Rapamycin, an autophagy activator, demonstrated enhanced anticancer effectiveness when combined with TLR4/9 agonists in melanoma treatment [120]. This indicates the potential of combining immunotherapy with autophagy activators for cancer treatment. Besides, GL-V9, an AMPK activator, prevents colorectal cancer associated with colitis by limiting the NLRP3, nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain-containing receptor (NLRP3) inflammasome through the process of autophagy [121]. Ergosterol peroxide induces ROS-dependent autophagy and reduces NLRP3 inflammasome activity, inhibiting lung cancer cell migration and proliferation. However, it is still unclear if autophagy directly suppresses inflammasome activity [122].

Inflammation regulates the hallmarks of cancer

New evidence has strengthened the idea that inflammation plays a crucial role in the development of tumors. Sites of infection, persistent irritation, and inflammation are the origin of many malignancies. It is becoming evident that the tumor microenvironment, which is predominantly regulated by inflammatory cells, plays a crucial role in cancer development by promoting cell division, survival, and migration. It fosters the proliferation of mutant cells and facilitates the spread of malignancy. The hallmarks of inflammation-induced cancer include proliferative and survival signaling promotion, genomic destabilization, angiogenesis promotion, invasion, migration and metastasis induction, and reduced sensitivity of tumors to chemotherapy drugs.

Promoting proliferation and survival signaling

The concept that inflammation enhances cell proliferation has been proposed since 1863, and continuous cell proliferation increases the risk of tumor occurrence [1]. Various inflammatory molecules, as the main component of the tumor microenvironment, contribute to the proliferation of cancer [123]. Chronic inflammation results in the continuous release of pro-inflammatory chemokines and cytokines such as interleukins (ILs) 6 and TNFα, as well as transforming growth factor beta (TGF-β), which promote the survival of tumor cells [124, 125]. Under the stimulation of inflammatory factors such as IL-6 and IL-1β, NFκB and STAT3 were activated. Then, the expression of various oncogenic genes was dysregulated, promoting cancer cells' survival and proliferation [126].

Destabilizing genome

As an enabling characteristic of cancer, genome instability is essential for cancer cell evolution [127, 128]. Accurate DNA synthesis and effective DNA repair processes are crucial for maintaining genomic stabilization. Chronic inflammatory processes promote the development of normal cells, their growth, and their transition to malignancy by disrupting cellular homeostasis, producing various DNA damage products, impairing DNA repair pathways, producing an excess of pro-inflammatory cytokines, and lowering the rates at which damaged cells undergo apoptosis [129, 130]. Abundant evidence indicates that inflammation contributes to genomic instability [131–133]. Inflammation generates reactive oxygen and nitrogen species (RONS) [132, 134, 135] and ROS [136] during the inflammatory response, which results

in direct DNA damage. The inflammation-associated DNA damage contributes to colon carcinogenesis in mice [137]. The DNA damage-induced sustained p53 activation contributes to inflammation-associated hepato-carcinogenesis in rats [138].

Promoting angiogenesis

Angiogenesis is recognized as the process of growth and remodeling that transforms an initial vascular system into the intricate branching network that characterizes adult vasculature [139]. Anastomosis, migration, survival, proliferation, and ECM breakdown are all part of this intricate multi-step process [140]. Abnormal vessel growth and function are hallmarks of cancer [141, 142]. Abundant evidence showed that in pathological circumstances such as cancer, angiogenesis, and inflammation are closely related [143]. Various pro-inflammatory chemokines and cytokines released during inflammation are potent activators for endothelial cells (ECs) to attract blood-derived inflammatory cells [144]. Adhesion molecules play a vital role in this process, and they're regulated by various pro-inflammatory mediators [145]. Alternatively, angiogenesis maintains inflammation by providing oxygen and nutrients to meet the metabolic needs of cells at the site of inflammation. The tumor microenvironment is rich in inflammatory molecules such as TNFα, IL-1, IL-6, IL-8, COX-2, and vascular endothelial growth factor (VEGF) [146, 147]. For example, as one of the best-characterized inflammatory mediators in carcinogenesis, TNF α activates NF-κB [148], which is involved in angiogenesis [149]. VEGF production contributes to angiogenesis, fostering tumor development [150, 151]. Since angiogenesis is essential for the formation and spread of tumors, there were substantial expectations that inhibiting this process would have therapeutic benefits. To demonstrate the utility of anti-angiogenic medicines, more than thirty years and multiple pre-clinical investigations employing a variety of anti-angiogenic strategies were required [152, 153]. As one of the most studied targets in clinical trials, VEGF shows significant biological functions [154]. The first antiangiogenic agent anti-VEGF mAb, has been approved to treat metastasis colorectal cancer combined with chemotherapy [155]. Anti-inflammatory medications have also been demonstrated to have antiangiogenic properties, suggesting that their use may be advantageous for neoplastic therapy.

Inducing invasion, migration, and metastasis

Inflammatory cells and mediators participate in the invasion, migration, and metastasis of malignant cells. Many cells begin to produce chemokines when they are transforming. As a result, they can use chemokines to help migrate to and survive at locations distant from the original tumor [156–158]. For example, cell migration is influenced by the C-X-C chemokine receptor (CXCR) 4 and its ligand (C-X-C motif) ligand (CXCL) 12 in both healthy and pathological conditions [158]. Malignant cells often express CXCR4 [156]. The degree of CXCR4 expression in primary human malignancy is correlated with lymph node metastasis in colorectal, breast, liver, and esophageal cancer [159–161]. Besides, malignant cells from a variety of tissues also express other functional chemokine receptors, such as CX3Chemokine receptor 1 (CX3CR1), CC-chemokine receptor 1 (CCR1), CCR7, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR5, and CXCR7. These receptors are implicated in organ-specific metastasis [162–167]. For instance, the expression of CCR7 is correlated with lymph node metastasis, and CCR9 is correlated with melanoma metastasis to the small intestine. Many of the receptors are expressed by malignant melanoma cells, which could account for melanomas' high rate of metastasis. Several mechanisms may help malignant cells acquire the ability to express chemokine receptors, including genetic and epigenetic alterations, and autocrine and paracrine extracellular signals. The inflammatory cytokines such as TNF-α, IL-6, and IL-1β, can enhance the invasive ability of tumor cells in ovarian cancer, breast cancer, and others [168–170]. Higher levels of the cytokine IL-6 are associated with increased risk of distant recurrence of HER2-negative early breast cancer [171]. TGF-β promotes epithelial-mesenchymal transition (EMT) [172, 173] and metastasis [174–178] at a late stage of cancer. Inflammatory macrophages contribute to ovarian cancer cell migration in vitro [179] and ovarian cancer model [180]. Macrophage-deficient mice could develop tumors but can't form pulmonary metastasis in a breast cancer model [181]. In conclusion, malignant cells and invading leukocytes interact with autocrine and paracrine by coordinating chemokines and cytokines. Due to these interactions, malignant cells are more likely to migrate, invade, and survive.

Reducing the sensitivity of tumors to chemotherapeutic drugs, radiotherapy and immunotherapy

Chemotherapy, radiotherapy and immunotherapy are common treatment options utilized for various cancer types. One of the side effects of chemotherapy is producing inflammatory cytokines related to the side effects and drug resistance. Similarly, radiation-induced DNA damage response (DDR) also promotes the release of cytokines and chemokines, which will cause the invasion and metastasis of cancer by triggering the inflammatory process and suppressing the immune function [182, 183]. Resistance has been the significant barrier to effective cancer treatment [184–187]. Inflammatory mediators

such as GM-CSF, IFN-γ, IL-1β, IL-5, IL-10, and tumor necrosis factor alpha (TNF-α) play crucial roles in the resistance associated with inflammation. For instance, CD4 + T helper 2 (TH2) cells, which are key regulators of inflammatory processes in cancer, can accelerate pulmonary metastasis and promote chemotherapy resistance through the activation of macrophages by IL-4 in breast cancer [188]. Activated downstream of IL-13, the signal transducer and activator of transcription 6 (STAT6) enhances anti-apoptotic pathways, potentially leading to resistance against cytotoxic CD8 + T cells and chemotherapy in breast cancer [189, 190]. NF-κB upregulates the Wnt family member Wnt16B, which attenuates the effects of cytotoxic chemotherapy in prostate cancer [191]. NF-κB can also be activated by chemotherapy drugs such as paclitaxel, cisplatin, doxorubicin, and bleomycin [192]. Therefore, inhibition of the inflammatory cytokines pathway and related molecules seems to be an up-and-coming method to improve chemotherapy efficacy. Phytochemicals such as resveratrol, curcumin, genistein, epigallocatechin-3-gallate (EGCG), lycopene, thymoquinone, quercetin, capsaicin, and other phytochemicals, that inhibit the NF-κB pathway have a preventive effect on drug resistance [193–196]. For example, resveratrol enhances doxorubicin-induced cytotoxicity in chemo-resistant B16 melanoma [197]. Curcumin can sensitize tumors to many chemotherapeutic drugs in various types of cancer, such as colon, breast, liver, lung, ovarian cancer, and others; curcumin also sensitizes tumors to gamma radiation in multiple types of cancer, such as colon cancer, cervical carcinoma, glioma, neuroblastoma, epidermal carcinoma, prostate cancer, and others [198, 199].

Radiation kills cancer cells via various mechanisms, while the dying cells promote the release of several cytokines, such as TGF-β [200]. TGF-β closely relates to radio-resistance by suppressing the immune system and regulating angiogenesis, invasion, and DNA damage [201, 202]. Inhibition of TGF-βRI can reverse the radio-resistance of irradiated cells [203]. In some clinical trials, TGF-β antagonists such as fresolimumab and LY2157299, have been applied to cancer patients undergoing radiotherapy and have obtained some promising results [201]. For example, TGF-β blocking antibody fresolimumab increases the overall survival of metastatic breast cancer patients [204]. These suggest that anti-TGF-β medications and radiation therapy together may improve tumor response and minimize side effects. Additionally, LIF mRNA, which is expressed in immune cells such as T-cells, macrophages, and monocytes, as well as in epithelial carcinoma cells and adjacent stromal cells, promotes radio-resistance in nasopharyngeal carcinoma by activating the mTORC1/p70S6K pathway [205]. The blockade of LIF altered macrophages, slowed tumor progression, and improved the effectiveness of anti-PD-1 therapies in colon cancer [206].

EMT is an important step during resistance [207], IL-6 cytokines can promote EMT by activating transcription factors such as STAT3 and Snail. This suggests that blocking IL-6 family cytokines may enhance the effectiveness of immunotherapy. Drugs that target IL-6 cytokines have been shown to improve the efficacy of immune checkpoint blockade (ICB) and reduce irAEs. Several clinical trials are currently underway to evaluate the combination of anti-IL-6 therapies with immunotherapy in cancer treatment [208]. In animal models of cancer, the upregulation of CD38 is associated with acquired resistance to anti-PD-L1 treatment. CD38 decreases the activity of CD8 T cells and reduces the effectiveness of anti-PD-L1 immunotherapy by contributing to the accumulation of adenosine in tumors [209]. Blocking CD38 made tumors more susceptible to anti-PD-L1 therapy. Moreover, inhibiting CD39's enzymatic activity leads to the depletion of intra-tumoral macrophages, modifies the inflammatory response, boosts T cell proliferation, and overcomes anti-PD-1 resistance in colon cancer [210]. Inhibition of A2A adenosine receptor increases the efficacy of anti-PD-1 and produces T cell-dependent anti-tumor activity in breast and colon cancers [211]. Inhibition of the CD39-CD73-adenosine axis appears to be a promising strategy for overcoming resistance to immunotherapy.

The relationship between inflammatory diseases and cancer

Crohn's disease (CD) and ulcerative colitis (UC) are two types of inflammatory bowel disease (IBD) that involve chronic inflammation of the gastrointestinal tract. Patients with Crohn's disease and ulcerative colitis are at a higher risk of being diagnosed with cancer compared to the general population [212], such as colorectal cancer [213], small-bowel cancer [214], colon cancer [215], and also the skin cancers, lymphomas and cervical abnormalities [216]. CD also increases the incidence of anal cancer and anorectal cancer [217]. The risk of cancer may depend on the severity and duration of inflammation. Pro-inflammatory cytokines such as IL-6, generated during gut inflammation, play a crucial role in cancer development by activating intracellular transcription factors like STAT3 and NF-κB [218]. Anti-tumor necrosis factor therapy at an intensified dose is the most effective medical treatment for perianal Crohn's disease, as it can lower the risk of anal tumors [219].Current data indicates that immunosuppression for IBD does not increase the risk of new or recurrent malignancies [220]. The blockade of IL-23 using neutralizing antibodies, which has been tested in clinical trials for Crohn's disease therapy, is

anticipated to be an effective method for treating colon cancer and colorectal cancer. This expectation is based on the regulatory role of IL-23 in carcinogenesis [215].

Aside from IBD, autoimmune diseases like rheumatoid arthritis (RA) and celiac disease are notable. Patients with RA have an increased risk of developing prostate cancer [221], lung cancer [222], nonmelanoma skin cancer (NMSC) [223], and non-Hodgkin's lymphoma [224]. Additionally, RA increases the risk of lymphoid, myeloid, cervical, and oropharyngeal cancers, while decreasing the risk of endometrial and colorectal cancers, according to a study of one million women [225]. Long-term immunological dysregulation, such as altered B cell activation and survival, along with the inflammatory reactions associated with RA development, may further increase the risk of developing cancer [226, 227]. Antagonists of TNF-α, Janus kinase (JAK), and IL-6 are commonly used therapeutics for RA, but their effects on tumor development are mixed. For instance, while TNF inhibitors have been found to increase the risk of NMSC in patients with RA, they can also reduce tumor size and metastasis in cases of colorectal and colon cancer [228, 229]. JAK inhibitors didn't increase the risk of cancer [230, 231]. Celiac disease is an autoimmune disorder that primarily affects the small intestine and is triggered by gluten consumption in genetically predisposed individuals [232]. The development of coeliac disease involves a complex immune response to gluten proteins. Celiac disease also increases the risk of non-Hodgkin lymphoma [233], small bowel carcinoma [234]. Additionally, it raises the mortality rate among cancer patients [235].

The gluten-free diet is the primary treatment for coeliac disease. It helps reduce damage to the small intestinal mucosa caused by repeated gluten ingestion, thus lowering the risk of lymphoproliferative malignancies [236]. Nutritional support, pharmacological agents, and autologous hematopoietic stem-cell transplantation are also recommended for non-responsive type 2 cases [237]. Additionally, utilizing new techniques such as gene silencing (e.g., RNA interference) or gene editing (e.g., CRISPR-Cas9) to reduce immunogenic gluten proteins could enhance the quality of life for individuals on a gluten-free diet [238]. A pilot study indicated that a low-gluten RNA interference wheat line did not provoke an immune response after a short-term oral challenge in patients with treated coeliac disease [239]. These methods may also offer innovative approaches for the primary prevention of celiac disease.

The role of inflammation in certain types of cancer

Several types of tumors are directly related to inflammation. For example, the development of colitis and colitis-associated tumors is closely related to chronic inflammation [240]. There are several pathogens that play an important role in inflammation-related tumors such as cervical cancer, gastric cancer, and liver cancer. For example, human papillomavirus (HPV) is a major risk factor for the development of cervical cancer, as its proteins are involved, either directly or indirectly, in inflammation that can lead to the onset of this disease [241]. Immune cell infiltration and the increased secretion of inflammatory cytokines are two primary factors in the development of cervical cancer [242].

Helicobacter pylori (H. pylori) is classified as a Group I carcinogen and infects over half of the world's population. It has unique properties that allow it to colonize the gastric epithelium in acidic environments. Infections caused by H. pylori can lead to chronic gastritis, which may progress to severe gastrointestinal conditions, including gastric cancer [243]. Understanding the complex bacterial virulence mechanisms and their interactions with the host immune system and environmental factors is crucial for comprehending the pathophysiology of H. pylori infection.

In China, the hepatitis B virus (HBV) is the primary cause of liver cancer [244]. While liver cancer is primarily caused by hepatitis C virus (HCV) infection in South Korea and Japan [245]. Chronic infections of HBV or HCV, along with factors such as nonalcoholic fatty liver disease (NAFLD) and excessive alcohol consumption, lead to liver injury, chronic inflammation, and ultimately liver cancer [246]. The transformation of inflammatory tumors in the liver is a gradual and dynamic process [247]. The chronic inflammation leads to an altered immune environment, increased secretion of inflammatory factors, and dysfunctional NK cells, ultimately resulting in liver cancer [248].

The role of patient-specific factors in inflammation-related cancer

Various patient-specific factors, such as the microbiome and genetics, play crucial roles in cancer related to inflammation.

The role of microbiome in inflammation-related cancer

The microbiome can influence key characteristics of cancer, including the promotion of harmful local inflammation that contributes to the development of tumors. For instance, Helicobacter pylori colonizes the human gastric mucosa, leading to chronic inflammation and resulting in gastric ulcers, which can eventually progress to stomach cancer [243]. Research has shown that Fusobacterium nucleatum in colorectal cancer activates NF-κB, an important modulator of inflammation associated with cancer, through its binding to Toll-like receptors and nucleotide-binding oligomerization domain-like

receptors [249]. Moreover, the carcinogenic potential of gut bacteria results in increased production of IL-6 and TNF, activation of STAT3, and activation of the IL-17–IL-23 pathway [250]. Innate and adaptive host immune responses triggered by microbiota can collaborate to promote the development and spread of malignancies by inducing inflammation that supports cancer growth and increases resistance to cell death.

The composition of microbiota can significantly influence the effectiveness and side effects of cancer treatments, as well as the quality of life after cancer therapy [251]. For example, there is a significant difference in the microbiome composition between responder and non-responder patients undergoing anti-PD-1 immunotherapy [252, 253]. The altered gut microbiome due to antibiotics reduced the effectiveness of ICIs in advanced cancer patients [254]. Moreover, the effectiveness of chemotherapeutic drugs can also be influenced by bacteria, affecting their metabolism and absorption [255]. Probiotics and microbiota transplants may be effective strategies for modifying the microbiome, potentially enhancing cancer therapy responses and improving quality of life. For instance, oral supplementation with A. muciniphila or Bifidobacterium can boost the effectiveness of PD-1 or PD-L1 immunotherapy in mouse models of melanoma and lung cancer [254, 256]. Importantly, certain probiotic strains, prebiotics like inulin and fructo-oligosaccharides, and synbiotics can reduce gastrointestinal side effects in cervical cancer patients. They do this by altering key metabolic pathways and inflammation, lowering oncogene activity, and ultimately reducing cancer progression [257]. Microbiome-regulating agents are relatively safe, making them potential adjuvants in clinical cancer treatment and paving the way for personalized therapies. However, more high-quality clinical trials are urgently needed.

The role of genetics in inflammation-related cancer

Cancer was once thought to be solely hereditary, but it is now understood to be influenced by a combination of dysregulated genetic and epigenetic pathways [258]. Genetic alterations are essential for cancer development and the creation of an inflammatory microenvironment, linking inflammation and cancer through an intrinsic pathway [259]. Genetic alterations, including oncogene activation through mutations, chromosomal rearrangements, or amplifications, as well as inactivation of tumor-suppressor genes, contribute significantly to cancer development. Among the most frequently mutated dominant oncogenes in human cancer are myelocytomatosis oncogene (MYC) and rats arcomaviral oncogene homolog (RAS), which induce tumor-promoting inflammatory mediators that play critical roles in tumor growth and angiogenesis [260, 261]. The Kirsten rats arcomaviral oncogene homolog (KRAS)-G12D mutation promotes immunosuppression and increases resistance to anti-PD-1/PD-L1 immunotherapy in non-small cell lung cancer (NSCLC) [262]. MYC promotes resistance to immunotherapy and IFNγ by downregulating JAK2 [263]. Targeting dysregulated MYC or RAS may enhance immunotherapy effects, as several studies have demonstrated. For instance, inhibiting MYC increased tumor immune cell infiltration and made tumors more responsive to anti-PD1 immunotherapy [264]. OmoMYC, a peptide and mini-protein that inhibits MYC, is currently being developed for evaluation in clinical trials for relapsed or refractory acute myeloid leukemia [265]. Currently, several inhibitors targeting RAS and MYC mutations are in clinical use or undergoing clinical trials. This offers a promising strategy to enhance anti-tumor effects and overcome the drug resistance of immunotherapy. Additionally, tumor-suppressor proteins like von Hippel-Lindau (VHL) and PTEN can regulate the production of inflammatory mediators [266, 267].PTEN treatment improves anti-PD-1 efficacy in mice and reverses the immune-suppressive phenotype of primary tumor-associated macrophages derived from patients [268]. Administering PTEN externally may serve as a promising cancer immunotherapy strategy.

Targeting inflammatory pathway for cancer chemoprevention

A growing tumor's inflammatory component may involve various leukocyte types, such as neutrophils, dendritic cells, macrophages, eosinophils, mast cells, and lymphocytes. These leukocyte types can produce a wide range of cytokines, as well as cytotoxic mediators like reactive oxygen species, serine and cysteine proteases, MMPs, and membrane-perforating agents, as well as soluble mediators of cell death like TNF-α, interleukins, and IFNs [269]. The detailed information about the inflammatory cells and molecules they secret are summarized and shown in Fig. 1. And the pro- or anti-tumor effect of these inflammatory molecules are also summarized and shown in Fig. 2 and Fig. 3. TNFα antibodies or inhibitors such as infliximab are undergoing phase 2 clinical trials in breast and renal cell cancer [270]. Chemokine receptor antagonists like bicyclam plerixafor are now in clinical use in non-Hodgkin lymphoma and multiple myeloma [271]. Trabedtedin as the cytotoxic drug to tumor-associated macrophages and circulating monocytes, has been used to treat soft-tissue sarcoma and ovarian cancer [272]. Fibroblast plays an important role in tumor development, and inhibitors of the fibroblast growth factor receptor have been studied in various tumors [273].

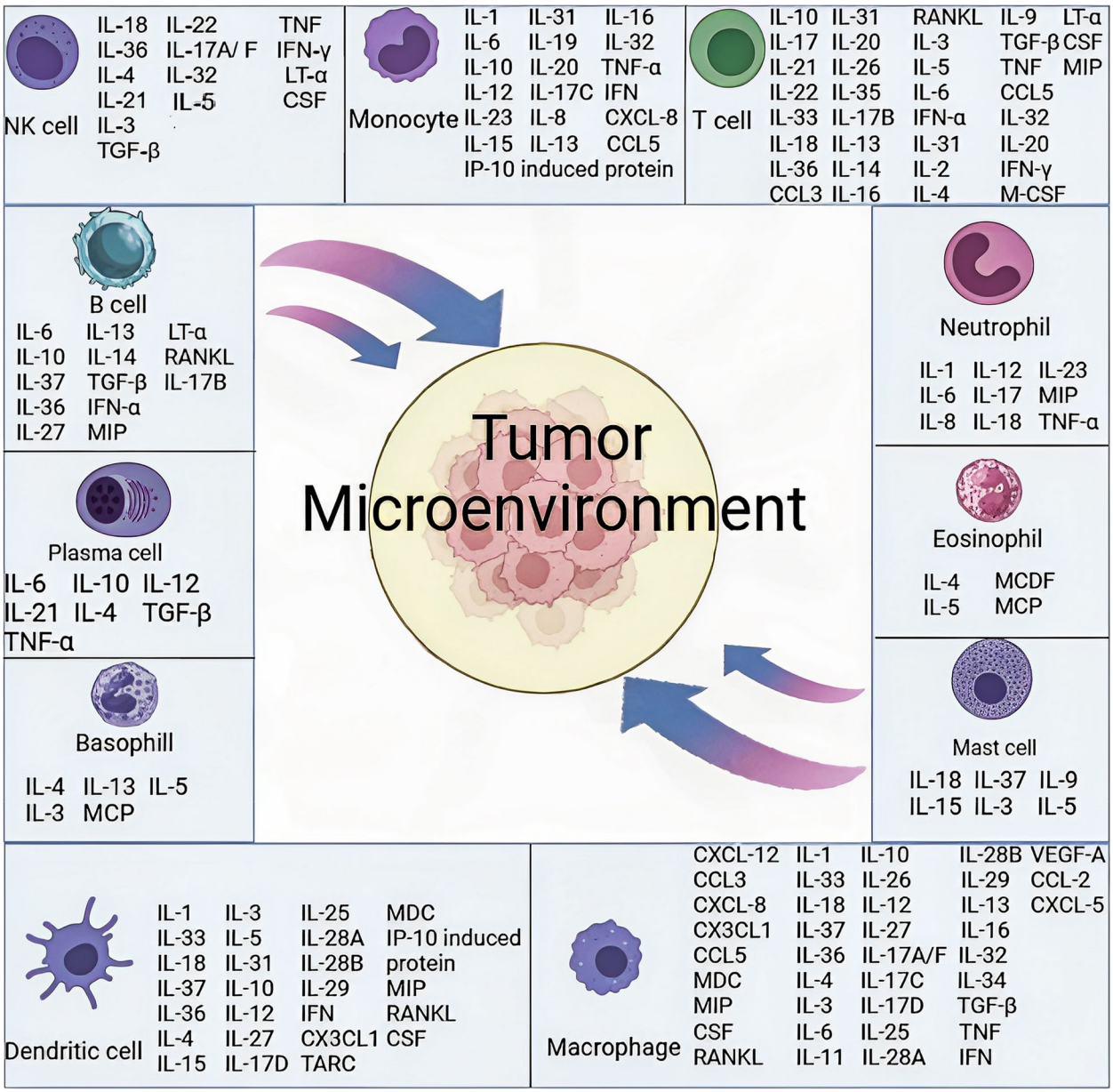

Fig. 1 The detailed information about the inflammatory cells and molecules they secret. The inflammatory cells include NK cell, monocyte, T cell, neutrophil, eosinophil, mast cell, macrophage, dentritic cell, basophill, plasma cell and B cell. NK cell secretes several kinds of interleukin (IL), interferon (IFN), tumor necrosis factors (TNF), transforming growth factors (TGF), colony-stimulating factor (CSF) and lymphotoxin alpha (LT-α); monocyte secrets several kinds of ILs, IFN, TNF, C-X-C motif) ligand (CXCL) and interferon-inducible protein-10 (IP-10) induced protein; T cell secrets several kinds of ILs, IFN, TNF, TGF, macrophage colony-stimulating factor (M-CSF), receptor activator of nuclear factor-kappa B ligand (RANKL), macrophage inflammatory protein (MIP) and LT-a; neutrophil secrets several kinds of ILs, TNF-a and MIP; eosinophil secrets IL-4, IL-5, MCDF and monocyte chemoattractant protein (MCP); mast cells secrets several kinds of ILs; macrophage secrets several kinds of CXCLs and ILs, TGF-b, TNF, IFN, CSF, vascular endothelial growth factor A (VEGF A), macrophage-derived chemokine (MDC) and MIP; dendritic cell secrets macrophage secrets several kinds of ILs, CX3CL1, IFN, RANKL, CSF, thymus and activation-regulated chemokine (TARC), MDC, MIP and IP-10 induced protein; basophill secrets MCP and several kinds of ILs; plasma cell secrets TGF-β, TNF-α and several kinds of ILs; B cell secrets several kinds of ILs, LT-α, RANKL, TGF-β, IFN-α and MIP

Targeting interleukins for cancer chemoprevention

As the means of communication for immune cells and non-immune cells, interleukins play important roles in the occurrence and development of tumors. Their importance as a target and therapeutic agent is demonstrated by the growing number of clinical trials that are presently ongoing. While the results of clinical trials are not satisfactory. Interleukin-6 monoclonal antibodies have been studied in phase 2 and 3 clinical trials in ovarian and renal cancer [274]. Anti-interleukin-6 receptor antibody-like tocilizumab successfully treats cachexia in lung cancer patients [275]. Treated with IL1R antagonists enhances the antitumor effect of gemcitabine and 5-fluorouracil [276]. More details regarding the function of interleukins and underlying mechanisms in cancer are provided in Table 1.

Activating interferons for cancer chemoprevention

As the most effective and widely distributed family of cytokines, IFNs are induced by nucleic acids and related to immunity and vascular. IFNs are composed of type I, II, and III IFNs. Type I IFNs include IFN-α, β, ε, κ, and ω; type II IFNs refer to IFNγ; type III IFNs include IFNγ1, FNγ2, FNγ3 (first called IL-28A, IL-28B, and IL-29) [277]. After stimulation, they are produced and secreted by body cells, such as T lymphocytes, B lymphocytes, macrophages, fibroblasts, and epithelial cells [278]. All IFNs activate the transcription of interferon-stimulated genes through the Janus kinase (JAK)/STAT pathway. Generally, JAK1 and JAK2 are activated by type II IFN signaling to cause STAT1 homodimerization, whereas TYK2 and JAK1 are activated by type I and III IFN signaling to cause STAT1-2 heterodimerization and IFN-stimulated gene (ISG) factor 3 (ISGF3) creation [277]. IFNα and IFNβ, which belong to type I interferons, directly control the transcription of over 100 downstream genes, resulting in direct (on cancer cells) and indirect (through immune effector cells and vasculature) effects on tumors [278]. Drug development and patient assessment of interferon-directed therapies have benefited from new understandings of the endogenous and external activation of type I interferons in the tumor and its microenvironment. Modulation of the interferon system may further reduce cancer morbidity and death when paired with other efficacious cancer treatment methods or with previous observations. Clinical trials were started by the Finnish National Red Cross and Hans Strander and Kari Cantell using partially purified IFNα, which was made from human blood donor leukocytes in Cantell's Helsinki laboratory [279]. Abundant evidence indicated the anti-tumor effects of leukocyte-derived INFα on various metastasis solid tumors and hematological malignancies [280]. Recombinant INFα2 was the first human immunotherapeutic approved by the FDA for cancer [281].

However, exogenous INFα2 and IFNβ also lead to systemic adverse effects. The discovery of the molecular and cellular aspects of pathways of induction and action of interferon, such as effects of protein products of interferon-stimulated genes (ISGs), cellular actions of interferons, and endogenous nucleic acid-induced pathways, which may provide new opportunities for enhancing the anti-tumor effect of these cytokines. For example, it has been suggested that RNA is a more powerful transcription inducer of interferons regarding RIG-I (retinoic acid-inducible gene I) or Toll-like receptors (TLR3, TLR7, and TLR8). A TLR3 agonist ARNAX facilitates the effect of immunotherapy on patients [282]. TLR 3 and 7 agonists induce a hot triple-negative breast cancer immune environment [283]. TLR7/8-agonist-loaded nanoparticles promote the polarization of tumor-associated macrophages to enhance cancer immunotherapy [284]. Besides, cytoplasmic protein cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) (cGAMP) synthase (cGAS) binds to DNA and initiates the synthesis of cGAMP, activating the stimulator of interferon genes (STING), then activates the endogenous interferon system [279], which provides a fresh understanding of how immune effector cells' endogenous interferon system is activated. And the cGAS-STING pathway plays a fundamental and vital function in identifying immunogenic cancer cells. When the intracellular STING protein is activated, various immunostimulatory molecules are produced, which can lead to the maturation of dendritic cells, the polarization of anti-tumor macrophages, the priming and activation of T cells, the activation of natural killer cells, vascular reprogramming,

(See figure on next page.)

Fig. 2 The the pro-tumor effect of these inflammatory molecules are summarized. **A** Inflammatory molecules which are involved in promoting proliferation, invasion, migration and metastasis are summarized. **B** Inflammatory molecules which contributes to angiogenesis, epithelial-messenchymal transition, lymph angiogenesis and drug resistance are summarized. **C** Inflammatory molecules which participates in promoting tumor-related inflammation, malignant progress and tumor recurrence, inhibiting cancer cell death, increasing the motility of cancer cells, promoting tumor growth, enhancing radiation resistance and promoting tumorigenesis. **D** Inflammatory molecules which contribute to promoting osteolysis and immunosuppression, enhancing tumor immune tolerance, promoting the occurrence of precancerous lesions, culture promoting tumor microenvironment, promoting immune-escape, enhancing adhesion and promoting the stemness of cancer cells

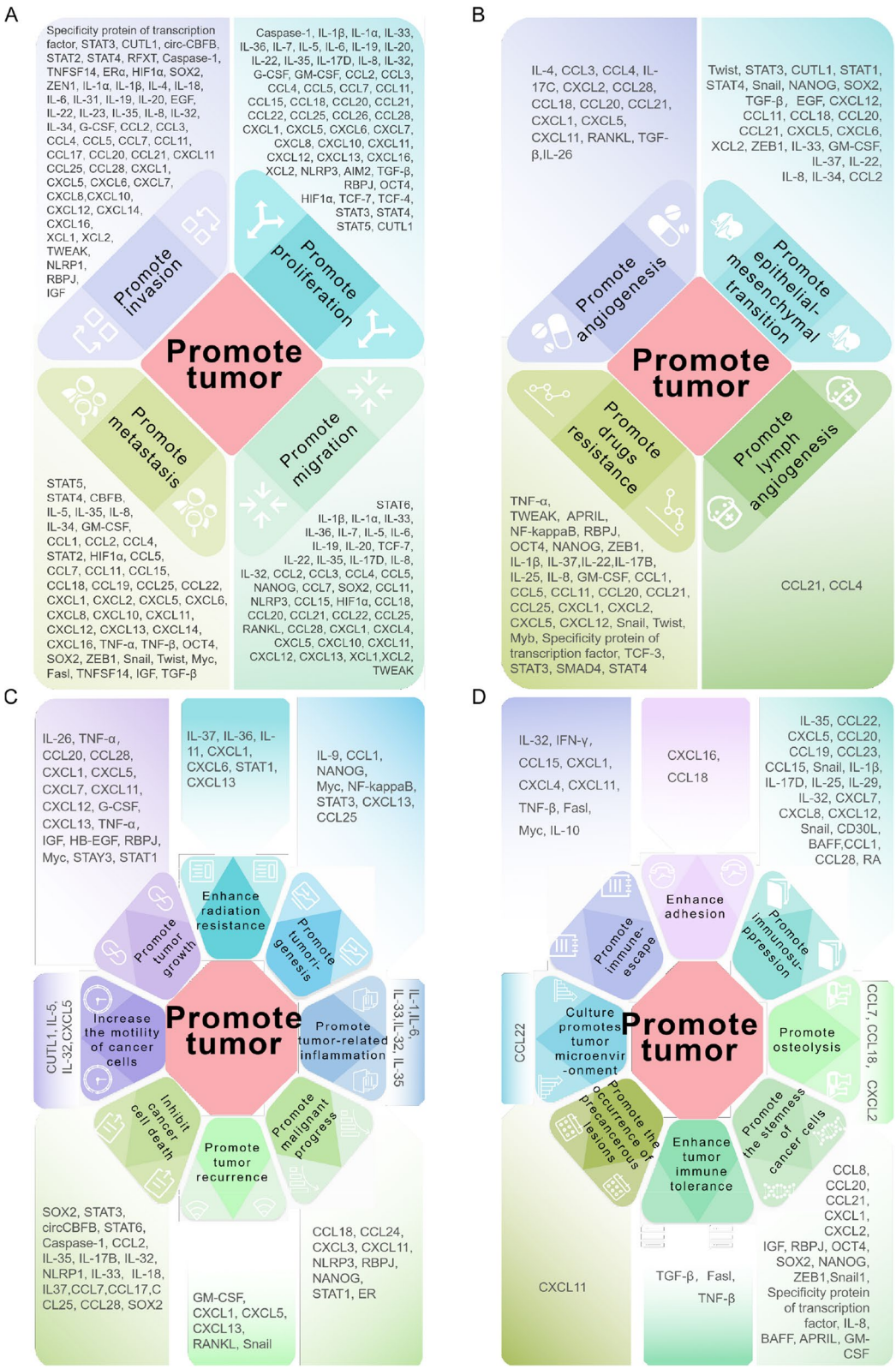

Fig. 2 (See legend on previous page.)

and/or the death of cancer cells. These processes can result in the immune system eliminating tumors and producing anti-tumor immune memory [285]. STING inhibits the reactivation of dormant metastasis in lung adenocarcinoma [286]. STING agonist promotes CAR T cell trafficking and persistence in breast cancer [287]. cGAS-STING-mediated type I interferon signaling enhances the development of stem cell-like CD8 + T cells by inhibiting Akt activity [288]. The combination of STING agonists with radiotherapy or chemotherapy can enhance the antitumor effect and reduce the side effects caused by conventional treatments [289, 290]. Moreover, co-administering STING agonists with CTLA4 and PD1 antibodies demonstrated a significant survival advantage in a preclinical model of HPV + oral tumors [291]. The combination of the STING agonist DMAXX and CAR T cell therapy significantly increases the number of CAR T cells [287]. Recent studies have improved our understanding of the cGAS/STING pathway in cancer treatment, but prolonged STING activation can promote carcinogenesis. Analysis of the TCGA database shows that several cGAS-encoding genes are significantly upregulated in malignant tissues compared to normal controls, indicating that cGAS/STING signaling may be active in these cancers [292]. Current research indicates that STING can increase the expression of the immune checkpoint indoleamine-2,3-dioxygenase (IDO), which may directly or indirectly reduce T-cell function and numbers, thereby promoting immunological escape [293]. The enzyme cGAS, found in mitochondria, suppresses ferroptosis and promotes the progression of hepatocellular carcinoma [294]. These reports suggest that cGAS may be a potential target for cancer interventions. The inhibitory effects of astin C, a novel STING-specific inhibitor, on Trex1/BMDMs highlight the potential of astin C for cancer treatment [295]. Further research is necessary to evaluate the effectiveness of cGAS-STING pathway inhibition in cancer treatment.

The role of IFNs in cancer is complex, based on the time, cells present, total IFN-I signal levels, and the IFNα/β sub-types mediating the effects, frequently producing different results. Additionally, it's becoming evident that the timing of IFN-I delivery or blockade can have radically different outcomes, illuminating the complex biology at play. More details regarding the function of TLRs and STING and the role of their agonists in cancer are provided in Table 2 and Table 3 respectively.

Targeting TNFs for cancer chemoprevention

In the late 1970s, macrophages were discovered to create a cytokine called TNF, also known as TNFα, which can inhibit tumor cell growth and cause tumor regression [296]. Lymphotoxin, derived from lymphocytes, has a 50% homologous amino acid sequence and binds to the same receptor with TNFα, it came to be called TNFβ [297]. The TNF superfamily, composed of 19 ligands and 29 receptors, participates in multiple biological functions. Since their role in inflammation, apoptosis, proliferation, invasion, angiogenesis, metastasis, immune, and others, TNF superfamily members were promising targets for drug development. Numerous investigations showed TNF superfamily members to be a kind of strong inflammatory cytokines that both stimulate complicated immune responses and have anti-tumor properties. TNF superfamily actions can be both advantageous and dangerous. On the one hand, TNF acts as the major mediator of cancer-related inflammation, and many antagonists against the TNF family and their receptors have been approved by the FDA, and some of these are already undergoing clinical testing. For example, anti-TNF treatment (infliximab) enhanced the effects of chemotherapy in colon cancer treatment [298]. On the other hand, TNF can cause cancer cell death, which makes it a possible cancer therapy. As the first cytokine to be employed for cancer treatment, TNFα has been used in the clinic for the treatment of soft tissue sarcoma [35] and melanoma [36]. However, reducing TNF's toxicity is a major task before TNF can be administered consistently. The advancement of TNF-α therapy in the future will depend on reducing systemic therapy's toxicity and raising TNF-α dosages to increase the direct tumor response. On the other hand, through indirect tumor effects, the use of innovative modes of action may improve safety and efficacy. More details regarding the function of interleukins in cancer are provided in Table 4.

(See figure on next page.)

Fig. 3 The anti-tumor effect of these inflammatory molecules are summarized. **A** Inflammatory molecules which are involved in enhancing radiation efficacy, suppressing migration and malignant progression of tumor, inhibiting angiogenesis, lymph angiogenesis and stemness, promoting synergistic apoptosis and enhancing drug sensitivity are summarized. **B** Inflammatory molecules which contributes to inhibiting inflammation, promoting immunity and tumor cell lysis, preventing immune escape, reducing epithelial-messenchymal transition and promoting cancer cell apoptosis. **C** Inflammatory molecules which participates in restraining movement, suppressing occurrence, driving cell senescence, inhibiting adhesion and driving non-apoptotic cellular death. **D** Inflammatory molecules which contribute to suppressing invasion, inhibiting metastasis, restraining growth and inhibiting proliferation

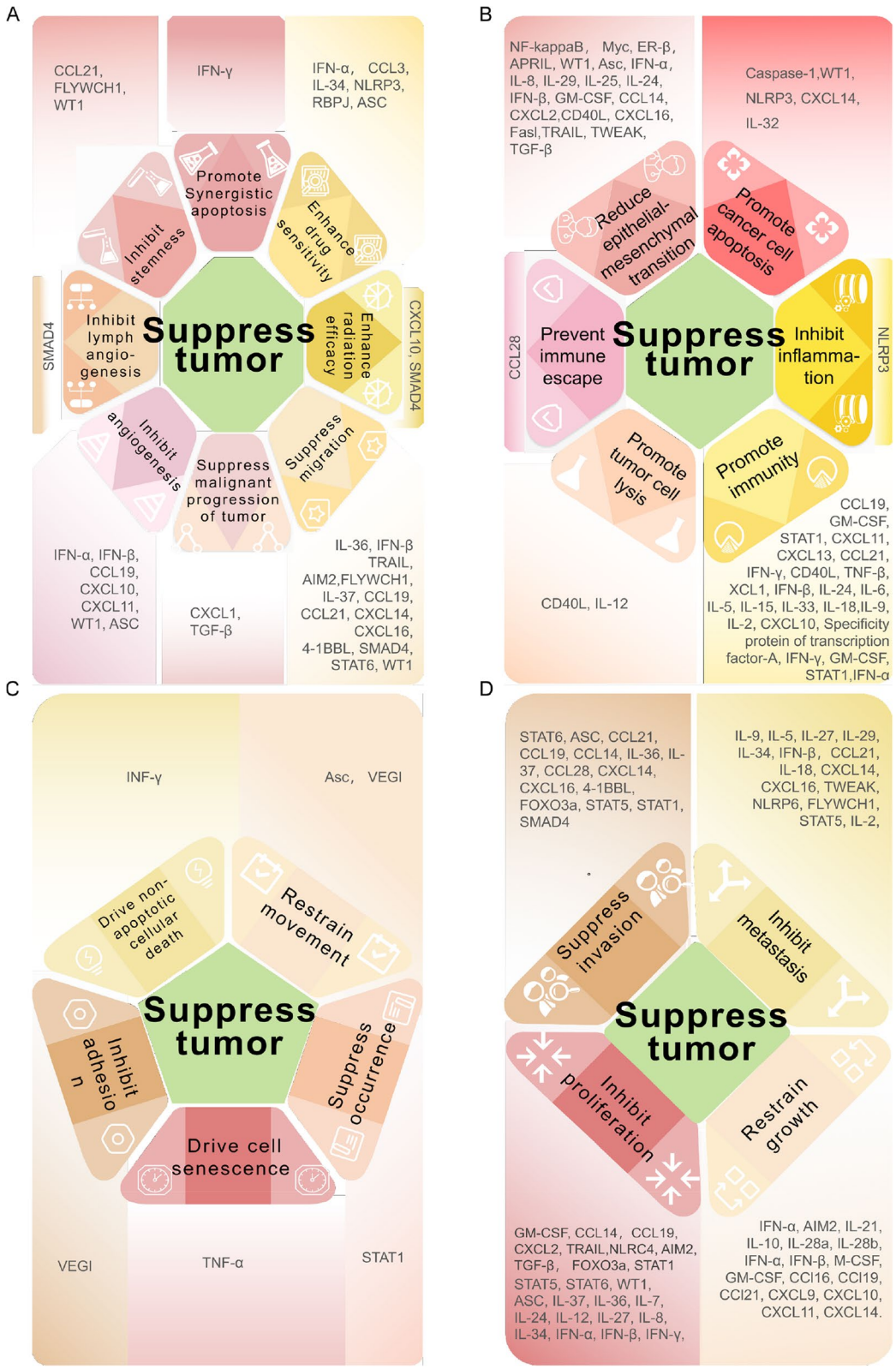

Fig. 3 (See legend on previous page.)

Table 1 The role and mechanisms of interleukins in cancer

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-37	IL-1R8, IL-1R5	Colon cancer	Promote	Promotes colitis-related carcinogenesis through SIGIRR-mediated cytotoxic T cell dysfunction	Wang Z et al., 2022
		Pancreatic cancer	Promote	Drives gemcitabine resistance through negative feedback signal of IL-37/STAT3/HIF-1α	Zhao T et al., 2020
		Skin cancer	Promote	Inhibits tumor immune surveillance by regulating CD103(+) DCs and establishing a relationship between metabolism and immunity	Ceng F et al., 2023
		Gallbladder cancer	Inhibit	Inhibits the EMT induced by HIF-1α	Wu T et al., 2018
		Renal cancer	Inhibit	Inhibits IL-6/STAT3 signal transduction	Jiang Y et al., 2015
		Cervical cancer	Inhibit	Inhibits proliferation and invasion by suppressing STAT3	Wang S et al., 2015
		Lung cancer	Inhibit	Inhibits migration, invasion and proliferation, and promotes apoptosis through IL-6/STAT3 pathway and Bcl-2, NEDD9 and cyclin D1	Deng Y et al., 2018
IL-36α, IL-36β and IL-36γ	IL-1R6, IL-1R3	Oral squamous cell carcinoma	Promote	Stimulates proliferation of cells with high IL-36R expression, and promotes migration of cells with low IL-36R expression	Li Z et al., 2024
		Colorectal cancer	Promote	Induces proliferation by promoting the expression of different genes involved in the IL-17/IL-23 axis	Baker J et al., 2023
		Liver cancer	Inhibit	Inhibits the proliferation,activity and migration of HCC in vitro	Song Y et al., 2023
IL-2	sIL-2Rα, IL-2/IL-15Rβ–γc, IL-2Rα, IL-2/IL-15Rβ–γc	Gastric cancer	Promote	Mediates the impairment of T cell function	Tsubono M et al., 1990
		Pancreatic cancer	Inhibit	Inhibits tumor growth by enhancing the immune function of spleen lymphocytes	Zhang J et al., 2009
				Inhibits lymph node metastasis by suppressing the expression of VEGF-D mRNA	Tang R et al., 2009

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-4	IL-4Rα–γc, IL-4Rα, IL-13Rα1	Pancreatic cancer	Promote	Promotes cancer progression, invasion and angiogenesis by enhancing the ability of TIM-derived cathepsin	Shi J et al., 2021
		Lung cancer	Promote	Increases cells invasion, migration and vascular remodeling by promoting the differentiation of M0 into M2 macrophages	Zhag Y et al., 2024
		Liver cancer	Promote	Enhances the radiation resistance byactivating ERK pathway	Liu Y et al., 2023
IL-7	IL-7Rα–γc, sIL-7Rα	prostatic cancer	Promote	Stimulates invasion and migration through AKT/NF-κB pathway	Qv H et al., 2016
		Breast cancer	Inhibit	Activates CD8 + T cells and stimulates IFNγ- secretion	Yuan C et al., 2014
		Hepatocellular carcinoma	Inhibit	Reshapes the immune system by improving T cell function and antagonizing immunosuppression network	Zhang S et al., 2024
		Colon cancer	Inhibit	Amplifies TIL in tumor lesions	Maeurer M et al., 1997
		Non-small cell lungcancer	Inhibit	Reduces tumor proliferation by changing cell surface molecular expression and enhancing anti-tumor reactivity	Sharma S et al.,1996
IL-9	IL-9R–γc	Liver cancer	Promote	Increases proliferation by driving the expression ofCCL20 and STAT3; induces the occurrence and metastasis through AKT, β catenin and vimentin	Gerlach K et al., 2019
		Lung cancer	Promote	Promotes autonomous cells growth, malignant cell transformation and better adhesion through JAK/STAT3	Gerlach K et al., 2019
				Enhances tumor growth	Pajulas A et al., 2023
		Bladder cancer	Promote	Promotes tumor immune escape by reducing the cytotoxicity of CD8(+) T cells and NK cells	Zhou Q et al., 2020
		Gastric cancer	Inhibit	Enhances the function of CD8(+) T cells	Fang H et al., 2020
		Breast cancer	Inhibit	Eliminates the metastatic potential bycontrolling extracellular matrix remodeling and cell contractility	Das S et al., 2021
IL-15	IL-15, IL15Rα + IL-2, IL-15Rβ–γc	Colon cancer	Inhibit	Enhances the cytotoxicity of TIL	Chen Z et al., 2010
IL-21	IL-21R–γc	Lung cancer	Inhibit	Inhibits tumor growth by increasing the cytotoxicity of NkG2D CAR-NK cells	Zhang Y et al., 2024
IL-3	IL-3Rα–βc	Pancreatic cancer	Inhibit	Mediates CD4(+) T-eff reaction in IL-3 (-/-)	Zaidi N et al., 2019

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-5	IL-5Rα–βc	Bladder cancer	Promote	Enhances migration and invasion through MMP-9/NF-κB/AP-1 pathway mediated by ERK1/2	Li O et al., 2013
		Colon cancer	Promote	Promotes cell growth by enhancing the effect of IGF-II	Makins R et al., 2005
		Esophageal cancer	Promote	Acts as an PAX2 metastasis effector	Liu P et al., 2015
		Lung cancer	Inhibit	Blocks metastasis by reducing endothelial barrier permeability through Cd3 T cells	Li F et al., 2020
		Rectal cancer	Inhibit	Contributes to host defense and releases their toxic granular proteins by activating eosinophils	Tajima K et al., 1998
		Pancreatic cancer	Promote	Stimulates the migration and activation via STAT5 signaling	Gitto S et al., 2020
IL-6	IL-6Rα–p130 (classic), sIL-6Rα–gp130 (trans)	Prostatic cancer	Promote	Promotes cell growth through JAK-STAT signaling	Lou W et al., 2000
				Promotes the occurrence by providingTh2 cytokine environment and up-regulating genes related to cell proliferation and angiogenesis	Feurino L et al., 2007
		Breast cancer	Promote	Inhibits apoptosis and drives cell proliferation and invasion through JAK-STAT signaling	Manore S et al., 2022
		Ovarian cancer	Promote	Promotes adhesion and invasion through Ras/MEK/ERK and PI3K/AKT pathways	Wang D et al., 2016
		Breast cancer	Promote	Promotes the development of BrCAIL-6 by down-regulating HIC1 through paracrine or autocrine signal	Sun X et al., 2020
		Colorectal cancer	Inhibit	Promotes the activities of macrophage and lymphokine-activated killer cell	Turano M et al., 2021
IL-11	IL-11Rα–p130 (classic), sIL-11Rα–gp130 (trans)	Cervical cancer	Promote	Mediates radiation-resistance through PI3K/AKT signaling pathway	Sun R et al., 2021
		Pancreatic cancer	Promote	Activates AKT, ERK and STAT3 signaling	Jaclyn K et al., 2014
		Gastric cancer	Promote	Increases the activation of STAT3	Zhou R et al., 2019

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-31	IL-31Rα–OSMRβ	Liver cancer	Promote	Drives hepatocytes to develop into LCSC by obtaining dryness and stimulates their growth and malignant progress	Yuan C et al., 2021
		Breast cancer	Inhibit	Increases the activity of cytotoxic T cells and decreases the levels of CD4(+) T cells, MDSC and tumor-associated macrophages	Kan T et al., 2020
IL-10	IL-10Rα,IL-10Rβ	Lung adenocarcinoma	Promote	Down-regulates STAT1 activity by enhancing the expression of SOCS1 and SOCS3 induced by IFN-γ	Gao Y et al., 2020
		Gastric cancer	Promote	Drives immunity to escape from microenvironment	Zhang H et al., 2022
		Carcinoma of colon	Inhibit	Inhibits cell growth by suppressing STAT3 pathway	Won D et al., 2011
		Salivaryadenoc-arcinoma	Inhibit	Induces TNF-driven apoptosis	Skrypnyk M et al., 2024
IL-19	IL-20Rα,IL-20Rβ	Breast cancer	Promote	Enhances tumor development and affects the clinical outcome through JAK/STAT signaling	Sofi S et al., 2023
				Directly promotes tumor proliferation, migration and indirectly provides microenvironment for tumor progress	Chen Y et al., 2013
		Lung cancer	Promote	Enhances proliferation by stimulating IL20RB expression and activating JAK1/STAT3 signaling	He Y et al., 2022
IL-20	IL-20Rα,IL-20Rβ, IL-22Rα1,IL-20Rβ	Oral cancer	Promote	Increases proliferation, migration, ROS production and colony formation by promoting TNF-α,IL-1β, MCP-1, CCR4 and CXCR4 expression through activating STAT3and AKT/JNK/ERK signaling	Xu Y et al., 2012
		Prostatic cancer	Promote	Increases migration and colony formation by activating p38, ERK1/2, AKT and NF-κB signals	Xu Y et al., 2015
		Breast cancer	Promote	Enhances proliferation and migration by up-regulating MMP-9, MMP-12, cathepsin k and G	Xu Y et al., 2012
		Bladder cancer	Promote	Promotes the migration through MMP-9 protein mediated by ERK	Li S et al., 2013
		Hepatocellular carcinoma	Promote	Promotes tumor progress by inducing TGFβ and MMP-9 expression, and phosphorylating JNK/STAT signaling	Ding W et al., 2018

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-22	IL-22Rα1, IL-10Rβ, IL-2Rα2 (also known as IL-22BP)	Lung cancer	Promote	Increases proliferation by activating STAT3 and enhancing the expression of anti-apoptotic B-cell lymphoma 2	Kobold S et al., 2013
				Promotes tumor cell survival and drug resistance by up-regulating anti-apoptosis proteins	Zhang W et al., 2008
		Gastric cancer	Promote	Promotes invasion through STAT3 and ERK activation	Fukui H et al., 2014
				Promotes migration and invasion through IL-22R1 /AKT/MMP-9	Ji Y et al., 2014
		Breast cancer	Promote	Promotes proliferation in a STAT3-dependent manner	Zhang Y et al., 2020
		Ovarian cancer	Promote	Promotes tumor development Through STAT3 signaling	Lei B et al., 2018
		Colorectal cancer	Promote	Promotes proliferation through STAT3 signaling	Wu T et al., 2013
		Non-small cell lung cancer	Promote	Confers EGFR-TKI resistance through AKT and ERK signaling	Wang X et al., 2019
		Pancreatic cancer	Promote	Promotes proliferation, invasion and migration by stimulating AKT signal transduction	Wang X et al., 2020
IL-24	IL-20Rα,IL-20Rβ, IL-22Rα1, IL-20Rβ	Lung cancer	Inhibit	Inhibits proliferation and promotes apoptosis	Qi Q et al., 2014
		Pancreatic cancer	Inhibit	Induces apoptosis and CTL to kill cancer cells and produces anti-tumor immunity	Xv B et al., 2014
		Breast cancer	Inhibit	Promotes apoptosis and cell arrest in G2/M phase through PI3K/β-catenin signaling	Deng L et al., 2020
		Colorectal cancer	Inhibit	Inhibits cell growth by inducing tumor-lysis and apoptosis, and stimulating immunity	Deng L et al., 2020
		Endometrium cancer	Inhibit	Inhibits proliferation by promoting apoptosis through mitochondrial intrinsic signal pathway	Liao S et al., 2020
IL-26	IL-20Rα,IL-10Rβ	Non-small cell lung cancer	Promote	Increases net angiogenic activity and tumor growth by promoting CXCR-2 dependent angiogenesis	Numasakl M et al., 2005
		Breast cancer	Promote	Dephosphorylates and down-regulates EphA3 and phosphorylates endoplasmic reticulum induced by EGFR-TKI via AKT and JNK	Itoh T et al., 2021

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-12	IL-12Rβ1,IL-12Rβ2	Lung cancer	Inhibit	Enhances the cytolytic activity of PBMC on lung cancer cells	Hiraki A et al., 2002
		Ovarian cancer	Inhibit	Inhibits cell proliferation	Wang J et al., 2006
				Promotes the self-renewal of CD133(+) cancer stem cell-like cells	Wang D et al., 2017
		Oral cancer	Promote	Promotes proliferation promoting by nuclear trans-activation of RelA	Fukuda M et al., 2010
IL-27 and IL-30 (also known as IL-27 subunit p28)	IL-7Rα (also known as WSX1)–gp130	Lung cancer	Inhibit	Reduces proliferation and metastasis through miR-935	Wang T et al., 2019
		Ovarian cancer	Inhibit	Inhibits proliferation by enhancing STAT3 and inhibiting AKT signaling	Zhang Z et al., 2016
		Cervical cancer	Inhibit	Restricts angiogenesis by paracrine	Zhang B et al., 2017
		Prostatic cancer	Inhibit	Inhibits tumor growth and improves the survival rate of patients	Sorrentino C et al., 2019
IL-35	IL-12Rβ2–gp130, IL-12Rβ2, IL-12Rβ2 gp130–gp130, IL-27Rα,IL-12Rβ2	Breast cancer	Promote	Promotes invasion and metastasis	Wang A et al., 2018
				Promotes tumor progression by inhibiting proliferation of infiltrating T-conv cells and inducing iTr35 cells	Hao S, et al., 2018
		Colorectal cancer	Promote	Inhibits proliferation of T cells and may participate in tumor immune tolerance through STAT1 and STAT3	Ma Y et al., 2016
		Lung cancer	Promote	Inhibits CD4 T cell-mediated immune response	Hao Y et al., 2022
				Promotes tumor progression by inducing T cell differentiation	Zhou A et al., 2021
		Prostatic cancer	Promote	Promotes cell proliferation, tumor angiogenesis and limits the antitumor immune response by increasing the ratio of Tregs to MDSC and decreasing the ratio of CD4 + and CD8 + T cells	Zhu J et al., 2020
		Pancreatic cancer	Promote	Promotes tumor growth by enhancing proliferation and inhibitingapoptosis	Nicholl M et al., 2014
		Colon cancer	Inhibit	Inhibits migration, invasion, proliferation, colony formation and cancer stem cells by inhibiting β-catenin	Zhang J et al., 2017
IL-17A/F	IL-17RA,IL-17RC	Lung cancer	Promote	Promotes tumor growth and progressthrough the coordination of immune cells (i.e. macrophages)	Ferreira N et al., 2020

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-17B	IL-17RB	Breast cancer	Promote	Promotes tumor resistance to paclitaxel by activating ERK1/2 pathway	Laprevotte E et al., 2017
				Promotes tumor occurrence through NF-κB mediated anti-apoptosis pathway	Huang Z et al., 2014
		Lung cancer	Promote	Promotes metastasis by activating ERK/β-catenin	Yang Y et al., 2018
		Pancreatic cancer	Promote	Promotes invasion and the survival of cancer cells through ERK1/2	Wu H et al., 2015
		Gastric cancer	Promote	Enhances proliferation and migration-through IL17B activated mesenchymal stem cells	Bi Q et al., 2017
				Activates IL-17RB/AKT/β-catenin pathway	Bi Q et al., 2016
IL-17C	IL-17RA,IL-17RE	Lung cancer	Inhibit	Increases the expression of neutrophil chemokine, keratinocyte derived chemokine and macrophage inflammatory protein 2 induced by NTHi and TNF-α	Jungnickel Cet al., 2017
		Colorectal cancer	Promote	Promotes cancer development by improving survival rate	Song X et al., 2014
				Promotes angiogenesis by producing VEGF through STAT3/miR-23a-3p/SEMA6D axis	Li Y et al., 2020
IL-17D	Unknown	Lung cancer	Promote	Promotes tumor progression via p38 MAPK signaling pathway	Li Z et al., 2022
		Ovarian cancer	Promote	Promotes cell growth by changing of MICA expression level	Zhang J et al., 2014
				Accelerates cell proliferationand enhances migration and invasion by activating NF-κB	Fan Y et al., 2024
		Breast cancer	Promote	Exerts immuno-suppressive effect by producing IL-17D	Ruan J et al., 2021
IL-25 (also known as IL-17E)	IL-17RA,IL-17RB	Lung cancer	Promote	Promotes cisplatin resistance by increasing the major fornix proteins through activating NF-κB	Shen W et al., 2019
		Colorectal cancer	Promote	Maintains tumor infiltrating MDSC by promoting IL-C2	Jou E et al., 2022
		Breast cancer	Inhibit	Activates caspase-mediated apoptosis	Furuta S et al., 2022
IL-28A and IL-28B	IL-28Rα (IFNLR1), IL-10Rβ	Lung cancer	Inhibit	Inhibits growth and induces apoptosis through STAT1 phosphorylation	Tezuka Y et al., 2012

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-29	IL-28Rα,IL-10Rβ	Multiplemyeloma	Promote	Activates STAT1 and STAT3	Novak A et al., 2008
		Pancreatic cancer	Inhibit	Overexpresses P21 and Bax	Balabanov D et al., 2019
		Cervical cancer	Inhibit	Inhibits proliferation and promotes apoptosis by up-regulating the expression of TRAILR1	Ha L et al., 2024
		Skin cancer	Inhibit	Increases MHC class 1,P21 and Rb protein	Romee R et al., 2014
		Lung cancer	Inhibit	Promotes cell arrest and apoptosis by up-regulating p21 through STAT	Barrera L et al.,2015
		Gastric cancer	Inhibit	Decreases Bcl-2 and caspase cascade	Gao Z et al., 2014
				Induces a possible NK cell-mediated immune response	Bu X et al., 2014
		Colorectal cancer	Inhibit	Increases NK and NKT cell activity	Aulino P et al., 2010
		Esophageal cancer	Inhibit	Increases MHC class 1, P21 and Rb protein	Li Q et al., 2010
IL-8 (also known as CXCL8)	CXCR1, CXCR2 ACkR1/DARC	Breast cancer	Promote	Promotes invasion and migration by promoting Wnt/β-catenin signaling	Mou C et al., 2018
		Ovarian cancer	Promote	Enhances invasion and migration by promoting EMT	Wang S et al., 2018
				Stimulates cell adhesion and invasion by activating PI3K/AKT and Raf/MEK/ERK signaling and increasing MMP-2 and MMP-9 activity and expression	Niu X et al., 2013
		Bladder cancer	Promote	Improves drug resistance by maintaining the characteristics of cancer stem cells	Zhu K et al.,2014
		Renal carcinoma	Promote	Promotes EMT through PKC/ERK signaling	Bi L et al.,2012
		Pancreatic cancer	Promote	Promotes invasion by regulating MMP-2 activity	Kuwada Y et al., 2003
		Gastric cancer	Promote	Promotes metastasis through c-Jun and Ets-1	Chen H et al., 2017
		Renal carcinoma	Promote	Induces migration by activating AKT signaling through CXCR2	Bi L et al., 2014
		Ovarian cancer	Promote	Induces chemo-resistance by increasing the expression of MDR1, Bcl-2, Bcl-xL and XIAP, and activating Raf/MEK/ERK and PI3K/AKT signaling	Niu X et al., 2012
		Cervical cancer	Promote	Promotes proliferation, invasion and migration by activating ERK and up-regulating MMP-9	Ye K et al., 2022

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
				Promotes the carcinogenic potential by increasing the expression of IL-RA, IL8RB and ERK and decreasing the expression of NUMB	Jia L et al., 2018
		Prostate cancer	Inhibit	Promotes proliferation and inhibits apoptosis through STAT3/AKT/NF-κB pathway	Guo Y et al., 2017
IL-13	IL-13Rα1,IL-4Rα, IL-13Rα2	Pancreatic cancer	Promote	Promotes proliferation by enhancing p44/42 MAPK (ERK1/2) phosphorylation and tyrosine and PI3 kinaseactivity	Shi J et al., 2021
		Colon cancer	Promote	Promotes malignancy by inducing the expression of 11βHSD2 in an IL-13Rα2-dependent manner	Jiang L et al., 2016
IL-14α andIL-14β	IL-14R	N/A			
IL-16	CD4	Breast cancer	Promote	Promotes tumor progression by recruiting immune cells infiltrating into tumors	Richmond J et al., 2014
		Lung cancer	Promote	Contributes to the implantation of tumor cells into lung parenchyma	Donati K et al., 2017
IL-32 (also known as Nk4)	Unknown	Lung cancer	Promote	Promotes immune escape by developing immuno-suppressive microenvironment	Zhao S et al., 2024
		Cervical cancer	Promote	Promotes tumor progress by forming a positive regulatory loop with NF-κB/miR-205	Liu J et al.,2024
		Pancreatic cancer	Promote	Regulates downstream molecules and promotes invasion	Takagi K et al., 2021
		Gastric cancer	Promote	Increases invasion	Tsai C et al., 2014
		Colon cancer	Promote	Creates a favorable environment for tumor growth by up-regulating IL-8, TNF and CCL2	Catalán V et al., 2017
		Esophageal cancer	Promote	Induces polarization of M2 macrophages via FAK/STAT3 pathway	Sun Y et al., 2022
		Triple negative breast cancer	Promote	Increases migration and invasion through EMT by up-regulating VEGF-STAT3 pathway	Park H et al., 2012
		Thyroid cancer	Promote	Contributes to cell survival by inducing cytokine IL-8	Sloot Y et al., 2019
		Multiplemyeloma	Promote	Produces immuno-suppression and allows tumor growth through NF-κB pathway	Yan H et al., 2019
		Gastric cancer	Promote	Inhibits autophagy through PI3K/AKT/mTOR signaling	Wang X et al., 2022

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Lung adenocarcinoma	Promote	Promotes migration and invasion by up-regulating NF-κB	Zeng Q et al., 2014
		Osteosarcoma	Promote	Stimulates invasion and movement by activating AKT and up-regulating MMP13	Zhou Y et al., 2015
		Liver cancer	Promote	Inhibits apoptosis and increases cell survival by activating NF-κB and p38/MAPK pathways	Kang H et al., 2012
		Gastric cancer	Promote	Promotes tumor progression by increasing metastasis through activating AKT, β-catenin and HIF-1α	Cai C et al., 2014
		Liver cancer	Promote	Stimulates cell survival and growth by activating and maintaining NF-κB	Han X et al., 2019
		Lymphoma	Promote	Stimulates cell proliferation by activating MAPK and NF-κB	Hiraku S et al., 2013
		Colon cancer	Inhibit	Inhibits tumor development by promoting the death signal of TNFR1	Yun M et al., 2015
				Inhibits dryness and EMT by suppressing STAT3-ZEB1 pathway	Bak Y et al., 2016
		Colorectal cancer	Inhibit	Enhances TNFα-mediated apoptosis by up-regulating p32-MAPK signaling	Yun M et al., 2023
		Thyroid cancer	Inhibit	Induces caspase-mediated apoptosis	Heinhuis B et al., 2015
		Melanoma	Inhibit	Inhibits proliferation and increases apoptosis by up-regulating p21, p53, and TRAILR1	Nicholl M et al., 2016
		Pancreatic cancer	Inhibit	Reduces EMT by inhibiting JAK/ST T3 signal and the expression of EMTmarkers and MMP2, 9 and 7	Bak Y et al., 2016
		Skin cancer	Inhibit	Improves survival rate by increasing the number of tumor-specific CD8 + T cells	Gruber T et al., 2020
		Bladdercancer	Inhibit	Inhibits tumor growth by enhancing the cytotoxicity of NK-92	Wu K et al., 2022
		Breast cancer	Inhibit	Increases proliferation and decreases apoptosis	Wang S et al., 2015
		Cervical cancer	Inhibit	Inhibits tumor development by inducing the production of pro-nflammatory cytokines and down- regulating E7 and COX2 through negative feedback loop	Lee S et al., 2011

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-34	CSF1R	Mastadenoma	Promote	Promotes epithelial cell transformation	Poudel M et al., 2021
		Gastric cancer	Promote	Promotes proliferation and EMT	Li C et al., 2022
		Colon cancer	Inhibit	Inhibits cell proliferation and enhances the susceptibility of cells to oxaliplatin-induced death by suppressing ERK1/2	Franze E et al., 2018
		Liver cancer	Inhibit	Inhibits tumor growth and metastasisby inhibiting proliferation and EMT	Tian B et al., 2023
IL-1α	IL-1R1, IL-1R3 sIL-1R3	Gastric cancer	Promote	Increases the percentage of S phase fraction of cells, stimulates cell proliferation	Furuya Y et al., 2000
		Breast cancer	Promote	Promotes proliferation, invasion or migration	Qiu J et al.,2021
IL-1β	IL-1R 1, IL-1R3 IL-1R2, IL-1R3, sIL-1R2, sIL-1R3	Gastric cancer	Promote	Promotes invasion by activating NF-κB and MMP-9 expression	Yamanaka, N et al., 2004
		Ovarian cancer	Promote	Increases expression of IL-1β and may lead to early steps of cancer	Woolery T et al., 2014
		Cervical cancer	Promote	Promotes proliferation and migration through MEK/ERK signaling pathway	Zhang J et al., 2022
		Breast cancer	Promote	Induces a cascade reaction of TP63 subtype ΔNP63α signal, and leads to cisplatin resistance	Mendoza-Rodriguez M et al., 2019
		Osteosarcoma	Promote	Enhances tumor growth by regulating NF-κB signaling and miR-376c /TGFA axis	Liu B et al., 2017
IL-33	IL1R3, IL-1R4, sIL-1R4	Gastric cancer	Promote	Promotes invasion and migration by stimulating the secretion of MMP-3 and IL-6 through ST2-ERK1/2 pathway	Yu X et al., 2015
		Colorectal cancer	Promote	Promotes cell proliferation through its receptor ST2, and up-regulates COX2 through NF-κB signaling	Li Y et al., 2018
		Ovarian cancer	Promote	Promotes cell proliferation and inhibits apoptosis by down-regulating p27, Fas and TRAILR1 in vitro	Liu N et al., 2021
		Breast cancer	Promote	Promotes cell transformation and tumorigenesis	Cui H et al., 2015
		Lung cancer	Inhibit	Inhibits tumor growth and lung metastasis by promoting proliferation and activation of CD8 T cells and NK cells through NF-κB signaling	Yang K et al., 2022

Table 1 (continued)

Interleukin	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
IL-18	IL-1R5 IL-1R7 IL-18BP	Lung cancer	Promote	Enhances metastasis by down-regulating E-cadherin	Jiang D et al., 2003
		Pancreatic cancer	Promote	Promotes cell proliferation and movement	Sun Q et al., 2020
		Colon cancer	Inhibit	Inhibits tumor growth and prolongs the survival by blocking the secretion of TGF-β and IL-4, increasing the secretion of TIIFN-Y, enhancing its cytotoxicity	Chen Z et al., 2010
				Enhances the ability of cancer cells to resist T lymphocytes by up-regulating FasL protein	Zhang W et al., 2002
		Breast cancer	Inhibit	Inhibits osteolytic bone metastasis	Nakata A et al., 1999
		Colorectal cancer	Inhibit	Promotes tumor immune surveillance by up-regulating FasL and death ligand	Dupaui J et al., 2015

Table 2 The role and mechanisms of Toll-like receptor (TLR) in cancer

TLR	Expressed cell	Cancer types	Promote/inhibit	Mechanisms	References
TLR7	B lymphocy te,T lymph ocyte, neuron mature dendritic cell, macro phage	Pancreatic cancer	Promote	Increases cell proliferation and promotes chemo-resistance	Grimmig T et al., 2015
Lmiquimod (TLR7 agonist)		Breast cancer	Inhibit	Blocks IL-10	Yusuf N et al., 2014
		Basal cell carcinoma	Inhibit	Modulates immune response	Stockfleth E et al., 2003
TLR5	Epithelial cell, dendritic cell, macrophage, fibroblast B lymphocyte	Oral cancer	Promote	Promotes tumor progression	Kauppila J et al., 2013 An
TLR4	Endothelial cell, fibroblast, liver cell, macrophage, dendritic cell, epithelial cell	Oral cancer	Promote	Enhances invasion	Kong Q et al., 2020
		Cervical cancer	Promote	Promotes proliferation and apoptosis resistance partially through Toll-like receptor 4/NF-κB pathway	Jiang N et al., 2018
		Breast cancer	Promote	Promotes tumor progression via TLR4/NF-κB/STAT3 signaling	Ochi A et al., 2012
		Skin cancer	Promote	Up-regulates immunosuppressive and pro-inflammatory cytokines and chemokines	Sato Y et al., 2009
		Lung cancer	Promote	Promotes migration and counterattack of cells by inducing autophagy	Mi-Jeong K et al., 2022
		Prostate cancer	Promote	Promotes tumor cell activation, proliferation, survival and tumor transformation	Gonzalez-Reyes S et al., 2011; Huang B et al., 2009
				Promotes tumor development by reducing immune function	Engblom C et al., 2016; Ugel S et al., 2015
		Ovarian cancer	Promote	Contributes to tumor growth through TLR4-MyD88 signaling	Kelly M et al., 2006
		Colon cancer	Promote	Escapes from immune surveillance by inhibiting the functions of T and NK cells	Huang B et al., 2005
		Gastric cancer	Promote	Promotes tumor occurrence and progress through NF-κB pathway	Yue Y et al., 2011
		Intestinal tumor	Inhibit	Decreases tumors induced by azoxymethane/sodium dextran sulfate	Fukata M et al., 2011
			Inhibit	Silence of TLR4 increases metastasis, and TLR4 induces effective cancer antigen-specific cytotoxic T cell immune response	Ahmed A et al., 2013
		Prostate cancer	Inhibit	Initiates innate immunity to invasive pathogens	Kundu S et al., 2008; Gonzalez-Reyes S et al.,2011; Huang B et al., 2009

Table 2 (continued)

TLR	Expressed cell	Cancer types	Promote/inhibit	Mechanisms	References
Coli toxin BCG vaccine (TLR-4 agonist)		Gastric cancer	Inhibit	Induces exfoliation and autophagy	Galluzzi L et al., 2012
TLR2	Macrophage, dendritic cell, epithelial cell, fibroblast, endothelial cell, B lymphocyte	Colon cancer	Promote	Promotes proliferation, migration, and invasion through PI3K/AKT and NF-κB	Wang X et al., 2018
		Gastric cancer	Promote	Increases proliferation and survival of gastric epithelial cells	Liu Y et al., 2019; West A et al., 2017; Cui L et al., 2021
				Weakens the function of CD8 + lymphocyte	Yang H et al.,2014
				Promotes tumorigenesis independent of inflammation in STAT3-driven cancer	Jenkins B et al., 2012
		Breast cancer	Promote	Promotes tumor progression and resistance to chemotherapy	Di Lorenzo A et al., 2022
		Oral cancer	Inhibit	TLR2 deficiency enhances tumor susceptibility by promoting an inflammatory environment	Li B et al., 2024
Polysaccharide Krestin (TLR2 agonist)		Breast cancer	Inhibit	Has potent anti-tumor effects via stimulating both innate and adaptive immune pathways	Lu H et al., 2011
Bacteria Peptidoglycan (TLR2 agonist)		Breast Cancer	Promote	Promotes invasion and adhesion by targeting Toll-Like receptor 2 in the cancer cells	Xie W et al., 2010
Coli toxin BCG vaccine (TLR2 agonist)		Gastric cancer	Inhibit	Induces exfoliation and autophagy	Galluzzi L et al., 2012
TLR8	Monocyte, macrophage, dendritic cell, neutrophil	Pancreatic cancer	Promote	Increases cell proliferation and promotes chemo-resistance	Grimmig T et al., 2015
TLR9	Dendritic cell, B lymphocyte, macrophage, fibroblast, epithelial cell	Skin cancer	Promote	Enhances invasion and promotes proliferation through activation of NF-κB and Cox-2 and secretion of IL-8, IL-1α (41) and TGF-β (42)	Di J et al., 2009
		Lung cancer	Promote	Promotes tumor progression	Ren T et al., 2009
TLR3	Dendritic cell, fibroblast, macrophage, epithelial cell, B lymphocyte	Lung cancer	Promote	Promotes migration and counterattack of cells by inducing autophagy	Mi-Jeong K et al., 2022
		Oral squamous carcinoma	Inhibit	Promotes apoptosis	Luo Q et al., 2012

Targeting colony-stimulating factors for cancer chemoprevention

The ability to produce in vitro colonies of mature myeloid cells from bone marrow precursor cells after the proliferation and differentiation of these cells was the initial defining characteristic of granulocyte/macrophage colony-stimulating factor (GM-CSF; also known as CSF2), macrophage colony-stimulating factor (M-CSF;

Table 3 The role and mechanisms of stimulator of interferon genes (STING) in cancer

STING	Cancer types	Promote/Inhibit	Mechanisms	References
STING	Ovarian cancer	Promote	Makes cancer-associated fibroblasts sensitive to platinum chemotherapy by inhibiting CGAS-STING pathway	Liu J et al., 2024
	Colorectal cancer	Promote	Promotes proliferation and induces drug resistance by regulating AMPK-mTOR pathway	Yao H et al., 2022
	Colon cancer	Promote	Activates reprogrammed tumor-associated macrophages to M1 phenotype and transforms immune cold peritoneal tumor into T cell inflammatory tumor; STING agonists cooperate with PD-1 and/or COX2 blocker to further inhibit carcinogenesis	Lee S et al., 2021
	Breast cancer	Promote	Down-regulation of STING reduces cell survival rate and increases the sensitivity of genotoxicity treatment in a cell-independent way	Cheradame L et al., 2021
			Induces cell survival and immunosuppression by IL-6-mediated STAT3 activation through NF-κB	Vasiyani H et al., 2022
	Gastric cancer	Promote/Inhibit	Knocking down STING and activating STING with 2′3′-c-GAMP promote polarization of TAMs into pro-inflammatory subtype, and induce apoptosis through IL6R-JAK-IL24 pathway	Miao L et al., 2020
		Inhibit	Inhibits proliferation, migration and immune escape by activating cGAS-STING/IFN-β	Yuan M et al., 2022
	Pancreatic cancer	Inhibit	Produces type I IFN and activates T cells through CD8α + DC	Cheng H et al., 2020
			Constant stimulation of the cGAS–STING leads to cell death, inhibits tumorigenesis	Gulen M et al., 2017
			Has anti-tumor impact on TME by producing type I IFN and priming T cells via CD8α + DCs	Corrales L et al., 2017
	Colorectal cancer	Inhibit	Weakens the tumorigenesis of colitis-related colorectal cancer by enhancing intestinal epithelial focal death	Gong W et al., 2022
	Breast cancer	Inhibit	Promotes the anti-tumor immune response of tumor-specific CD8 + T cells	Lu Z et al., 2022
	Lewis lung cancer	Inhibit	Activates the anti-tumor immune response of T cells and inhibits tumor progression	Zhang X et al., 2023
	Ovarian cancer	Inhibit	Enhances the anti-tumor activity	Zhang J et al., 2020
	Prostate cancer	Inhibit	Induces immune system rejection and eliminates PCa cells	Alnukhali M et al., 2024
	Skin cancer	Inhibit	Induces antigen-specific reactive T cells by promoting the transcription of type I IFN through activating TBK1 and enhances the phosphorylation of IRF3 or STAT6	Honda T et al., 2013 Sawada Y et al., 2015
	Squamous cell carcinoma of skin	Inhibit	Enhances the anti-tumor effect by combining with DNA damaging agents	Hayman T et al., 2021 Baird J et al., 2018 Liang D et al., 2015
			Promotes the activation of NK cells and DC induced by cetuximab	Lu S et al., 2018

Table 3 (continued)

STING	Cancer types	Promote/Inhibit	Mechanisms	References
	Adult T cell leukemia/ lymphoma	Inhibit	Enhances the formation of IRF3-Bax complex and leads to the apoptosis of adult T-cell leukemia/lymphoma	Bladé J et al., 2010
	Bladder cancer	Inhibit	Activates cytoplasmic pattern recognition receptor and downstream IFN1 pathway	Koti M et al., 2019
DMXAA series (agonist)	Pancreatic cancer	Inhibit	Improves patients' survival rate and anti-tumor immunity by prompting T cells; reduces tumor size by activating cytolytic T cells	Jing W et al., 2019
3′3′-cGAMP (agonist)	Pancreatic cancer	Inhibit	Reduces metastasis and tumor growth, and promotes anti-tumor immune response	Lu X et al., 2020
ADU-V19 type (agonist)	Pancreatic cancer	Inhibit	Enhances vaccine immunogenicity, vaccine-specific T cells and anti-tumor immune response	Kinkead H et al., 2018
ADU-S100 type (agonist)	Pancreatic cancer	Inhibit	Stimulates immune response by increasing the expression of CXCR3 in T cells	Vonderhaar E et al., 2021
CdGMP series (agonist)	Pancreatic cancer	Inhibit	Increases immune cells by activating APC	Lorkowski M et al., 2021
			Activates endogenous tumor-specific lymphocytes and inhibits metastasis by activating APCs	Smith T et al., 2017
IACS-8803 model (agonist)	Pancreatic cancer	Inhibit	Increases lymphoid myeloid population and strengthens checkpoint block	Ager C et al., 2021
c-di-AMP (agonist)	Breast cancer	Inhibit	Induces apoptosis	Vasiyani H et al., 2021
DMXAA or cGAMP (agonist)	Breast cancer	Inhibit	Enhances the therapeutic effect of Th/Tc17 CAR T cells by up-regulating CXCL9 and CXCL10 to promote the infiltration of CAR T cells into tumor tissues	Tian Z et al., 2022
cGAMP (agonist)	Breast cancer	Inhibit	Inhibits tumor growth and prolongs the survival time of pancreatic cancer mouse	Da Y et al., 2022
ADU-S100 (agonist)	Prostate cancer	Inhibit	Inhibits tumor progression	Esteves A et al., 2021

also known as CSF1), and granulocyte colony-stimulating factor (G-CSF; also known as CSF3). As the main regulators of granulocyte and macrophage populations, CSF can mobilize stem cells to peripheral blood in sufficient quantities for transplantation, speed up the regeneration of protective white blood cells damaged by chemotherapy, boost anticancer immune responses, and possibly contribute to the development of myeloid leukemias [299]. More details regarding the function of colony-stimulating factors in cancer are provided in Table 5.

Targeting chemokines for cancer chemoprevention

Chemokines are 8–12 kDa proteins that are released and bind to Gai-protein-coupled seven-transmembrane-spanning receptors (GPCRs), also known as classical chemokine receptors, to control directed cell movement (chemotaxis), adhesion, cell orientation, and cell–cell interactions [300]. Comprising around 50 chemokine ligands, 20 signaling GPCRs, and 4 ACKRs, the chemokine system is crucial for various pathological processes. Cancer cells, tissue-resident cells, and recruited immune cells that express a wide variety of chemokine ligands and chemokine receptors all influence the process of carcinogenesis. Chemokines govern the invasiveness, proliferation, and stem-like characteristics of tumor cells. They also influence neoangiogenesis, neurogenesis, and fibrogenesis in stem cells [301]. Chemokines play a crucial role in guiding immune cell movement when mounting and subsequently delivering an efficient anti-tumor immune response [300]. Meanwhile, chemokine systems also contribute to pro-tumorigenic immune responses by controlling immune cells' location and cellular interactions in lymphoid organs and the tumor microenvironment (TME). Chemokines have been attractive therapeutic targets because of their role in mediating the recruitment of anti-tumorigenic immune cells and

Table 4 The role and mechanisms of tumor necrosis factors (TNF) in cancer

TNF	Cancer types	Promote/Inhibit	Mechanisms	References
TNF-α	Gallbladder cancer	Promote	Autocrine mechanisms	Zhu, G et al.,2014
	Cervical cancer	Promote	Increases the expressions of TNF-alpha	Li, J et al.,2018
	Pancreatic cancer	Promote	Higher expression in the serum of patients with metastatic disease	Karayiannakis, A et al.,2001
	Colorectal cancer	Promote	Increases distant tumor metastasis	Li, Z et al.,2017
	Rectal cancer	Promote	Contributes to distant tumor metastasis	Li, Z et al.,2017
	Breast cancer	Promote	Promotes tumor growth through the positive feedback loop of TNFR1/NF-κB (and/or p38)/p-STAT3/HBXIP/TNFR1	Cai, X et al.,2017
	Breast cancer	Inhibit	Shows cytotoxic effects against MCF-7 cells	Ghandadi,M et al.,2017
	Ovarian cancer	Inhibit	Overcomes the resistance of PTX	MIZUTANI,Y et al.,1994
			Overcome the resistance of CDDP	MIZUTANI,Y et al.,1993
			Inhibits H-3-thymidine uptake by PBMC	Hassan, M et al.,1999
	Prostate cancer	Inhibit	Inactivates the NF-κB signaling pathway	Wang, M et al.,2020
	Breast cancer	Inhibit	Drives cells to non-apoptotic cellular death via RIP1, activation of JNK and ROS production	MIZUTANI,Y et al.,1993
			Elevates induction of cellular death, increases or reduces CXCR4 expressions, decrease BCSCs population	Abdolvand M et al.,2023
	Gastric cancer		Paracrine TNF-α	Ma, G et al.,2013
TNF-β	Non-cardiac gastric cancer	Promote	The G/A + A/A genotype frequencies were significantly higher in patients with intestinal gastric cancer	Zheng, W et al.,2019
	Colorectal cancer	Inhibit	Suppresses TNF-β-stimulated NF-κB signaling	Buhrmann,C et al.,2019
CD40L	Colorectal cancer	Inhibit	Infects tumor cells and expresses CD40L; have dose-dependent lytic ability against tumor cells	Liu, D et al.,2019
			Induces the apoptosis	Pang, X et al.,2017
			Shows immunogenicity on colon 26/CD40L cells	Wu, L et al.,2010
	Lung cancer	Inhibit	DC pulsed by the tumor antigens from the reconstitution CD40L enhances its specific immunity capacity	Tian, K et al.,2017
			Has direct anti-tumor effects against CD40-positive lung cancers	Xu, W et al.,2015
			Activates human DCs to secrete interleukin-12	Wu, J et al.,2007
			Enhances the anti-tumor immunity efficiently	Noguchi, M et al.,2001

Table 4 (continued)

TNF	Cancer types	Promote/Inhibit	Mechanisms	References
FasL	Colorectal Cancer	Promote	Causes Duke's stage, lymph node and liver metastasis	Zhang, W et al.,2004
			Facilitates hepatic metastasis	Li, S et al.,2003
	Colon cancer	Promote	FasL was strong positive in all lymph node metastases of large intestine cancer	Zhu, Q et al.,2002
			Enhances the ability of cancer cells to counterattack T lymphocytes	Zhang, W et al.,2002
	Gastric cancer	Promote	Involves in the pathogenesis and the immune escape and in the degree of differentiation	Pu, W et a.,2003
	Cervical cancer	Promote	Induces TILs apoptosis	Anggraeni, T et al.,2020
	Non-small cell lung cancer	Inhibit	Abrogates counterattack	Lin, Y et al.,2013
	Lung cancer	Inhibit	Participates in the induction of cell apoptosis	Di, D et al.,2005
CD30L	Colon cancer	Promote	Increases the expression of PD-L1; promotes the up-regulation of PD-1 expression and inhibits their activation, differentiation and ability to secret effector cytokines	Wang, X et al.,2020
4-1BBL	Prostate cancer	Promote	Mediates cancer progression to castration-resistant prostate cancer via enhancing expression and function of AR	Zhu, H et al.,2019
	Colon cancer	Inhibit	Inhibits proliferation, migration and invasion, and retards tumor growth	Ge, Y et al.,2020
	Lung cancer	Inhibit	Decreases cell viability, induces apoptosis and autophagy	Ramos-Gonzalez, M et al.,2024
OX40L	Liver cancer	Inhibit	CD4 + and CD8 + T cells were significantly increased in the OX40L mRNA group	Deng, Z et al.,2022
	Breast cancer	Inhibit	Inhibits cell growth and up-regulates the key immune molecules Ox40L and 4-1BBL	Kaser, E et al.,2022
TNF-related apoptosis-inducing ligand (TRAIL)	Lung cancer	Promote	Inhibits TRAIL-induced apoptosis	Li, H et al.,2021
	Bladder cancer	Inhibit	Up-regulates the expression of TRAIL-R1 and TRAIL-R2	Szliszka, E et al.,2009
			Augments the cytotoxic effect of TRAIL	Szliszka, Ewelina et al.,2011
			Enhances the cytotoxic and apoptotic effects of TRAIL	Szliszka, E et al.,2012
			Inhibits cell proliferation, down-regulates XIAP and modulates tBid and Bax expression	Choi, Y et al.,2014
			Suppresses tumor growth	Zhao, Y et al.,2013
	Colon cancer	Inhibit	Up-regulates TRAIL receptor expression, enhances TRAIL-induced cell death partly via O-glycosylation	Semba, M et al.,2022
	Pancreatic cancer	Inhibit	Strengthens the apoptotic signaling pathway	Huang, M et al.,2021

Table 4 (continued)

TNF	Cancer types	Promote/Inhibit	Mechanisms	References
	Cervical cancer	Inhibit	Enhances TRAIL-induced apoptosis through increasing the expression of TRAIL-R2	Szliszka, E et al.,2012
	Non-small cell lung cancer	Inhibit	Induces cell death which is dependent on caspase-8 and caspase-3 activation	De Miguel, D et al.,2016
	Ovarian cancer	Inhibit	Enhances TRAIL sensitivity or reverses TRAIL resistance	Liang, R et al.,2020
	Colorectal cancer	Inhibit	Enhances the activation and apoptosis of ROS-dependent caspases 3/7, promotes the induction of the death receptor 5	Ishaq, M et al.,2015
			Enhances caspase-dependent apoptosis induction via both death receptor- and mitochondrial-mediate apoptosis pathways	Sophonnithiprasert, T et al.,2015
	Breast cancer	Inhibit	Induces miR-146a expression and suppresses CXCR4-mediated human breast cancer migration	Wang, D et al.,2013
LIGHT(TNFSF14)	Tongue cancer	Promote	Enhances proliferation and migration	Gao, W et al.,2015
	NSCLC		Promotes osteolytic bone metastases	Brunetti, G et al.,2020
RANKL	Oral squamous cell carcinoma	Promote	Promotes disease recurrence and a cell compartment	Grimm, M et al.,2015
	Cervical cancer	Promote	Recruits Tregs by up-regulating CTSS and enhancing the expression of phosphorylated AKT and mTORC	Wang, Y et al.,2019
			Strengthens the dialogue between cells and regulation of IL-8 secretion	Shang, W et al.,2015
	NSCLC	Promote	Activates NF-κB pathway, increases RANKL and M-CSF expression and induces osteoclastogenesis	Choi, J et al.,2020
			Promotes tumor angiogenesis	YU, Z et al.,2009
	Breast cancer	Promote	Promotes migration via the PI3K/AKT-HIF-1α pathway	Tang, Z et al.,2011
			The inhibition of RANKL sensitizes cancer stem cells to denosumab	Cuyas, E et al.,2017
			Induces cell migration	Tang, Z et al.,2011
	Gastric cancer	Promote	Induces migration partially through the activation of PI3K and MEK signaling	Wang, Y et al.,2013
			Induces cell migration	Wang, Y et al.,2018

Table 4 (continued)

TNF	Cancer types	Promote/Inhibit	Mechanisms	References
TWEAK	Pancreatic cancer	Promote	TWEAK expression rate was higher than that in chronic pancreatitis and normal pancreatic tissues	Wei, A et al.,2017
	Breast cancer	Promote	Relates to the metastatic ability	Zheng, Y et al.,2008
	Ovarian cancer	Promote	Promotes metastasis via NF-κB pathway activation and VEGF expression	Dai, L et al.,2009
	Colon cancer	Promote	Promotes cell proliferation and infiltration	Zhang, Y et al.,2014
	Ovarian cancer	Inhibit	Enhances cisplasin sensitivity by regulating apoptosis	Ma, N et al.,2013
			Promotes macrophage-derived exosomal miR-7 to cell through regulating Dicer	Qiu, X et al.,2018
			Activates autophagy and enhances the cisplasin sensitivity	Wang, W et al.,2013
	Colon cancer	Inhibit	Induces apoptosis	Dionne, S et al.,2010
	Cervical cancer	Inhibit	Promotes cell apoptosis	Wang, D et al.,2010
APRIL	Breast cancer	Promote	Mediates breast cancer cell stemness	Pelekanou, V et al.,2018
	Gastric cancer	Promote	Induces cisplatin resistance via activation of the NF-κB pathway	Zhi, X et al.,2015
	Colorectal cancer	Inhibit	Suppresses cell growth and promotes apoptosis	Wang, J et al.,2010
BAFF	Breast cancer	Promote	Mediates cell stemness	Pelekanou, V et al.,2018
	Cervical cancer	Inhibit	Promotes immunosuppression	Ding, J et al.,2023
VEGI	Prostate cancer	Inhibit	Inhibits cellular motility and adhesion	Zhang, N et al.,2009
	Bladder cancer	Inhibit	Inhibits cellular motility and adhesion	Zhang, N et al.,2010
EDA-A2	Breast cancer	Inhibit	Is down-regulated in breast cancer via promoter methylation	Punj, V et al.,2010

supporting their activity within TME. Similarly, inhibiting chemokines that draw in and support immune cells' suppressive roles is an intriguing avenue for future research to enhance treatment outcomes. Additionally, another therapeutic approach being investigated to enhance responses to cancer therapy is the activation or transduction of chemokine receptors on adoptively transferred anti-tumor T cells, which facilitates their ability to enter deeply into the tumor and license their functioning. Significant advancements in our comprehension of the immune system's function during carcinogenesis have resulted in the creation of innovative immunotherapeutic methods for treating diverse tumors, which have substantially aided cancer patients. Immunotherapy continues to be one of the most promising medical advancements of the twenty-first century. More details regarding the function of chemokines in cancer are provided in Table 6.

Targeting inflammasomes for cancer chemoprevention

As the innate immune system receptors and sensors, inflammasomes are multiprotein complexes, which react to recognized indicators of endogenous (linked to cellular damage, ATP, ROS, and DNA) and external (related to infections) stimuli [302]. Inflammasome components include the NACHT, leucine-rich repeat (LRR), and pyrin domain (PYD) domain-containing protein 1 (NLRP1), nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain-containing receptor (NLRP3)((also known as cryopyrin), NLR family caspase activation and recruitment domain-containing protein 4 (NLRC4), NOD-like receptor family pyrin domain containing 6 (NLRP6), and absent in melanoma 2 (AIM2). Detailed information on the structure of NLRP1, NLRP3, NLRP4, NLRP6, and AIM2 are shown in Fig. 4. Their products like interleukin 1β and interleukin 18, along with the adaptor, apoptosis-associated

speck-like protein containing caspase activation and recruitment domain (ASC) and the effector caspase-1 both play a major role in carcinogenesis [303]. The sensor protein on each type of inflammasome determines whether a form of the inflammasome is present by identifying pathogenic ligands and triggering the assembly of inflammasomes. NLRs convert the biologically inactive pro-IL-1beta and pro-IL-18 into their active forms through caspase-1 [304]. Genetic mutations in NLRP1, NLRP3, NLRC4, and AIM2 are linked with the development of auto-inflammatory diseases, enterocolitis, and cancer [305]. It is commonly known that inflammatory proteins and their byproducts have a role in developing several cancers, such as skin cancer [306], lung cancer [307], and others. Inflammasomes play both protective and detrimental roles in cancer. On one hand, mice that lack NLRP3, ASC, or caspase-1 exhibit increased susceptibility to colitis and to colitis-associated colorectal cancer induced by the chemical colitogen dextran sulfate sodium (DSS) [308, 309]. Infusion of recombinant IL-18 reduces tumor frequency in mice deficient in inflammatory components following azoxymethane (AOM) and DSS treatment [308]. IL-18 plays a role in repairing the epithelial barrier and preventing damage [309]. This may clarify the protective roles of NLRP3 and IL-18 in relation to colitis-associated colorectal cancer. Mice that lack IL-18 are more vulnerable to developing lung metastasis [310]. Mice that were injected daily with recombinant IL-18 for five days exhibited fewer lung metastases [311]. Other NLR sensors, such as NLRP6 and NLRP1b, have also shown protective effects against tumorigenesis. For instance, the NLRP1b inflammasome mediates the secretion of IL-1β and IL-18 in stromal colon cells, providing protection against colon tumorigenesis [312]. NLRP6 protects against chemical-induced colon cancer by activating caspase-1 and promoting IL-18 production in the intestine [313]. The blockade of ASC promotes the growth of melanoma tumors [314]. On the other hand, In some cases, the activation of the inflammasome can suppress antitumor immunity. For instance, when B16-F10 melanoma cells or RM-1 prostate cancer cells are delivered intravenously (as opposed to subcutaneously) into mice, the activation of NLRP3 is associated with increased lung metastasis. The harmful impact of NLRP3 in melanoma may stem from its inhibitory effect on the activation of NK cells, which are responsible for secreting IFNγ and killing tumor cells.In some cases, inflammasome activation can suppress antitumor immunity. For example, when B16-F10 melanoma or RM-1 prostate cancer cells are delivered intravenously into mice, NLRP3 activation is linked to increased lung metastasis. This detrimental effect may be due to NLRP3's inhibition of NK cell activation, which is crucial for secreting IFNγ and killing tumor cells [310]. Recombinant IL-18 increases lung metastasis when injected into mice twice a week [311]. The knockdown of the gene encoding ASC suppresses the growth of melanoma xenograft tumors [314]. The types of cells, tissues, and organs involved in an inflammasome significantly influence its characteristics related to tumor promotion and suppression. The biological link between inflammasomes and cancer offers promising opportunities for exploring novel anticancer therapies.

Besides, other studies also point to the tumor-suppressive function of inflammasomes like NLRP3, NLRP1, NLRP6, and Pyrin in the initiation and spread of some malignancies, including colorectal cancer [315]. Recently, some inhibitors and agonists of these inflammasomes exhibit anti-tumor effects. For example, the small molecule OLT1177 suppressed tumor growth by inhibiting NLRP3 [316]. OLT1177 and another NLRP3 inhibitor MCC950 reduced tumor growth in melanoma [317, 318]. Nigericin controls tumor growth by activating NLRP3 in breast cancer and neuroblastoma [319]. Since the multifaceted role of inflammasomes in carcinogenesis, clarifying the mechanism of action in different tumors will provide novel therapeutic approaches for cancer treatment and prevention. Here, we will summarize the promoting and suppressive effects of these inflammasomes and their inhibitors and agonists in cancer initiation and development. A comprehensive list of the role of these inflammasomes in cancer is also shown in Table 7.

The role of NLRP1 in inflammation-mediated carcinogenesis

The receptor NLRP1, the adaptor protein ASC, and the effector protein caspase-1 make up the multi-protein complex known as the NLRP1 inflammasome. NLRP1 is the first identified and currently recognized predominant inflammasome sensor protein in human keratinocytes, NLRP1 has its unique domain, which contains an effector C-terminal caspase recruitment domain (CARD), PYD, a central NBD, an LRP and a function to find domain (FIIND). In the absence of external stimuli, the NBD binds to LRR, inhibiting self-oligomerization and bringing the protein into an inactive state. When cells are exposed to external stimuli, such as viruses, UVB rays, and ribotoxic stress reactions, they bind to the LRR domain, then induce a conformational change in NLRP1 and expose PYD and CARD domains. The downstream proteins which containing PYD and CARD are then mediated, such as the homologous interaction between ASC and caspase-1. Dipeptidyl protease (DPP), anthrax lethal toxin (LT), and parasites can activate NLRP1 [320].

Database analysis indicates that NLRP1 has a distinct expression pattern across various tumors, and patients

Table 5 The role and mechanisms of granulocyte/macrophage colony-stimulating factor (GM-CSF) in cancer

GM-CSF	Cancer types	Promote/inhibit	Mechanisms	References
GM-CSF	Colon cancer	Promote	Promotes liver metastasis by down-regulating E- cadherin and up-regulating N- cadherin and MMP2	Ding X et al., 2018
			Makes cells more resistant to cytotoxic drugs through MAPK/ERK signal and EMT-induced transcription factor ZEB1	Chen Y et al., 2017
	Non small cell cancer	Promote	Promotes carcinogenesis	Oshika Y et al., 1998
	Large cell carcinoma of lung	Promote	Stimulates autocrine tumor through leukemia reaction and obvious eosinophilia	Lammel V et al., 2012
	Breast cancer	Promote	Promotes the tumor-promoting effect of WAT progenitor cells	Reggiani F et al., 2017
			The depletion of GM-CSF leads to the decrease of proliferation, invasion and dryness by inhibiting STAT3 phosphorylation and β -catenin signal	Shi H et al., 2020
			Promotes metastasis through the positive feedback loop between GM-CSF and CCL18	Su S et al., 2014
	Gastric cancer	Promote	Promotes chemotherapy induced- CSCs	Xue X et al., 2022
	Non-myeloid carcinoma	Promote	Contributes to cancer recurrence through new angiogenesis	Aliper A et al., 2014
	Lung cancer	Promote	Stimulates the growth or invasion of tumors	Liu Q et al., 2017
	Squamous cell carcinoma of head and neck	Promote	Increases of tumor recurrence or metastasis	Young M et al., 1997
			Induces angiogenesis and invasion, and related to immune evasion	Tenhuinink W et al., 2023
	Prostate cancer	Inhibit	Promotes the host immune monitoring of dendritic cells	Bandyopadhyay S et al., 2008
			Improves the efficacy of RM-1 prostate cancer cell vaccine	Yin W et al., 2010
	Colon cancer	Inhibit	Regulates immune response	Urdinguio R et al., 2013
			Inhibits DMH-induced colon cancer in rats	Dinc S et al., 2007
	Endometrium cancer	Inhibit	Inhibits tumor growth by interacting with TGF-β1 and regulating the expression of TGF-β1 and TGF-β II receptors	Ripley D et al., 2001
	Bladder cancer	Inhibit	Inhibits tumor growth and regresses established tumors by increasing the number of mature DC and up-regulating the expression of IFN-dependent PD-L1	Zhang X et al., 2018
	Breast cancer, pancreatic cancer	Inhibit	Enhances the anti-tumor immunity	Antonarakis E et al., 2010

Table 5 (continued)

GM-CSF	Cancer types	Promote/inhibit	Mechanisms	References
	Squamous cell carcinoma of head and neck	Inhibit	Stimulates the differentiation of dendritic cells, presents tumor antigens and regulates T cell function	Tenhuinink W et al., 2023
	Colon cancer	Inhibit	Regulating immune response	Urdinguio R et al., 2013
			Inhibits DMH-induced colon cancer in rats	Dinc S et al., 2007
	Laryngocarcinoma	Inhibit	Enhances the immunogenicity of cancer cells, induces proliferation of tumor infiltrating lymphocytes and the tumor-specific cytotoxicity of cytotoxic T lymphocytes	Qiu Z et al., 2001
	Esophageal cancer	Inhibit	Promotes the strong immune response	Miyashita T et al., 2008
			Inhibits proliferation and migration, induces apoptosis and regulates EMT through JAK2-PRMT5 signaling	Zhang J et al., 2017
	Ovarian cancer	Inhibit	Negatively induces myeloid suppressor cells (MDSC) and promotes tumor progression and metastasis	Zhang Y et al., 2013
	Lung cancer	Inhibit	Inhibits carcinogenesis by being combined with IL-2	Takahashi K et al., 2000
			Inhibits carcinogenesis by being combined with immunotherapy and IL-18	Tian H et al., 2023
			Enhances the anti-tumor effect of cisplatin	Luo D et al., 2017
	Bladder cancer	Inhibit	Inhibits tumor growth and leads to a significant increase in CD4(+), CD8(+) T cells and CD4(+) Foxp3(+) T cells	Peng J et al., 2019
	Cervical cancer	Inhibit	Promotes the anti-tumor response by inhibiting the expression of iNOS and COX-2 in a GM-CSFR independent manner	Jiang N et al., 2015
			Enhances the anti-tumor immune response wirh nanoparticles loaded with adriamycin and GM-CSF	Zhang X et al., 2023
	Lewis lung cancer	Inhibit	Enhances the anti-tumor immunity with the combination of FasL and GM-CSF	He M et al., 2008
FRG1 (inhibitor)	Breast cancer	Inhibit	Inhibits metastasis by regulating GM-CSF/MEK-ERK axis	Mukherjee B et al., 2022
COX-2 inhibitor (inhibitor)	Lung cancer	Inhibit	Improves the prognosis of lung cancer patients by reducing G-CSF or GM-CSF	Nakata H et al., 2003
Kaempferol and quercetin (agonist)	Prostate cancer	Inhibit	Stimulates the immune response by stimulating the production of GM-CSF, and then lead to DC recruitment to the tumor site	Bandyopadhyay S et al., 2008

Table 6 The role and mechanisms of chemokines in cancer

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
CCL1	CCR8	Esophageal cancer	Promote	Promotes tumor progression through 40 kDa/Akt target of mammalian rapamycin pathway/proline-rich Akt substrate	Fujikawa M et al., 2021
		Colorectal cancer	Promote	Promotes chemoresistance through TGF β/NF-κB signaling pathway	Li Z et al., 2018
		Colorectal cancer	Inhibit	Negatively regulates the progress of liver metastasis	Iwata M et al., 2024
		Breast cancer	Inhibit	Inhibits tumorigenesis, metastasis and chemotherapy resistance by reducing the binding of H3K27Me3 in p65 and CCL1 promoter regions to recruit Tregs	Xv Y et al., 2017
		Lung cancer	Inhibit	Inhibits the differentiation of Tregs and the metastasis of lung tumors	Wang M et al., 2022
CCL2	CCR2 CCR4 CCR5	Breast cancer	Promote	Promotes cell survival and invasion in vitro	Yao M et al., 2017
				Stimulates stem cell-specific spherical phenotype and CSC self-renewal	Tsuyada A et al., 2012
				Induces proliferation, survival, migration and glycolysis through MET-dependent mechanism	Acevedo D et al., 2022
				Promotes the growth and cell cycle process through SRC and PKC activation	Yao M et al., 2019
				CCL2-mediated matrix interaction drives macrophage polarization to increase tumor occurrence	Archer M et al., 2023
		Tongue cancer	Promote	Promotes invasion and metastasis through PI3K/AKT pathway	Dong Y et al., 2023
		Bladder cancer	Promote	LNMAT1 promotes lymphatic metastasis through CCL2-dependent macrophage recruitment	Atala A et al., 2019
				Promotes migration and invasion through PKC activation and tyrosine phosphorylation	Chiu H et al., 2012
		Ovarian cancer	Promote	Promotes tumor progression through MEK/ERK/ MAP3K19 signaling pathway	Liu W et al., 2023
				Inhibition of CCL2 enhances the treatment efficiency with paclitaxel and carboplatin	Mosan F et al., 2014
				Promotes ovarian peritoneal metastasis through p38-MAPK pathway	Yasui H et al., 2020
		Prostate cancer	Promote	Promotes the migration of prostate cancer	Lin T et al., 2013
				Promotes cell survival by inducing mTOR pathway	Roca H et al., 2009
				Stimulates cell proliferation	Loberg R et al., 2006
				Promotes bone metastasis	Li X et al., 2009
				Inhibiting CCL2 activity can enhance the therapeutic response to taxane therapy	Qian D et al., 2010

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
				Protects cells from autophagy through phosphatidylinositol 3- kinase /Akt/ survivin pathway	Roca H et al., 2008
		Cervical cancer	Promote	Promotes proliferation, migration, invasion and EMT	Huang T et al., 2020
		Lung cancer	Promote	Promotes EGFR-TKIs resistant cancer through AKT-EMT pathway	Diao Y et al., 2024
		Colorectal cancer	Promote	Plays a key role in tumor promotion by recruiting macrophages and influencing their functions	Zhang J et al., 2018
		Brain tumor	Promote	Astrocytes promote migration by secreting C–C motif chemokine ligand 2 (CCL2)	Hajal C et al., 2021
		Gastric cancer	Promote	CCL2-SQSTM1 positive feedback loop inhibits autophagy to promote chemotherapy resistance	Xv W et al., 2018
		Hormone dependent mammary gland	Promote	Anti-CCL2 or anti-CCL5 therapy inhibits the growth of cancer	Svensson S et al., 2015
		Negative breast cancer	Promote	Mediates the metastasis of dysmucin in ER-negative breast cancer	Nam J et al., 2006
CCL3	CCR1 CCR4 CCR5	Breast cancer	Promote	Promotes cell growth, leads to EMT and promotes cell migration and invasion through PI3K-AKT-mTOR pathway	Luo A et al., 2020
			Inhibit	Enhances the chemo-sensitivity of docetaxel by triggering the polarization of pro-inflammatory macrophages	Anonymous et al., 2022
		Colon adenocarcinoma	Promote	CCL3 -CCR5 axis promotes migration and invasion through AKT signaling pathway	Guan BG et al., 2022
				Recombinant Bacteroides fragilis enterotoxin –1 (rBFT-1) promotes proliferation through CCL3-related pathway	Xie XL et al., 2021
				Promotes proliferation, invasion and migration through TRAF6 and NF-κB	Ma XQ et al., 2022
		Oral cancer	Promote	Promotes tumorigenesis by inducing inflammation and angiogenesis, and the recruitment of eosinophils	da Silva J et al., 2017
		Esophageal squamous cell carcinoma	Promote	Promotes cell migration and invasion through CCR5 binding and phosphorylation of AKT and ERK, thus promoting the progress and poor prognosis of ESCC	Kodama T et al., 2020
		Human osteosarcoma	Promote	Promotes angiogenesis through the imbalance of miR-374b/VEGF-A axis	Liao Y et al., 2016
				Increases the expression of MMP-2 and enhances the migration ability	Xv C et al., 2013
		Glioma	Inhibit	CCL3 alone or in combination with anti-PD-1 may be an effective immunotherapy	Wang X et al., 2024
CCL4	CCR1 CCR2 CCR5	Endometrim cancer	Promote	Promotes proliferation, invasion and migration by targeting VEGF-A signaling pathway	Fu H et al., 2017

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Oral squamous cell carcinoma	Promote	Induces the expression of vascular endothelial growth factor C and lymphangiogenesis through miR-195-3p	Lian M et al., 2018
				Stimulates the expression of angiopoietin −2 and angiogenesis via MEK/ERK/STAT3	Lu C et al., 2022
		Human osteosarcoma	Promote	Stimulates migration through the miR-3927-3P/ integrin αvβ3 axis	Tsai H et al., 2022
		Breast cancer	Promote	Promotes bone metastasis by mediating the interaction between cancer cells and fibroblasts	Sasaki S et al., 2016
CCL5	CCR1 CCR3CCR4 CCR5	Breast cancer	Promote	Promotes tumor growth and metastasis	Yao X et al., 2007
				Promotes tumor invasion	Pinilla S et al., 2009
		Gastric cancer	Promote	Promotes proliferation, invasion and metastasis of gastric cancer cells	Ding H et al., 2016
				Gastric cancer cells use CCL5 derived from CD4 + cells to grow and prevent tumor elimination with CD8 + cells	Sugasawa H et al., 2008
				KLF5 leads to low survival rate and promotes cancer progression by activating CCL5/CCR5 axis	Yang T et al., 2017
		Prostate cancer	Promote	Promotes the up-regulation of androgen receptor (AR) and leads to enzalutamide resistance by activating AKT	Xiong Z et al., 2024
		Lung cancer	Promote	Promotes the migration of human lung cancer cells	Hang C et al., 2009
		Pancreatic cancer	Promote	Promotes migration and invasion	Singh S et al., 2018
		Colon cancer	Promote	CCL 5 is involved in cancer progression mediated by tumor-associated dendritic cells through non-coding RNA MALAT-1	Guan Z et al., 2015
CCL6	CCR1 CCR2 CCR5 CCR5	N/A			
CCL7	CCR1 CCR2	Gastric cancer	Promote	Inhibition of CCL7 weakens proliferation, migration, invasion and induces apoptosis	Chen M et al., 2023
		Colon cancer	Promote	Accelerates the early stage of tumor growth and leads to higher lung metastasis rate	Kurzejamska E et al., 2019
				Promotes metastasis through ERK-JNK signaling pathway	Li Y et al., 2016
		Ovarian cancer	Promote	CCL7-induced invasion needs to express MMP 9 by activating ERK signaling	Zheng M et al., 2021
		Pancreatic cancer	Promote	Pancreatic stellate cells promote pancreatic cancer invasion through CCL7/CCR5 axis in hypoxic microenvironment	Wu Y et al., 2017

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Lung cancer	Promote	ABCE1 participates in tumor occurrence and progression through CCL7 signaling	Wu Z et al., 2018
		Lung adenocarci-noma	Promote	LINC01094/SPI1/CCL7 Axis promotes macrophage accumulation and tumor cell spread in lung adenocarci-noma	Wu Z et al., 2022
CCL8	CCR1 CCR2	Breast cancer	Promote	Promotes metastasis by regulating the tumor-promoting activity of tumor microenvironment and promotes tumor growth by recruiting macrophages	Farmaki E et al., 2020
		Glioblasto-ma	Promote	CCL8 secreted by tumor-associated macrophages promotes invasion and dryness through ERK1/2 signal	Zang X et al., 2020
		Colon cancer	Promote	Accelerates tumor progression through CCL-8 /CCR5/mTORC1 axis	Zhou H et al., 2023
CCL9	CCR1CCR3	Lung cancer	Promote	Enhances the survival rate of tumor cells in lung before metastasis	Yan H et al., 2015
		Pancreatic ductal adenocarci-noma	Promote	Carcinogenic Kras enhances pancreatic ADM through its new downstream target molecule CCL9 to start PDAC supply	Liou G et al., 2024
		Liver cancer	Promote	Recruits MDSC to promote tumor growth in mice with orthotopic liver cancer	Li B et al., 2023
CCL10	CCR1CCR4	N/A			
CCL11	CCR2 CCR3	Ovarian cancer	Promote	Plays an important role in the proliferation and invasion	Levina V et al., 2009
		Head and neck cancer	Promote	Cancer-related fibroblasts promote tumor invasion of head and neck cancer through CCL11 and CCR3 signal transduction pathway	Huang W et al., 2010
		Glioblasto-ma	Promote	Promotes proliferation, migration and invasion	Tian M et al., 2016
		Non-small cell lung cancer	Promote	Activates AKT and ERK signaling and promotes metastasis through epithelial-mesenchymal transition (EMT)	Lin S et al., 2021
		Colon cancer	Promote	CCL11 aggravates colitis and inflammation-related colon tumors	Polosukhina D et al., 2021
		Breast cancer	Promote	Accelerates tumor growth and induces drug resistance and metastasis	Liu Y et al., 2017
				Asthma-related inflammation promotes lung metastasis through CCL11-CCR3 pathway	Bekaert S et al., 2021
			Inhibit	CCL11 has anti-tumor effect in BRCA	Chen X et al., 2024
		Anaplastic large cell lymphoma (ALCL)	Promote	Increases cell survival rate and proliferation , induces ERK1/2 phosphorylation, induces the expression of anti-apoptosis proteins Bcl-xL and survivin and enhances tumor growth	Tomomitsu M et al., 2011
		Pancreatic cancer	Inhibit	Autochemokine-lipolytic signal transduction inhibits CCL11- eosinophil axis to promote tumor progress	Bhattacharyya S et al., 2024
CCL12	CCR2	N/A			
CCL13	CCR2 CCR3	N/A			

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
CCL14	CCR1 CCR5	Thyroid cancer	Promote	CCL14 may be involved in the recurrence of THCA	Zhang M et al., 2023
		Myeloma	Promote	Promotes tumor growth and survival signals by activating PI3K/AKT and ERK/MAPK pathways and c-myc	Li Y et al., 2015
		Pancreatic cancer	Promote	Up-regulates migration and invasion	Messex J et al., 2022
		Colon cancer	Promote	Myeloid suppressor cells promote invasion through CCL15 -CCR1 chemokine axis	Itatani Y et al., 2014
				MDSCs accumulate and invade the primary cancer through CCL15 -CCR1 chemokine axis, and promotes tumor progression	Inamoto S et al., 2015
				CCL15 secreted by SMAD4 deficient cells recruited CCR1(+) cells to promote lung metastasis	Yamamoto T et al., 2017
			Inhibit	Inhibits proliferation and invasion by inhibiting the formation of M2-like TAM	Li N et al.,2021
				Long-chain noncoding RNA CCL14-AS inhibits invasion and lymph node metastasis by regulating MEP1A	Li M et al., 2023
		Hepatocellu-lar carcinoma	Promote	Recruits inhibitory monocytes to promote the immune escape and CCL15-CCR1 axis creates a complex tumor-promoting inflammatory microenvironment	Liu L et al., 2019
			Inhibit	Inhibits proliferation and promotes apoptosis by inhibiting the activation of Wnt/β-catenin pathway	Zhu M et al., 2019
CCL16	CCR1 CCR2	Hepatocellu-lar carcinoma	Promote	Promotes tumorigenesis by recruiting M2-like tumor-associated macrophages through CCL16-CCR1 axis	Dai Z et al., 2024
		Breast cancer	Inhibit	Inhibits tumor growth and prevents metastasis	Guiducci C et al., 2004
CCL17	CCR4 CCR8	Cervical cancer	Promote	Promotes cell proliferation through JNK and STAT5 signaling pathways	Liu L et al., 2015
		Colitis- related cancer	Promote	Promotes tumor occurrence by affecting the composition of intestinal microbiota and reducing cell apoptosis	Metzger R et al., 2023
CCL18	CCR8	Breast cancer	Promote	Induces cytoskeleton aggregation through its receptor and promotes migration	Chen J et al., 2014
				Promotes angiogenesis and tumor progression	Lin L et al., 2015
				Induces migration and invasion through PCAF-dependent acetylation	Song X et al., 2018
				Promotes infiltration and migration through integrin aggregation	Chen J et al., 2014
				Promotes invasion by inhibiting e-cadherin expression mediated by EZH2	Jia H et al., 2023
				Promotes invasion and metastasis, and cancer passes through Annexin A2	Zhao C et al., 2024
				Promotes malignant behavior by up-regulating Src/PI3K/Akt signaling mediated by ARF6	Huang X et al., 2022
				Promotes metastasis by down-regulating miR98 and miR27b	Lin X et al., 2015

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Gastric cancer	Promote	Promotes invasion and migration through ERK1/2/NF-κB signaling pathway	Hou X et al., 2016
		Human pancreatic ductal adenocarcinoma	Promote	Accelerates the progress of PDAC by promoting epithelial-mesenchymal transformation, invasion and migration	Meng F et al., 2015
		Oral cancer	Promote	CCL18-NIR1 promotes the growth and metastasis by activating JAK2/STAT3	Jiang X et al., 2020
		Non-small cell lung cancer	Promote	Enhances the adhesion of NSCLC cells by activating ELMO1- integrin 1 signal	Shi L et al., 2016
		Mastocarci-ncma	Promote	CCL18 derived from TAMs plays a key role in promoting breast cancer metastasis through its receptor PITPNM3	Chen J et al., 2011
		Lung cancer	Promote	Induces epithelial-mesenchymal transition and enhances the invasion potential	Ploenes T et al., 2013
		Bladder cancer	Promote	Promotes migration, invasion and EMT by binding CCR8	Liu X et al., 2019
		Ovarian cancer	Promote	As a component of ascites, CCL18 plays an important role in tumor cell migration	La D et al., 2016
				Enhances invasion, migration and adhesion in vitro	Zhang W et al., 2013
				Promotes invasion through mTORC2 pathway	Wang Q et al., 2016
		Prostate cancer	Promote	The up-regulation of CCL18 may be related to the malignant progress of PCa	Chen G et al., 2014
		Oral squamous cell carcinoma	Promote	Stimulates growth and invasion in an autocrine way through Akt activation	Jiang X et al., 2016
		Esophageal cancer	Promote	Promotes the malignant progression of tumor by up-regulating the expression of HOTAIR	Wang W et al., 2019
CCL19	CCR1 CCR7	Colon cancer	Promote	Promotes the proliferation, migration and invasion of SW620 cells	Lu J et al., 2014
		Small cell lung cancer	Promote	Relates to metastasis and poor prognosis, promotes tumor progression and metastasis and damages the function of CD8 +T cells	Liu Q et al.,2021
		Gastric cancer	Inhibit	Enhances the immune effect of mice against gastric cancer	Chen Z et al., 2021
				Inhibits proliferation, migration and invasion in CCL-19 /CCR7/AIM2 pathway	Zhou R et al., 2020
		Colon cancer	Inhibit	Activates the immune system	Liu X et al., 2019
				Inhibits angiogenesis by promoting miR-206 and inhibiting Met/ERK/Elk-1/HIF-1α/VEGF-A pathway	Xv Z et al., 2018
		Lung cancer	Inhibit	Chemically attracts dendritic cells and T lymphocytes, which has anti-tumor effect	Hillinger S et al., 2003
				Reduces the tumor load through extensive mononuclear infiltration of the tumor	Hillinger S et al., 2006

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
				Inhibits tumor growth by promoting local anti-tumor T cell response	Cheng H et al., 2018
CCL20	CCR6	Colon cancer	Promote	Induces proliferation and migration through autocrine HGF-c-Met and MSP-MSPR signaling pathways	Nandi B et al., 2021
		Pancreatic cancer	Promote	Promotes migration, epithelial-mesenchymal transformation and invasion	Liu B et al., 2016
		Breast cancer	Promote	Reduces the expression of IFN-γ secreted by CD8 + T cells through CCR6 + Tregs	Xu L et al., 2010
				Recruits immature dendritic cells into tumor tissues to impair immune response	Treilleux I et al., 2004
				Promotes migration and invasion	Kim K et al., 2009
				Promotes angiogenesis	Lee S et al., 2017
				Recombinant human CCL20 induces VEGF expression	He H et al., 2017
				Promotes angiogenesis	Marsigliante S et al., 2016
				Recruits macrophages into tumors to promote their growth	Lee SK et al., 2017
				Up-regulates ABCB1 to promote chemical resistance to taxanes	Chen W et al., 2018
				Regulates PMN-MDSCs and promotes dryness through CXCL2-CXCR2 pathway	Zhang R et al., 2023
CCL21	CCR1 CCR7	Colon cancer	Promote	Up-regulates P-gp, Bmi-1, Nanog and OCT-4 by up-regulating AKT/GSK-3β/Snail, and promotes the chemotherapy resistance and stem cell characteristics	Lu S et al., 2016
				Promotes the chemotherapy resistance and stem cell characteristics of CRC cells	Lu L et al., 2016
		Breast cancer	Promote	Promotes the migration and proliferation of BC cells	Peng J et al., 2023
		Lung cancer	Promote	Triggers migration and invasion through ERK and EMT signaling	Zhong G et al., 2017
				COPD promotes tumor progress by enhancing the migration of CCL21-dependent cancer cells	Kuznar-Kaminska B et al., 2016
		Non-small cell lung cancer	Promote	Promotes invasion and metastasis by changing the intracellular Ca2 + concentration	Liu J et al., 2012
		Oral squamous cell carcinoma	Promote	Promotes EMT and enhances the dryness of OSCC through JAK2/STAT3 signaling pathway	Chen Y et al., 2020
		Pancreatic cancer	Promote	Promotes tumor progress by inducing angiogenesis and lymphangiogenesis	Unver N et al., 2021
		Ovarian cancer	Promote	CCL21 and SPARCL1 may contribute to the drug resistance of ovarian cancer	Yin F et al., 2013

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Colon cancer	Inhibit	Inhibits migration and invasion, and weakens their stem cell-like phenotype	Rong Y et al., 2017
		Lung cancer	Inhibit	Dome nanocapsules can effectively deliver CCL21 to maintain anti-tumor activity and inhibit tumor growth	Kar U et al., 2011
		Adenocarci-noma	Inhibit	Inhibits tumor growth and metastasis	Yousefieh N et al., 2009
		Non-small cell lung cancer	Inhibit	CCL21-DC overcomes drug resistance of immunotherapy and produces systemic tumor-specific immunity	Salehi-Rad R et al., 2023
		Neuroblast-oma	Inhibit	The new nano-preparation of CCL21 is an effective treatment for neuroblastoma	Poelaert B et al., 2020
CCL22	CCR4	Oral cancer	Promote	Cultivates pre-tumor environment by promoting cell transformation and Treg infiltration	Huang Y et al., 2019
		Gastric cancer	Promote	Retinal opacification is a suitable microenvironment for migration, survival and metastasis. The CCL22-CCR4 axis is helpful to this selective permeation process	Cao L et al., 2014
		Prostate cancer	Promote	CCL17 and CCL22 promote the migration and invasion of prostate cancer cells by enhancing Akt phosphorylation	Maolake Aerken et al., 2017
		Lung cancer	Promote	RANKL-induced chemokines derived from CCL22/macrophages produced by osteoclasts promote bone metastasis	Nakamura E et al., 2006
		Squamous cell carcinoma of head and neck	Promote	CCR4/CCL22 promotes lymph node metastasis in head and neck squamous cell carcinoma	Takahiro T et al., 2013
CCL23	CCR1	Ovarian cancer	Promote	Promotes the immunosuppression of TME by inducing depleted T cell phenotype	Kamat K et al., 2022
		Liver cancer	Inhibit	Progress of CCL-23 inhibits liver cancer through CCR1/AKT/ESR1 feedback loop	Meng J et al., 2021
CCL24	CCR3CCR2B CCR5	Hepatocellu-lar carcinoma	Promote	CCL24 leads to HCC malignant tumor through RhoB-VEGFA-VEGFR2 angiogenesis pathway	Jin I et al., 2017
CCL25	CCR9	Breast cancer	Promote	Promotes invasion by regulating various EMT markers	Zhang Z et al., 2016
				Promotes proliferation and up-regulates anti-apoptosis signal transduction	Johnson-Holiday S et al., 2011
		Ovarian cancer	Promote	Contributes to migration and invasion	Johnson S et al., 2010
				Inhibits cisplatin-induced apoptosis and supports the drug resistance	Johnson S et al., 2010
		Lung adenocarci-noma	Promote	The expression of CCR9 was positively correlated with tumor size, lymph node metastasis, TNM late stage and overall survival rate	Zhong Y et al., 2015
		Non-small cell lung cancer	Promote	CCR9/CCL25 interaction induces migration, invasion, anti-apoptosis and tumorigenesis of NSCLC cells	Li B et al., 2015
				Induces the tumorigenesis by activating PI3K/Akt pathway	Li B et al., 2015
		Hepatocellu-lar carcinoma	Promote	Promotes the migration and invasion of HCC cells by regulating EMT markers	Zhang Z et al., 2016

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
				CCR9 enhances proliferation and tumorigenicity	Zhang Z et al., 2014
		Breast cancer	Promote	Activates Akt in PI3K-dependent and FAK-independent ways to promote cisplatin resistance in breast cancer cells	Johnson-Holiday C et al., 2011
CCL26	CCR3	Pancreatic cancer	Promote	Promotes the invasion of PDAC by activating PI3K/AKT/mTOR pathway	Chen X et al.,2021
		Colon cancer	Promote	Participates in tumor progression by regulating EMT signaling pathway	Sun A et al., 2022
				Participates in promotion and invasion by stimulating tumor-associated macrophage infiltration	LAN Q et al., 2018
CCL27	CCR 10	N/A			
CCL28	CCR3	Breast cancer	Promote	Promotes proliferation and inhibits apoptosis, which may be regulated by Bcl-2	Lin F et al., 2013
				Promotes tumor progress through ERK/MAPK-mediated anti-apoptosis and metastasis signaling pathway	Yang X et al., 2017
		Pancreatic ductal adenocarcinoma	Promote	CCL28 blockade can inhibit tumor growth through tumor-cell-internal and external mechanisms	Yan J et al., 2021
		Ovarian cancer	Promote	Hypoxia induces CCL28 series to recruit Treg cells to promote cancer progression through tumor-specific immune paralysis	Facciabene A et al., 2012
		Lung adenocarci-noma	Promote	Hypoxia induces CCL28 series to recruit Treg cells to enhance angiogenesis of lung adenocarcinoma	Liu B et al., 2021
				Hypoxia-induced CCL28 series promotes angiogenesis by targeting CCR3	Huang G et al., 2016
		Hepatocellu-lar carcinoma	Promote	Hypoxia-induced CCL28 series promotes the recruitment of regulatory T cells and tumor growth	Ren L et al., 2016
		Liver cancer	Promote	High expression of CCL28 in hypoxic microenvironment promotes migration and invasion	Zhou Y et al., 2013
		Colon cancer	Inhibit	Transcription activates CCL28, inhibits M2 polarization of macrophages and prevents immune escape	Liu S et al., 2024
		Oral squamous cell carcinoma	Inhibit	CCL28 series-induced RARβ expression inhibits bone invasion of oral squamous cell carcinoma	Park J et al., 2019
CXCL1	CXCR2	Gastric cancer	Promote	Overexpression of CXCL1-1 and its receptor CXCR2-2 promotes tumor invasion	Cheng W et al., 2011
				CXCL1 promotes tumor growth by activating VEGF pathway	Wei Z et al., 2015
				Drives cells into the lymphatic system by activating integrin β1/FAK/AKT signaling	Wang Z et al., 2017
		Colon cancer	Promote	Enhances metastasis by cell migration, MMP-7 expression and EMT	Xv T et al., 2018

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
				Promotes the occurrence and development of colon cancer by activating NF-κB/P300	Zhuo C et al., 2022
				TADCs under SW620 condition enhance CSC characteristics with the support of enhancing anchor-independent growth, CD133 expression and aldehyde dehydrogenase activity	Xv T et al., 2018
				Promotes immune escape through autophagy-mediated MHC-I degradation	Kong J et al., 2024
		Breast cancer	Promote	Promotes tumor growth and development	Ma K et al., 2018
				Promotes breast cancer metastasis by activating NF-κB/SOX4 signaling	Wang N et al., 2018
				Promotes survival, invasion and tumor progression through CXCR2-dependent mechanism	Zou A et al., 2023
				Promotes proliferation and migration via AKT/NF-κB signaling pathway	Yang L et al., 2015
		Cervix cancer	Promote	Promotes growth and migration in both autocrine and paracrine ways	Man X et al., 2022
		Oral squamous cell carcinoma	Promote	Inducement of IL-1 β after CXCL1 stimulates CAFs mediates the invasion of cancer cells	Wei L et al., 2019
				CXCL1 can transform NOFs into aging CAFs through autocrine mechanism	Zhang S et al., 2023
		Bladder cancer	Promote	Promotes tumor recurrence, progression and drug resistance by enhancing invasion	Miyake M et al., 2016
		Oral cancer	Promote	Promotes proliferation, migration and invasion of oral cancer cells	Zhang S et al., 2023
		Pancreatic cancer	Promote	Fibroblast activation protein α-positive pancreatic stellate cells promote migration and invasion by CXCL1-mediated Akt phosphorylation	Editorial O et al., 2021
		Ovarian cancer	Promote	Stimulates tumor growth through epithelial-matrix communication activated by p38	Park G et al., 2021
				Adiponectin promotes angiogenesis in ovarian cancer through CXCL1	Ouh Y et al., 2018
				Promotes the proliferation and invasion of A2780 cells in vitro	Bolitho C et al., 2010
		Osteosarco-ma	Promote	CXCL1 plays a key role in promoting the metastasis of osteosarcoma to the lung	Zhang H et al., 2017
		Prostate cancer	Promote	The paracrine axis of CXCL1-1 -LCN2 promotes tumor progress through Src activation and EMT	Lu Y et al., 2019
		Esophageal squa-mous cell carcinoma	Promote	CAF secretes CXCL1-1, which regulates DNA damage in a ROS-dependent manner in esophageal squamous cell carcinoma, thus conferring radiation resistance	Yang X et al., 2023
		ER negative breast cancer	Promote	CXCL1-1 stimulates the migration and invasion of endoplasmic reticulum negative breast cancer by activating ERK/MMP2/9 signal axis	Yang C et al., 2019

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Hepatocellu-lar carcinoma	Promote	CXCL1 plays a key role in the growth and apoptosis of HCC	Han K et al., 2015
		Prostate cancer	Inhibit	Inhibits malignant tumor, limits tumor cells from escaping from primary tumor and strengthens growth stagnation	Benelli R et al., 2013
		Ovarian cancer	Inhibit	MiR-27b-5p may inhibit the progression of ovarian cancer by targeting CXCL1	Liu C et al., 2020
CXCL2		Epithelial ovarian cancer	Promote	CXCL2 plays an important role in platinum tolerance of epithelial ovarian cancer (EOC)	Nie S et al.,2021
		Colon cancer	Promote	Promotes tumorigenesis through Gi-2 and Gq/11, and contributes to CSC characteristics	Chen M et al., 2019
				The adhesion and growth is mediated by CXCL2-CXCR2 signal and αV integrin-dependent adhesion to ECM protein	Lepsenyi M et al., 2021
				ETTL3 promotes lung metastasis by targeting the m6A-Snail-CXCL2 axis to recruit M2-type immunosuppressed macrophages	Ouyang P et al., 2024
				Promotes the infiltration of M2 macrophages and metastasis of tumor cells	Bao Z et al., 2022
		Non-small cell lung cancer	Promote	CXCL2 contributes to the resistance of ANODINI in NCI-H1975 cells	Lu J et al., 2019
		Oral squamous cell cancer	Promote	CXCL2 synthesized by oral squamous cell carcinoma is involved in cancer-related bone destruction	Oue E et al., 2012
		Gastric cancer	Promote	Omental adipocytes trigger GC cells to form an invasive phenotype through CXCL2 secretion, induce angio-genesis, cell growth and metastasis	Natsume M et al., 2020
		Hepatocellular cancer	Inhibit	Overexpression of CXCL2 inhibits and promotes apoptosis	Ding J et al., 2018
		Osteosarc-oma	Inhibit	MiR-532-5p plays an anti-tumor role in OS cells by regulating CXCL2	Ma Y et al.,2020
CXCL3	CXCR2	Prostate cancer	Promote	Overexpression of CXCL3 type cancer can enhance the carcinogenic potential of prostate	Gui S et al., 2016
		Uterine cervix cancer	Promote	Overexpression of CXCL3 promotes the tumorigenic potential of cervix cancer cells pass through MAPK/ERK pathway	Qi Y et al., 2019
		Pancreatic cancer	Promote	Promotes metastasis through a novel myofibroblast-hijacked cancer escape mechanism	Sun X et al., 2021
		Oral squamous cell cancer	Promote	Overexpression of CXCL3 affects the malignant behavior through MAPK signaling pathway	Wong J et al., 2021
		Colon cancer	Promote	Promotes the malignant behavior of tumor cells in an ERK-dependent manner	Cheng Y et al., 2023
CXCL4	Not found yet	Colon cancer	Promote	Through the negative immuno-modulatory function of CXCR3, non-platelet derived CXCL4 can be hijacked by cancer cells to escape the host immune system	Deng S et al., 2019
		Breast cancer	Promote	Specific CXCL4-CXCL12 heterodimers inhibit migration at least partially by competing for CXCR4 receptors	Nguyen K et al., 2021
CXCL5	CXCR1 CXCR2	Ovarian cancer	Promote	CXCL5 promotes ovarian cancer and achieves cell proliferation by up-regulating the expression of cyclin D1	Jian F et al., 2018

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Liver cancer	Promote	Increases migration and invasion through autocrine and paracrine mechanisms	Xv X et al., 2014
		Colon cancer	Promote	Promotes metastasis by activating ERK/Elk-1/Snail and AKT/GSK3β/β-catenin	Zhao J et al., 2017
				Induces tumor angiogenesis by enhancing the expression of FOXD1 mediated by AKT/NF-κB pathway	Chen C et al., 2019
		Uterine cervix cancer	Promote	Contributes to oncogenic potential of Hela uterine cervix cancer cells	Feng X et al., 2018
		Pancreatic cancer	Promote	CXCL5 promotes PC cell growth and EMT process	Wang Z et al., 2022
				Necrotic apoptosis before invasion promotes migration and invasion through CXCL5-CXCR2 axis	Ando Y et al., 2020
		Breast cancer	Promote	DDR1/CXCL5 promotes immune infiltration of Tregs and drives tumor growth and metastasis	Li H et al., 2023
				CXCL5 is sufficient to promote the proliferation and colonization of breast cancer cells in bones	Romero-Moreno, R et al., 2019
				Increases cancer progression through ERK/MSK1/Elk-1/Snail signaling pathway	Xv Y et al., 2013
				A S100A14-CCL2/CXCL5 signal axis drives breast cancer metastasis	Li X et al., 2020
		Cervical cancer	Promote	Promotes proliferation and migration through ERK signaling pathway and autocrine pathway	Chen S et al., 2021
		Bladder cancer	Promote	CXCL5 may promote mitomycin resistance by activating EMT and NF-κB pathways	Wang C et al., 2018
				CXCL5 is very important for the growth and progress of bladder tumor	Zheng J et al., 2014
				Promotes migration and invasion through activating PI3K/AKT-induced MMP2/MMP9 up-regulation	Gao Y et al., 2015
		Prostate cancer	Promote	Enhances cell migration and EMT through early growth response −1/ snail signaling pathway	Guo B et al., 2011
				CXCL5 can promote the growth of LNCaP cells by acting on its own receptor CXCR2	Qi Y et al., 2014
		Lung cancer	Promote	Promotes immune escape through autocrine and paracrine mechanisms by up-regulating the chemotaxis of lung cancer and neutrophils	Sun D et al., 2024
				Promotes proliferation and movement by activating MAPK/ERK1/2 and PI3K/AKT	Wang L et al., 2018
		Gastric cancer	Promote	The interaction between TAMs and gastric cancer cells promotes chemotherapy resistance through CXCL5/PI3K/AKT/mTOR pathway	Su P et al., 2022
				Promotes tumor occurrence by regulating tumor immunosuppression mediated by NF-κB and Wnt/β-catenin signals	Liu L et al., 2020

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Osteosarcoma	Promote	Promotes migration and invasion in autocrine- and paracrine-dependent manners	Dang H et al., 2017
		Glioblasto-ma	Promote	Promotes the tumorigenesis and angiogenesis through JAK-STAT/NF-κb	Mao P et al., 2023
		Cholangio- carcinoma	Promote	Promotes tumor metastasis and recurrence by recruiting infiltrating neutrophils	Zhou S et al., 2014
		Non-small cell lung cancer	Promote	A2AR-mediated CXCL5 upregulation on macrophages promotes NSCLC progression via NETosis	Lei Q et al., 2024
		Lung cancer	Inhibit	Inhibits tumor immunity by regulating PD-1/PD-L1 signal transduction	Xie X et al., 2022
CXCL6	CXCR1 CXCR2	Non-small cell lung cancer	Promote	CXCL6 promotes the survival and metastasis of non-small cell lung cancer cells by down-regulating miR-515-5p	Li J et al., 2018
		Hepatocell-ular cancer	Promote	Activates IFN-γ/p38 MAPK/NF-κB signal and promotes EMT and radiation resistance	Li X et al., 2023
				Promotes liver invasion through targeting MMP9	Zheng Y et al., 2016
		Esophageal squa-mous cell cancer	Promote	Enhances the growth and metastasis of ESCC cells in vivo and in vitro	Zheng S et al., 2021
		Melanoma	Promote	(GCP)−2/CXCL6 induces angiogenesis and promotes tumor growth	Verbeke H et al., 2011
CXCL7	CXCR1 CXCR2	Cholangiocarcinoma	Promote	Promotes the proliferation and invasion of cholangiocarcinoma cells	Guo Q et al., 2017
		Breast cancer	Promote	Promotes invasion, the expression of VEGF-C/D and heparanase	Yu M et al., 2010
				Secretion of CXCL7 by monocytes promotes the progress of breast cancer	Wang Y et al., 2021
				The interaction between breast cancer cells and monocytes promotes tumor progression through CXCL7-mediated signal transduction	Lin S et al., 2021
		Renal-cell carcinoma	Promote	CXCL7 /CXCR1/2 axis is the key driving factor for the growth of clear cell renal cell carcinoma	Grepin R et al., 2014
		Pancreatic cancer	Promote	IFNα- induced BST2 + tumor-associated macrophages promote immunosuppression and tumor growth through ERK-CXCL7 signal	Zheng C et al., 2024
		Triple negative breast cancer	Promote	The multiple positive feed-forward loops of MCT-1/IL-6/IL-6R/CXCL7/PD-L1 axis promotes the metastatic niche and immunosuppressive microenvironment	Aushia T et al., 2024
CXCL8	CXCR1 CXCR2	Gastric cancer	Promote	Participates in the immunosuppression microenvironment by inducing PD-L1 (+) macrophages	Lin C et al., 2019
		Colon cancer	Promote	CXCL8 gene silencing significantly inhibits proliferation and invasion via PI3K/Akt/NF-κB signaling	Ma J et al., 2015
				CXCL8 upregulates LSECtin through AKT, and promotes proliferation and invasion	Fang S et al., 2022
		Thyroid cancer	Promote	Promotes the tumor-promoting effect of TC cells	Coperchini F et al., 2024

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Ovarian cancer and gastric cancer	Promote	Promotes peritoneal metastasis	Awwad O et al., 2018
CXCL9	CXCR3 CXCR7	Prostate cancer	Promote	Promotes tumor progress by inhibiting cytokines in T cells	Tan S et al., 2018
		Ovarian cancer	Inhibit	Inhibits tumor growth	Seitz S et al.,2022
CXCL 10	CXCR2 CXCR3 CXCR4	Breast cancer	Promote	Promotes proliferation and Tamoxifen-resistant MCF7 cells through AKT pathway	Wu X et al., 2020
				Induces migration through a novel crosstalk between Cxcr3 and Egfr receptor	Tsutsumi E et al., 2022
				CXCL10 signal transduction promotes the metastasis of ING4 deficient breast cancer	Tsutsumi E et al., 2023
		Gastric cancer	Promote	Targeted autophagy promotes T lymphocyte migration by inducing the expression of CXCL10	Meng Q et al., 2022
				Promotes gastric invasive cancer through PI3K/AKT dependent MMP production	Zhou H et al., 2016
		Colon cancer	Promote	Enhances metastasis by triggering small GTP enzymes such as RhoA and cdc42	Wang Z et al., 2021
		Cervical cancer	Promote	Promotes M2 polarization of macrophages in tumor microenvironment and enhances proliferation, migration and invasion via activating STAT3/NF-κB/CCL2 signal	Li A et al., 2024
		Ovarian cancer	Inhibit	Promotes CTL activation to inhibit ovarian cancer	Dong M et al., 2024
				Enhances the killing effect of T cells and inhibits angiogenesis	Li W et al., 2021
		Prostate cancer	Inhibit	Inhibits proliferation and reduces PSA production by up-regulating CXCR3 receptor	Nagpal M et al., 2006
		HER2 positive breast cancer	Inhibit	Induces activation of CD8 ~ +T cells to promote effect of immunotherapy on HER2-positive breast cancer	Zhang X et al., 2022
		Breast cancer	Inhibit	controlling the self-regulation of CXCL10 and the characteristics of malignant tumor by mediating NF-κB signaling pathway	Jin W et al., 2017
		Colon cancer	Inhibit	Inhibits tumor growth, increases CD8+T cell infiltration and induces tumor blood vessels to normalize by making colorectal cancer cells overexpressing cetuximab	Yan W et al., 2023
		Cervical cancer	Inhibit	Enhances the radiotherapy effect of HeLa cells through cell cycle redistribution	Yang L et al., 2012
CXCL 11	CXCR3	Hepatocellular cancer	Promote	Promotes the proliferation and migration of HCC cells through LINC00152/miR-205-5p/CXCL11 axis	Liu G et al., 2022
		Squamous cell carcinoma of head and neck	Promote	Promotes tumor lymph node metastasis	Wang X et al., 2021
		Colon adenocarcinoma and rectal adenocarcinoma	Promote	Enhances the infiltration of TAMs into tumor environment, promotes EMT of cancer and promotes tumor metastasis by inducing the expression of TGF-β1	Liu M et al., 2021 Zeng YJ et al., 2016

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Renal cancer	Promote	EP300/CBP promotes proliferation and migration by stabilizing CXCL11 mRNA level	Zeng X et al., 2022
				Promotes tumor angiogenesis	Suyama T et al., 2005
		Oral cancer	Promote	Promotes tumor growth and immune escape	Wang X et al., 2021
				Promotes early malignant transformation and tumor development	Xia J et al.,2011
				Promotes the occurrence of precancerous lesions	Wang X et al., 2021
		Cutaneous melanoma	Promote	Induces cytoskeleton remodeling and promotes tumor metastasis	Kawada K et al., 2004
		Breast cancer	Promote	Activates ERK pathway and enhances tumor invasion	Hwang H et al., 2020
		Multiple myeloma	Promote	Activates tyrosine kinase, induces MMP-2 and MMP-9 secretion and promotes tumor growth and metastasis	Pellegrino A et al., 2004
		Ovarian cancer	Promote	The high expression of CXCR3-A in endometriosis inhibits cytotoxic T cells and promotes the occurrence of precancerous lesions	Furuya M et al., 2007 Furuya M et al., 2011
		Basal cell carcinoma	Promote	Promotes the proliferation of human immortalized keratinocytes and promotes tumor growth	Lo B et al., 2010
		Thyroid cancer	Promote	Promotes angiogenesis in metastatic THCA through EGF-EGFR positive feedback loop	Liang J et al., 2021
				Inhibits proliferation, migration, induces apoptosis, and inhibits tumor growth	Fallahi P et al., 2018
		Colon cancer	Promote	Down-regulation of CXCL11 inhibits cell growth and EMT	Gao Y et al., 2018
		Pancreatic cancer	Promote	Induces invasion and EMT by activating NF-κB signaling pathway	Sun L et al., 2019
		Cutaneous melanoma	Inhibit	Recruits immune cells, promotes bone marrow activation, enhances anti-tumor immune response and inhibit tumor growth	Harlin H et al., 2009
		Renal cancer	Inhibit	Has immunosuppressive activity on tumor vasculature and tumor angiogenesis	Gacci M et al., 2009
		Gastric adenocarcinoma	Inhibit	Activates CXCR3 and up-regulates PD-L1 expression through STAT and PI3K-Akt pathways, thus improving the effectiveness of immunotherapy	Zhang C et al., 2018
				Mediates the infiltration of cytotoxic T lymphocytes and inhibit angiogenesis	Verbeke H et al., 2012
				Activates Th1, promotes M1 polarization in macrophages and inhibits tumor growth	Pasini F et al., 2014
		Lung cancer	Inhibit	Induces CD8 T cell infiltration, inhibits angiogenesis and enhances the efficacy of immunotherapy	Mitsuhashi A et al., 2021
		Bladder Urothelial carcinoma	Inhibit	Improves the chemosensitivity	Zhang Y et al., 2019
CXCL 12	CXCR4 CXCR7	Lung cancer	Promote	The destruction of CXCL12 inhibits the growth and migration of lung cancer cells	Imai H et al., 2010

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
				CXCL12 induces lung cancer cell migration by polarized mtDNA redistribution	Ma J et al., 2014
		Gastric cancer	Promote	Promotes distant metastasis by activating CXCR4	Ishigami S et al., 2007
		Colon cancer	Promote	Silencing CXCL12 inhibits proliferation, invasion and angiogenesis by down-regulating MAPK/PI3K/AP-1 signaling	Ma J et al., 2018
		Pancreatic cancer	Promote	CXCL12 -CXCR4 promotes the proliferation of pancreas and invades cancer cells	Shen B et al., 2014
		Breast cancer	Promote	Signal transduction through CXCL12-CXCR4 is an important for migration	Nguyen K et al., 2020
				CXCL12-γ was identified as an effective transfer promoter	Lei P et al., 2015
		Prostate cancer	Promote	Promotes peripheral invasion of prostate cancer	Zhang S et al., 2009
		Non-small cell lung cancer	Promote	The interaction between cancer-associated fibroblasts and tumor epithelial cells through CXCL12/CXCR4 axis promotes tumor proliferation	Wald O et al., 2011
		Colon cancer	Promote	Enhances the metastatic potential through PI3K/Akt/mTOR pathway	Ma J et al., 2017
				Down-regulating CXCR4/CXCL12 axis can reduce cancer growth and metastasis	Song Z et al., 2015
				The combination of CXCR7 and CXCL12 promotes lung metastasis	Wang M et al., 2018
		Bladder cancer	Promote	Enhances immune escape by inhibiting autophagy degradation of PDL1 mediated by P62	Zhang Z et al., 2023
		Non-small cell lung cancer	Promote	CXCL12-CXCR4 biological axis is involved in regulating the metastasis of non-small cell lung cancer	Phillips R et al., 2003
		Intestinal gastric cancer	Promote	CXCL12/CXCR7 may be the biological axis of proliferation, invasion and lymph node and liver metastasis	Xin Q et al., 2016
		Ovarian cancer	Promote	Cancer-related fibroblasts induce EMT and cisplatin resistance through CXCL12/CXCR4 axis	Zhang F et al., 2020
		Thyroid carcinoma	Promote	CXCL12-CXCR4 biological axis plays an important role in the process of thyroid cancer metastasis	Wu Y et al., 2012
		Ovarian cancer	Promote	CXCL12 promotes cell invasion by inhibiting the expression of ARHGAP10	Luo N et al., 2020
		Cervical cancer	Inhibit	Inhibits anchorage independent cell growth	Yadav S et al., 2016
CXCL 13	CXCR4 CXCR7	Lung cancer	Promote	Mediates radiotherapy resistance of lung cancer by activating Akt	Geng S et al., 2020
				Promotes the migration of lung cancer cells	Zhao C et al., 2021
		Colon cancer	Promote	Plays a key role in carcinogenesis, tumor development, metastasis and recurrence	Qi X et al., 2013

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
				CXCL13-CXCR5 axis promotes growth, migration and invasion through PI3K/AKT	Zhu Z et al., 2015
				Promotes the occurrence of intestinal tumors by activating epithelial AKT signal	Zhao Q et al., 2021
		Prostate cancer	Promote	CXCL13 participates in AR regulating the growth of prostate cancer xenograft in mice	Tian Q et al., 2019
		Renal-cell carcinoma	Promote	Promotes proliferation and migration by binding to CXCR5 and activating PI3K/AKT/mTOR signaling	Zheng Z et al., 2019
		Human osteosarcoma	Promote	Promotes migration through phospholipase C β (PLC beta), protein kinase C α (PKC α), c-Src and nuclear factor-κB (NF-κB)	Liu J et al., 2020
		Breast cancer	Promote	CXCL13 inhibition causes the decrease of tumor growth via CXCR5/ERK signaling	Xv L et al., 2018
		Breast cancer	Inhibit	Triggers effective anti-tumor immunity by attracting immune cells to infiltrate	Ma Q et al., 2021
		Cervical cancer	Inhibit	Down-regulation of DNA methylation-dependent CXCL13 may promote tumor occurrence and progress	Ma D et al., 2020
CXCL 14	CXCR4 CXCR7	Non-small cell lung cancer	Promote	CXCL14 promotes metastasis of non-small cell lung cancer through ACKR2-dependent signaling pathway	Zhang Z et al., 2023
		Breast cancer	Promote	The CXCL14/ACKR2 pathway is a clinically relevant stimulator of EMT, invasion and metastasis	Sjoberg E et al., 2019
		Ovarian cancer	Promote	Up-regulating CXCL14 promotes the proliferation of ovarian cancer cells	Li X et al., 2021
		Pancreatic cancer	Promote	CXCL14 significantly increases the invasion of pancreatic cancer cells	Wente M et al., 2008
		Colon cancer	Inhibit	Inhibits the migration, invasion and EMT by inhibiting NF-κB signal transduction	Cao B et al., 2013
		Breast cancer	Inhibit	Inhibits cell proliferation and invasion, and weakens the growth and lung metastasis	Gu X et al., 2012
		Triple negative breast cancer	Inhibit	Inhibits tumor progress by changing the immune characteristics of tumor microenvironment, and it is mediated in a T cell-dependent manner	Gibbs C et al., 2024
CXCL 15	CXCR2	N/A			
CXCL 16	CXCR6 SR-PSOX	Lung cancer	Promote	Promotes the viability and invasion and leads to lung cancer metastasis	Zhou W et al., 2011
				Promotes proliferation and invasion by regulating NF-κB pathway	Liang K et al., 2018
				CXCL16-CXCR6 regulates lung cancer cell viability and invasion	Hu W et al., 2014
		Breast cancer	Promote	Blocking CXCR6-CXCL16/CXCR4-CXCL12 receptor-ligand interaction prevent brain metastasis	Chung B et al., 2017
		Prostate cancer	Promote	CXCL16/CXCR6 may be another independent axis of chemokines for bone metastasis	Zhou W et al., 2010

Table 6 (continued)

chemokines	Receptor	Cancer types	Promote/inhibit	Mechanisms	References
		Ovarian cancer	Promote	Maintains the high invasion and migration ability of cells by combining with CXCR6	Yang Y et al., 2015
		Colon cancer	Promote	CXCL16/CXCR6 may be involved in the proliferation, invasion and metastasis	Fu Y et al., 2017
		Gastric cancer	Promote	Promotes tumorigenesis by enhancing ADAM10-dependent CXCL16/CXCR6 axis activation	Han J et al., 2021
				Promotes cell proliferation	Takiguchi G et al., 2016
				Promotes tumor progress through the expression of Ror1 mediated by STAT3	Ikeda T et al., 2020
				Promotes tumorigenesis via ADAM10-dependent CXCL16/CXCR6 axis and activates Akt and MAPK signaling	Han J et al., 2023
		Adenocarci-noma	Promote	Enhances migration, invasion and adhesion with endothelial cells	Singh R et al., 2016
		Thyroid cancer	Promote	Enhances migration and invasion, and changes the phenotype of macrophages into M2 macrophages	Zhao S et al., 2016
		Breast cancer	Inhibit	Inhibits migration and invasion, and induces apoptosis of breast cancer cells	Fang Y et al., 2014
				Inhibits the migration and invasion of breast cancer cells in vitro	Fang Y et al., 2013
		Renal cancer	Inhibit	Inhibits migration of renal cell induced by CXCL16	Gutwein P et al., 2009
		Colon cancer	Inhibit	CXCL16 can inhibit the metastasis of liver through NKT cells in CRC	Kee J et al., 2013
				Inhibits liver metastatic by promoting tumor-associated macrophage α TNF- induced apoptosis	Kee J et al., 2014
CX3C	CX3CR1				
XCL1	XCR1	Breast cancer	Promote	Promotes the proliferation of drug-resistant cells by activating mTOR pathway	Bai Y et al., 2015
				The activation of ERK/HIF-1 α/EMT is involved in migration induced by XCL1	Do H et al., 2021
			Inhibit	Improves the survival rate by promoting cancer immunity	Zhou W et al., 2020
XCL2	XCR1	Clear cell renal cell carcinoma	Promote	Inhibit apoptosis and promotes the proliferation, migration, invasion and epithelial-mesenchymal transition	Cao Q et al., 2022

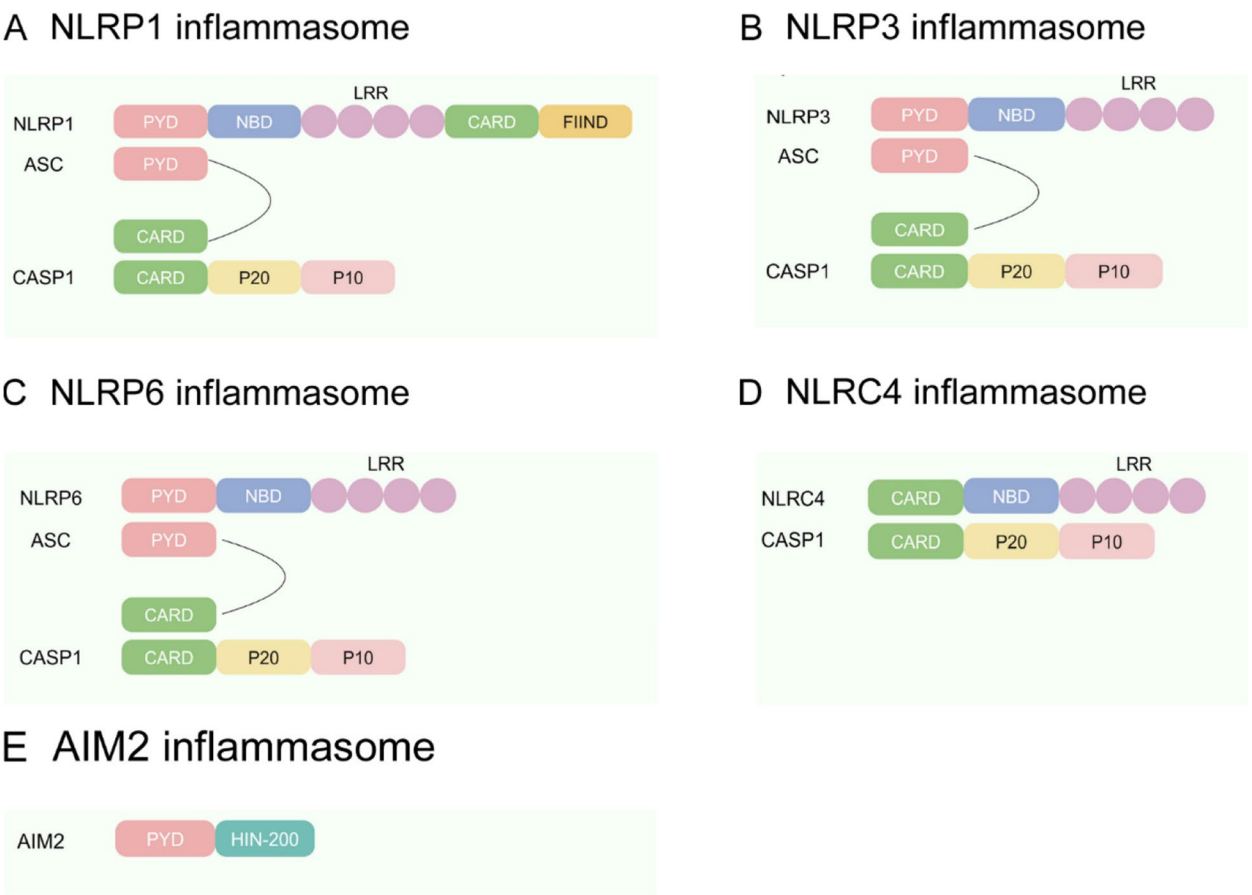

Fig. 4 Nucleotide-binding domain, leucine-rich repeat containing receptors (NLRs) upon activation form a multiprotein complex known as the "inflammasome". The inflammasome complex consists of an NLR protein, the apoptosis-associated speck-like protein (ASC) (an adaptor protein) and a caspase. The detailed information on the structure of NLRP1, NLRP3, NLRP4, NLRP6, and AIM2 inflammasome are shown. A NLRP1 consists of both pyrin domian (PYD) and caspase recruitment domain (CARD) along with the function to find domain (FIIND domain). NLRP1 directly recuits procaspase-1 through its CARD domain. B The Nlrp3 gene encodes an N-terminal PYD domain, a central nucleotide binding and oligomerization domain (NBD) and a C-terminal leucine-rich repeats (LRR). NLPR3 lacks a CARD domain and therefore, interacts with ASC to recruit procaspase-1. C The Nlrp6 gene encodes an N-terminal PYD domain, a central NBD domain and a C-terminal LRR. NLRP6 is recruited to the "specks" formed by ASC oligomerization, leading to procaspase-1 activation. D The Nlrc4 gene encodes an N-terminal CARD domain, a central NBD domain, and C-terminal LRR. The interaction of NLRC4 with ASC is unclear. NLRC4 results in pro-IL-1b and proIL-18 processing or caspase-1-dependent pyroptosis via an ASC-dependent mechanism or an ASCindependent mechanism. E The AIM protein consists of a N-terminal PYD domain, mediating homotypic interactions with ASC and a C-terminal HIN-200 domain for DNA binding

with high NLRP1 expression generally have a better prognosis in lung adenocarcinoma (LUAD) and pancreatic adenocarcinoma (PAAD) [321]. The activation of the NLRP1 sensor protects against colitis-associated CRC through mechanisms dependent on effector cytokines [315]. NLRP1 is also positively correlated with an increased risk of prostate cancer [322]. The dysfunctions in the NLRP1 pathway are also linked to skin cancers, including melanoma, Kaposi sarcoma, and squamous cell carcinoma [323]. Increased expression of NLRP1 was significantly associated with immune cell infiltration in gastric cancer [324]. An endogenous thioredoxin (TRX) has been identified as a binder to NLRP1 and inhibits NLRP1 inflammasome activation. This opens opportunities for therapeutic intervention in NLRP1 inflammasome activation in the future.

The role of NLRP3 in inflammation-mediated carcinogenesis

The NLRP3 inflammasome is widely present in immune cells. As the most thoroughly studied inflammasome, NLRP3 inflammasome includes the sensor NLRP3, the adaptor ASC, and the effector caspase-1. NLRP3 consists of three domains, a central nucleotide-binding domain (NBD), a C-terminal leucine-rich repeat (LRR), and an N-terminal PYD. ROS production, ionic flux, mitochondrial dysfunction, and lysosomal damage are the four

main activation mechanisms of NLRP3 inflammasome. Under the stimulation of microbial or endogenous molecules like TLR ligands, NF-κB is activated, and pro-IL-1β, pro-IL-18, and NLRP3 are induced. Then, various stimuli like extracellular ATP, glucose, bacterial and virus infection, mitochondrial damage/dysfunction, and more facilitated the maturation of pro-IL-1β and pro-IL-18, promoting the activation of NLRP3 inflammasome.

NLRP3 and NLRP3 inflammasome members like caspase-1, IL-1β and IL-18 are potential therapeutic targets due to their role in inflammation-associated diseases and cancer. Recent research reported that NLRP3 inflammasome-related genes were dysregulated in 15 cancers [325]. NLRP3 is overexpressed and activated in several cancers, like non-small cell lung cancer [326], melanoma [327], and more. Patients with cancer have a higher frequency of *Nlrp3* polymorphism, such as pancreatic cancer [328], melanoma [329], and others. They were introduced as a double-edged sword in tumorigenesis. On one hand, the NLRP3 inflammasome promotes tumor formation and metastasis in breast cancer [330], and overexpressed human IL-1β in mice stomach increases the risk of gastric cancer [331]. NLRP3 affects the adaptive immune system to promote carcinogenesis in pancreatic cancer [332], and pharmacologic blocking of NLRP3 enhances the efficacy of immunotherapy [318]. NLRP3 signaling promotes T cell differentiation into tumor-promoting T cell populations and restricts antitumor T cell immunity [333]. NLRP3-mediated IL-1β production promotes pancreatic ductal adenocarcinoma by immunosuppression [334]. On the other hand, mice deficient in NLRP3 are hypersusceptible to carcinogen-induced colitis-associated cancer (CAC) [335]. While NLRP3 inhibition via mitophagy prevents CAC, indicating a harmful role of NLRP3 in CAC [336]. The differences in gut microbiota, genetic background, and experimental technique may explain the inconsistent effects of NLRP3 in CAC. Besides, NLRP3 is down-regulated in hepatic cancer tissues [337], and the up-regulation of NLRP3 inhibits hepatic cancer cell growth [338]. The varying functions of NLRP3 in the etiology of cancer present novel prospects and obstacles in comprehending its dual roles of pro- and anti-tumorigenic effects. The tumor microenvironment may have an impact on these many functions by altering NLRP3 activity. Furthermore, it appears that NLRP3 plays distinct roles in the pathophysiology of cancers that originate in particular organs due to its variable expression in different cells and tissues, and elucidating the role and mechanism of NLRP3 in different cancers will contribute to precision therapy.

The role of NLRC4 in inflammation-mediated carcinogenesis

NLRC4 contains three domains: the N-terminal CARD domain, the C-terminal LRR domain, and the NACHT domain. NACHT domain is composed of the NBD, helical domain 1 (HD1), winged helix domain (WHD), and helical domain 2 (HD2). A functional type IV secretion system (T4SS) for L. pneumophila or a functional type III secretion system (T3SS) for S. Typhimurium, S. flexneri, and P. aeruginosa is necessary for NLRC4 inflammasome activation [339]. Regulatory mechanisms also impact NLRC4 activation, mostly comprising transcription control and post-translation changes, specifically phosphorylation and perhaps ubiquitination. Interferon regulatory factor (IRF) 8 induces NLRC4 transcription, and infection with S. *typhimurium* induces NLRC4 phosphorylation at serine 533 [340]. Flagellin also induces NLRC4 phosphorylation but can't activate NLRC4 inflammasome [341]. NLRC4 has been shown to express differently yet variably across various tumor tissues. For example, NLRC4 mRNA level is increased in stomach cancer, glioma, and breast cancer, but it is decreased in colorectal cancer compared with normal adjacent tissues [339]. However, NLRC4 mRNA is almost unchanged in hepatocellular carcinoma [342]. And there is no agreement regarding its role in any form of cancer development, even in the same tumor type. Knocking out NLRC4 promotes tumor formation in colon cancer [343] and melanoma [344]. Higher NLRC4 expression is closely related to poor prognosis in breast cancer [345] and glioma [346]. Activated NLRC4 inflammasome activates IL-1β, which promotes breast cancer progression by adipocyte-mediated vascular endothelial growth factor A (VEGFA) expression and angiogenesis [345]. Besides, in colitis-associated tumorigenesis, the role of NLRC4 depends on how NAIPs function. NAIPs have protective effects on colon cancer development, which is independent of NLRC4 [347]. Even though there isn't a consensus on the involvement of NLRC4 or NAIP in cancer, the necessity to employ littermate controls in these experiments will improve future research consistency and reproducibility. Furthermore, the discovery of NAIPs' or NLRC4's inflammasome-independent activities in carcinogenesis is intriguing because it might reveal new route targets for the creation of immunotherapies.

The role of NLRP6 in inflammation-mediated carcinogenesis

As a recently identified receptor in the mammalian innate immune system, the NOD-like receptor family pyrin domain containing 6 (NLRP6) was formerly known as PYPAF5 [348]. It comprises N-terminal PYD, central NBD, and C-terminal LRR domain. Following the recognition of PAMP and DAMP, NLRP6 forms the NLRP6 inflammasome by assembling with ASC and Caspase-1. This process facilitates the maturation of pro-IL-1β and pro-IL-18, as well as gasdermin-D-induced pyroptosis. NLRP6 functions as an inflammasome or

Table 7 The role and mechanisms of inflammasome in cancer

Inflammasome	Cancer types	Promote/inhibit	Mechanisms	References
NLRP1	Breast cancer	Promote	Promotes tumorigenesis and proliferation	Wei, Y et al.,2017
	Prostate cancer	Promote	Enhances tumorigenesis by promoting the maturation and release of pro-inflammatory cytokines IL-1β	Liang, K et al.,2023
	Metastatic melanoma	Promote	Enhances inflammasome activation and suppresses apoptosis	Zhai, Z et al.,2017
High p62 (NLRP1 inhibitor)	Cutaneous SCC cells	Promote	Suppresses the NLRP1 inflammasome and increases stress resistance	Hennig, P et al.,2022
	Non-melanoma skin cancer	Promote	Lower NLRP1 level is associated with worse clinical outcomes and poorer prognosis	Tan, J et al.,2023
	Triple-negative breast cancer	Inhibit	Contribute to the antiproliferative effects of celecoxib	Arzuk, E et al.,2024
NLRP3	Colorectal cancer	Promote	Contributes to cell migration and invasion	Deng, Q et al.,2019
			Promotes invasion and migration	Zhang, L et al.,2022
	Ovarian cancer	Promote	Contributes to the malignant process of DDP-resistant cells	Li, W et al.,2023
3,4-Methylenedioxy-β-nitrostyrene (MNS) (NLRP3 inhibitor)	Pancreatic ductal adenocarcinoma	Inhibit	Inhibits inflammation and restores immunity	Liu, H et al.,2020
MCC950 (NLRP3 inhibitor)	Pancreatic ductal adenocarcinoma	Inhibit	Inhibits LPS-induced pancreatic adenocarcinoma inflammation	Yaw, A et al.,2020
Vitamin D (NLRP3 inhibitor)	Breast cancer	Inhibit	Mediates the modulation of stemness	Zheng, W et al.,2024
Caffeic Acid Phenethyl Ester (NLRP3 inhibitor)	Colon cancer	Inhibit	Inhibits NLRP3 Inflammasome	Dai, G et al.,2020
RNF20 (NLRP3 inhibitor)	Liver cancer	Inhibit	Reduces cell proliferation and Warburg effect by promoting NLRP3 ubiquitination	Liu, D et al.,2024
Metformin (NLRP3 inhibitor)	Colorectal cancer	Inhibit	Delays tumor progression	Liu, G et al.,2024
Fermented Quercetin (NLRP3 inhibitor)	Colorectal cancer	Inhibit	Decreases resistin-induced chemo-resistance to 5-Fluorouracil	Lee, K et al.,2022
Inhibition of HDAC2 (NLRP3 agonist)	Breast cancer	Inhibit	Sensitizes anti-tumour therapy by promoting NLRP3/GSDMD-mediated pyroptosis	Guan, X et al.,2024
H. pylori CagA (NLRP3 agonist)	Gastric cancer	Promote	Promotes invasion and migration by activating NLRP3 inflammasome pathway	Zhang, X et al.,2021
	Cervical cancer	Promote	Promotes migration, invasion and EMT by regulating macrophage differentiation	Zhou, H et al.,2020
miR-223-3p (NLRP3 inhibitor)	Prostate cancer	Inhibit	Reduces tumor growth and immunosuppression	Zhang, L et al.,2019
miR-22 (NLRP3 agonist)	Prostate cancer	Inhibit	Inhibits PI3K/AKT signaling pathway	Wu, H et al.,2021

Table 7 (continued)

Inflammasome	Cancer types	Promote/inhibit	Mechanisms	References
NLRC4	Glioma	Promote	Contributes to a poor prognosis	Lim, J et al.,2019
	Lung adenocarcinoma Cells	Promote	Induces apoptosis and immune infiltration	Hu, B et al.,2023
	Melanoma tumor	Promote	Suppresses tumor growth in an inflammasome-independent manner	Janowski, A et al.,2016
	Breast cancer	Inhibit	Weakens the ability of flagellin to inhibit tumor proliferation	Zhang, J et al.,2019
NLRP6	Colorectal cancer	Promote	Promotes liver metastasis by modulating M-MDSC-induced immunosuppressive microenvironment	Chang, L et al.,2024
	Gastric cancer	Inhibit	Suppresses tumorigenicity	Wang, Q et al.,2018
			Suppresses tumor growth via GRP78 ubiquitination	Wang, X et al.,2020
			Mediates P14ARF-Mdm2-P53-dependent cellular senescence	Wang, H et al.,2018
AIM2	Prostate cancer	Promote	IFN-inducible AIM2 protein is a cytosolic DNA sensor in macrophages and keratinocytes	Ponomareva, L et al.,2013
	Colon cancer	Inhibit	Suppresses colon tumorigenesis via DNA-PK and AKT	Wilson, J et al.,2015
	Bladder cancer	Inhibit	Inhibits tumorigenesis and enhances the therapeutic effect	Zhou, H et al.,2022
	Colorectal cancer	Inhibit	Inhibits cell proliferation and migration through suppressing Gli1	Xu, M et al.,2020

a non-inflammasome in a variety of ways. Various factors can regulate the activation of NLRP6. For example, mouse macrophages bind to lipoteichoic acid and stimulate the assembly of the NLRP6 inflammasome [349]; microbial signals of type I IFN and PPAR-γ agonists regulate NLRP6 transcription [350, 351]; microbial metabolites activate or inhibit the NLRP6 inflammasome [352].

NLRP6 gene-deficient mice got more colitis-associated colorectal tumors after AOM/DSS treatment [313]. Elinav's experiment suggests that the main source of active IL-18 generation through NLRP6 may be intestinal epithelial cells [353], which explains that NLRP6 gene-deficient animals' serum and colon tissue showed decreasing levels of IL-18 with time but not IL-1. NLRP6 also plays a critical regulatory role in the linked pathogenic changes before HCC. For example, NLRP6 inflammasome and effector protein IL-18 suppress the development of NAFLD/nonalcoholic steatohepatitis (NASH) and metabolic syndrome by regulating intestinal microbiota [354]. NLRP6 overexpression reduces steatosis, inflammation, and fibrosis and lowers the production of CCL20 in alcoholic hepatitis (AH) animal models [355]. On the contrary, inhibiting the activation of NLRP6 inflammasome may improve liver steatosis in mice [356]. The contradictory conclusions regarding the role of NLRP6 in HCC may be due to the different stages of the disease and the differences in experimental models and methods. Further studies are needed to define the role of NLRP6 in the development and spread of HCC and comprehend the extent to which NLRP6 switches from inhibiting tumor growth to promoting malignancy. Besides, NLRP6 functions as a tumor suppressor factor in gastric cancer (GC) [357] while promoting small cell lung cancer (SCLC) metastasis [307]. Even though there is low or no expression of NLRP6 in other organs except for the colon, liver, and stomach, it's also related to other organ diseases such as brain injury [358] and acute renal injury [359]. These suggest the potential role of NLRP6 in the carcinogenesis of these organs, and further studies are needed to expand the cognitive boundaries of NLRP6 research.

The role of AIM2 in inflammation-mediated carcinogenesis

As the best-characterized member of the AIM2-like receptors (ALRs), AIM2 contains the N-terminal PYD domain and one or two C-terminal HIN domains (hematopoietic, interferon-inducible, and nuclear localization). The multicomponent AIM2 inflammasome is formed when AIM2 recognizes dsDNA and recruits the adaptor protein ASC, which then activates caspase-1 [360]. AIM2 can be directly activated by transfection of dsDNA into the cytoplasm [361] and DNA derived from the gut microbiota or host-DNA released after intestinal injury [362]. While AIM2 activation is negatively regulated by several factors such as IFI16-β [363], IFN-inducible protein PYD-only protein 3 (POP3) [364], and the viral protein pUL83 released during human cytomegalovirus (HCMV) [365], herpes simplex virus-1 (HSV-1) tegument protein VP22 [366], hepatitis B e-antigen (HBeAg) [367], HCMV IE86 protein [368] and others. Besides, ubiquitinated TRIM11 promotes p62-dependent selective autophagy-induced AIM2 inflammasome degradation following DNA stimulation [369].

AIM2 has bidirectional roles in tumorigenesis in different types of cancer. In hepatic and colon cancer, AIM2 suppresses tumor growth [370], whereas in cutaneous squamous cell carcinoma, it promotes tumor growth [371]. AIM2 contains a site for microsatellite instability, which leads to gene mutations in CRC and inhibits its development [372, 373]. Additionally, it was demonstrated that AIM2 has a role in the pathophysiology of DNA damage caused by chemotherapy, suggesting that medications targeting AIM2 may offer therapeutic advantages during radiation therapy [362]. These indicate that suppressing the activity of AIM2 inflammasome could be investigated due to their role in carcinogenesis. During the past decade, several synthetic inhibitors of AIM2 such as suppressive oligodeoxynucleotides [364], pyrin-containing proteins, and antimicrobial cathelicidin peptides [374] have been discovered, and exploring their anti-tumor effect and underlying mechanisms are promising strategies for cancer prevention and treatment.

The role of inflammasome adaptor ASC in inflammation-mediated carcinogenesis

In human leukemia cells treated with chemotherapeutics drugs, ASC was first identified as a protein that aggregates (or "specks"), which was also known as PYCARD/Target of Methylation-induced Silencing-1 (TMS1). The ASC/TMS1 protein has a 22 kDa structure and comprises two domains: the C-terminal CARD domain and PYD domain [375]. Several immune and normal epithelial cells express ASC/TMS1, which localizes in the nucleus, redistributes in the cytoplasm during activation, and finally aggregates into specks [376].

ASC can be either increased in tumor cells and overexpressed in the myeloid compartment (mostly TAMs) within the tumor microenvironment, or downregulated in malignancies, primarily due to aberrant methylation. On one hand, it is a key adapter molecule of the inflammasome complex, which is responsible for mediating the release of inflammatory cytokines of IL-1β and IL-18, which were known to have tumor-promoting effects [377–379]. Besides, ASC also exhibits pro-tumor effects through other indirect pathways such as chronic inflammation, macrophage recruitment, IL-17 pathway activation, angiogenesis, and others [378]. On the other hand, ASC was downregulated in several types of cancer, and the tumor-suppressive effect of ASC was supported by the discovery that methylation silences its expression and prevents tumor cells from passing through apoptosis [380]. Besides, the regulatory effect of ASC on thymic stromal lymphopoietin (TSLP) secretion by cancer-associated fibroblasts (CAFs) contributes to improving the overall survival of pancreatic cancer patients [381]. ASC delays UV-induced skin tumorigenesis [382]. ASC inhibits lung cancer suppression via Bcl-2 and pSrc [383]. Restoring ASC expression makes colorectal cancer cells more susceptible to caspase-independent cell death caused by genotoxic stress [380]. In addition, ASC showed dual roles even in the same type of tumor. For example, ASC inhibits tumorigenesis in primary melanoma, while ASC promotes tumorigenesis in metastatic melanoma [314]; mice had fewer tumors when ASC was specifically deficient in myeloid cells, while mice had more tumors when ASC was specifically deficient in keratinocyte cells [384]. These opposing functions of ASC may be due to the tissue or cell-specific expression context, and dissecting the role of ASC in different cancer types and additional research on ASC and its upstream and downstream mediators may improve our comprehensive of molecular processes behind carcinogenesis and contribute to the ASC targeting strategies for cancer treatment and prevention.

Targeting components of the extracellular matrix for cancer chemoprevention

As a highly dynamic structure, the extracellular matrix (ECM) is present in all tissues and constantly undergoing controlled remodeling. ECM comprises large, insoluble proteins mainly formed of separate structural domains with highly conserved sequences and arrangements. These domains are glycosylated and often have sulfated glycosaminoglycan chains, resulting in negative charges [385]. This characteristic of ECM molecules gives them great potential to interact with other charged molecules, like growth factors and chemokines, to affect the accessibility or local concentration of these factors [386]. Since

collagen, the most abundant ECM component, was first identified and characterized in the 1930s.

In chronically inflamed tissues, the ECM fragments or ECM molecules are upregulated, and they're modulated by proteases, especially MMPs, and inflammatory cytokines such as TNF, IFNγ, and TGFβ generated by extravasating cells or activated tissue-resident cells. Recent research has found that immune cells can be stimulated by ECM components or fragments that are increased during inflammation, thus sustaining the inflammatory response. On the one hand, ECM can serve a structural role as a barrier or scaffold for cells that invade inflamed tissues. On the other hand, the biophysical characteristics and their biochemical makeup provide immune cells with specific signals that regulate proliferation, migration, apoptosis, adhesion, differentiation, and survival.

Aberrant ECM influences immune cell behavior, such as infiltration and activation, and plays a role in cancer metastasis. For example, activating the collagen receptor DDR1 can enhance macrophage infiltration in atherosclerotic plaques [387]. The size and density of collagen fibrils can influence the migration of immune cells [388]. Although immune cell infiltration is promoted, collagen type I hinders macrophages from effectively killing cancer cells by blocking their polarization and subsequent activation [389]. This highlights the complex characteristics of how ECM deregulation modulates the immune response. Furthermore, breast cancer cells with high levels of the hyaluronan receptor CD44 have a better survival rate compared to those with low CD44 levels [390]. This indicates that hyaluronan and possibly other components of the extracellular matrix support the survival of metastatic cancer cells.

Tenascin-C (TNC) is a glycoprotein that plays a significant role in the ECM and is notably expressed in pathological conditions, particularly in cancer and chronic inflammatory diseases. TNC activates TLR4, which in turn stimulates macrophages and fibroblasts to release pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α [391], and affects the recruitment of immune cells [392]. Higher TNC expression was observed in melanoma cells from advanced tumors and metastases, while early melanoma tumors and normal melanocytes displayed weak or absent TNC expression [393]. Tenascin-C is located in the bone endosteum and contributes to the development of prostate bone metastases [394]. TNC deficiency in human breast cancer cells significantly decreases metastasis to the lungs and bones in xenograft models [395].

Dysregulated ECM remodeling leads to many diseases, including cancer. As one of the major components of cancer, the ECM plays various crucial roles in signaling regulation, microenvironment modulation, and mechanical support. The ECM shows multifaceted effects in regulating multiple hallmarks, including angiogenesis, tumor progression, immune response, and cancer cell migration of cancer. Under specific circumstances, the ECM restrains malignant tumor progression [396]. However, the ECM also promotes tumor progression [389]. Collagen IV over-expression boosts cell survival of lung cancer [397]. The ECM also facilitates the metastasis of cancer cells [398]. The miR-29 over-expression inhibits metastasis by regulating gene expression in ECM remodeling in breast cancer [399]. This suggests that blocking the ECM molecules may be therapeutically beneficial for cancer prevention and treatment. The ECM components including tenascin C, endostatin, tumstatin, canstatin, arresten, and hexastatin also have pro- and anti-angiogenic functions. For example, tenascin C promotes cancer cell proliferation and induces angiogenesis [400]. Arresten suppresses the angiogenesis of HUVECs by blocking PI3K/Akt signaling pathway [401]. The ECM plays a vital role in regulating immune responses. For example, the ECM niche in the spleen promotes the differentiation and survival of marginal zone B cells to support antibody production [402]. Besides, matrikines regulate immune cell behaviors such as the interaction of immune cells with cancer cells [403], the recruitment and activation of immune cells [404], and more. Here, we will summarize the role of the ECM components including ECM proteins, ECM fragments, the proteases that cleave the ECM, the MMPs that degrade the ECM, and others, the underlying mechanisms are also illustrated. A deeper comprehension of the biological activities of the ECM will provide intriguing opportunities for therapeutic intervention of cancer. More details regarding the function of ECM proteins and fragments in cancer are provided in Table 8.

The chemo-preventive effects of FDA-approved anti-inflammatory drugs in cancer chemoprevention

Long-term users of aspirin or other NSAIDs had a decreased incidence of cancer, which offers encouraging opportunities for cancer chemoprevention. Aspirin can reduce the risk of tumor occurrence [405], prevent colorectal cancer [406], inhibit metastasis of melanoma and breast cancer [407], and more. Besides, steroidal anti-inflammatory drugs such as dexamethasone, suppress tumor growth of non-small cell lung cancer [408], enhance gynecologic cancer chemotherapy [409], and more. These FDA-approved anti-inflammation drugs have well-established safety profiles, making them potentially valuable tools for cancer chemoprevention. Clarifying the anti-tumor effects and underlying mechanisms of the

anti-inflammation drugs will provide novel options and targets for cancer prevention and treatment. Here, we will summarize the effects and underlying mechanisms of FDA-approved anti-inflammatory drugs, and the advantages and disadvantages of these drugs' application in cancer chemoprevention will be also be discussed.

The anti-tumor effect of non-steroidal anti-inflammatory drugs

The chemo-preventive effect of NSAIDs in cancer was proposed in 2002 [410]. Epidemiological studies have shown a consistent 40–50% reduction in the risk of developing CRC by taking NSAIDs [411]. The epidemiological evidence supporting the efficacy of aspirin for the prevention of CRC is substantial [412]. As a classic NSAID, the role of aspirin in cancer chemoprevention has been well-studied. For example, aspirin reduces the risk of breast cancer [413] and pancreatic cancer [414], reduces mortality in endometrial cancer patients [18] and colon cancer [415], inhibits tumor progression of HCC [22], and pancreatic cancer [416] and others. Except for aspirin, other NSAIDs like indomethacin, acetaminophen, ibuprofen, meloxicam, and others also exhibit anti-tumor effects in various cancers. For example, indomethacin inhibits cell proliferation and invasion in colorectal cancer [417] and breast cancer [418], induces apoptosis of colon cancer [419], and suppresses angiogenesis of colon cancer [420] and others. A comprehensive list of the anti-tumor properties of NSAIDs is shown in Table 9.

The anti-tumor effect of steroidal anti-inflammatory drugs

Unlike NSAIDs, the anti-tumor effect of steroidal anti-inflammatory drugs is controversial. As a commonly used class of steroid anti-inflammatory drugs, on the one side, glucocorticoids (GCs) such as dexamethasone as an adjunctive treatment strategy for lymphoma in the clinic, they can reduce tumor size and improve patient's tolerance to chemotherapy [421]. About other solid tumors, GCs reduce treatment-related toxicity after surgery or radiotherapy in brain tumors [422] and reduce the risk of lung cancer [423]. On the other side, GCs favor pancreatic cancer progression [424], promote metastasis of breast cancer [425], induce resistance in prostate cancer [426], and others. A comprehensive list of the anti-tumor properties of steroidal anti-inflammatory drugs is shown in Table 10.

The outcome of clinical application of anti-inflammation drugs in cancer chemoprevention

Although cytokines are important regulators of both innate and adaptive anticancer immunity, their extreme toxicity, pleiotropy, and poor drug-like qualities make them challenging to utilize as treatments [427, 428]. Developments in immune checkpoint blocking, protein engineering, and receptor biology and biochemistry drive rekindled interest in developing cytokine therapies [429, 430]. Clinical prospects have emerged from engineering strategies targeted at disentangling cytokines' pro- and anti-tumorigenic characteristics, which have shown encouraging preclinical outcomes [431]. Cytokines are the first effective cancer immunotherapy to provide humans with long-lasting anti-tumor immunity. Recombinant interferon (IFNα2b) and IL-2 are approved cytokine therapeutics for cancer clinical treatment [432].

Other cytokines such as IL-4, IL-6, IL-7, IL-9, IL-10, IL-12, IL-15, IL-18, IL-21, IL-2R, IL-4R, IL-5R, IFNα, IFNβ, IFNγ, TNFα and more have also been applied in clinical trials. For example, in a phase I/II study (NCT00000769), IL-4 at the dose of 1.5 microg/kg/day is poorly tolerated in patients with advanced AIDS-related Kaposi's sarcoma (KS) and didn't show an effective role in KS [433]. The anti-tumor effect of IL-4 in patients is ambiguous, and more clinical trials are recruiting or undergoing in other cancers such as recurrent malignant astrocytoma (NCT00003842) and ER + breast cancer (NCT05967884). In phase II clinical trial (NCT00433446), a monoclonal antibody against IL-6 (CNTO328, also called siltuximab) was applied to pretreated patients with castration-resistant prostate cancer, CNTO328 resulted in a prostate-specific antigen (PSA) response rate of 3.8% and a response evaluation criteria in solid tumors (RECIST) stable disease rate of 23% [434]. In a phase 2 randomized study (NCT00911859), CNTO328 at 8.3 and 11 mg/kg doses were well tolerated, while CNTO328 didn't significantly improve the complete response (CR) and long-term outcomes in patients of multiple myeloma [435].

Besides, several clinical trials have examined the combination of anti-inflammatory agents and ICIs. For instance, a phase 2 trial study (NCT03631407) investigated the combination of vicriviroc (a CCL5 antagonist) administered at doses of 150 or 250 mg alongside pembrolizumab at 200 mg. This combination demonstrated limited antitumor activity in patients with advanced or metastatic microsatellite stable (MSS) or mismatch repair-deficient (dMMR) CRC. However, the toxicity associated with this combination treatment was manageable [436]. In another phase 2 trial study (NCT03396952), the efficacy of high-dose aspirin in combination with ICIs is similar to that of ICI alone [437]. In a phase Ib/II trial study (NCT02807844), the combination of lacnotuzumab (CSF-1 inhibitor) and spartalizumab (PD-1 inhibitor) did not meet the gating criteria for efficacy [438]. Numerous clinical trials are currently recruiting participants or ongoing. For

Table 8 The role and mechanisms of extracellular matrix (ECM) and related proteins in cancer

ECM proteins	Cancer types	Promote/inhibit	Mechanisms	References
Collagen	Non-small cell lung cancer	Promote	Regulates overall survival and cell differentiation	Fang, S et al., 2019
	Lung cancer	Promote	Collagen XXIII is highly expressed in lung cancer	Spivey, K et al., 2010
	Esophageal squamous cell carcinoma	Promote	Regulates overall survival and cell differentiation	Fang, S et al., 2019
			Drives invasion through a YAP-centered transduction loop	Khalil, A et al., 2024
	Breast cancer	Promote	Promotes tumor progression and metastasis	Xiong, G et al., 2014
	Hepatocellular carcinoma	Promote	Promotes cell proliferation, adhesion, invasion, metastasis and angiogenesis	Zhang, J et al., 2022
	Lung cancer	Promote	Promotes metastasis, invasion and anoikis resistance	Zhang, H et al., 2018;
			Promotes cell growth in a three- dimensional culture system	Li, J et al., 2014
	Pancreatic cancer	Promote	Stimulates proliferation, migration, and inhibits apoptosis via autocrine loop	Ohlund, D et al., 2013;
			Promotes the malignant phenotype of pancreatic cancer cells	Armstrong, T et al., 2004
			Promotes metastasis by activating c-Jun NH2-terminal kinase 1 and up-regulating N-cadherin expression	Shintani, Y et al., 2006
	Prostate cancer	Promote	Lactate supports ECM production to sustain metastatic behavior	Ippolito, L et al., 2024
			Correlates with recurrence and distant metastasis	Banyard, J et al., 2007
	Head and neck squa mous cell carcinoma	Promote	Promotes cancer cell invasion	Chen, Yin-Q et al., 2019
	Ovarian cancer	Promote	Influences proliferation	Sarwar, M et al., 2022
			Increases proliferation	Fogg, K et al., 2020
	Liver cancer	Promote	Promotes inflammatory response and proliferation	Shen, X et al., 2024
	Gastric cancer	Promote	Promotes fibroblast collagen synthesis	NAITO, Y et al., 1984
	Squamous cell carcinoma, prostate cancer, colorectal cancer, lung cancer	Promote	Collagen remodeling along cancer progression and provides a novel opportunity for cancer diagnosis and treatment	Song, K et al., 2022
	Non-small cell lung cancer	Inhibit	Inhibits CAF-mediated collagen remodeling, cell migration and invasion	Zeltz, C et al., 2022
	Colorectal cancer	Inhibit	Inhibits cell differentiation and promotes a stem cell-like phenotype	Kirkland, S et al., 2009
	Breast cancer	Inhibit	Regulates adhesion and migration after the collagen is mineralized	Choi, S et al., 2019
Proteoglycans	Brain cancer	Promote	Modulates migration, cell adhesion, tumor invasion, and neurite outgrowth	Yan, Z et al., 2020
			Promotes receptor tyrosine kinase signaling and progression	Wade, A et al., 2013
	Liver cancer	Promote	Interacts with many growth factors and relates to tumor invasion	Baghy, K et al., 2016
	Breast cancer	Promote	Restores FGF-2 mitogenic activity	Delehedde, M et al., 1996
	Esophageal squamous cell carcinoma	Promote	Regulates cell survival, invasion and metastasis	Li J et al., 2019
	Pancreatic cancer	Promote	Stimulates cell growth	Zvibel, I et al., 2001

Table 8 (continued)

ECM proteins	Cancer types	Promote/inhibit	Mechanisms	References
testican-1	Colorectal cancer	Promote	Promotes cell proliferation and invasion through PI3K/AKT pathway	Zhao P et.al, 2016
testican-1	Gastric cancer	Promote	Induces EMT	Kim HP et.al, 2014
lumican	Pancreatic cancer	Inhibit	High expression correlates with favorable survival after surgery	Li X et.al, 2014
	Breast, hepatocellular, lung and prostate cancer , melanoma and multiple myeloma	Inhibit	Inhibits heparanase and growth factor-growth factor receptor active complex formation, sequestrates growth factors in ECM, inhibits cell proliferation, metastasis and angiogenesis	Koo, C et al., 2008
syndecan-1, endostatin, decorin	Esophageal squamous cell carcinoma	Inhibit	Regulates cell survival, invasion,metastasis and angiogenesis	Ji C et.al, 2015
Glycoproteins	Colorectal cancer	Promote	Decreases the sensitivity of doxorubicin	Hotta, T et al., 1999
	Breast cancer	Promote	Relates with doxorubicin and vincristine resistacne	SANFILIPPO, O et al., 1991
	NSCLC	Promote	Associates with both performance status and lymph node metastasis	Yildirim, A et al., 2007
	Bladder cancer	Promote	Promotes cell proliferation, migration, and invasion and relates to the poor differentiation and recurrence	Zhang, Y et al., 2017
	Colorectal cancer	Promote	Associates with clinic pathologic features and shorter overall survival	Wei, F et al., 2019
	Breast cancer	Inhibit	Modulates multi-drug resistance via inhibiting P-glycoprotein efflux	Tripathi, A et al., 2016
	Breast cancer	Inhibit	Suppresses cell proliferation and migration	Pan, P et al., 2012
	Erythroleukemia, breast and epiderm oid cancer	Inhibit	Inhibits p-glycoprotein, reverses drug resistance and restores intracellular drug accumulation	Pan Q, et al., 2005
Endostatin	Ovarian cancer	Inhibit	Inhibits the growth of ovarian cancer cell by inducing apoptosis	Liu M et al., 2007
			Inhibits angiogenesis by regulating bcl-2/bax and induces apoptosis	Liu M et al., 2006
	Non-small cell lung cancer	Inhibit	Inhibits cell proliferation by inducing HMGB1	Meng F et al., 2019
	Lung cancer		Inhibits tumor growth when combined with PD-1 inhibitor	Fu S et al., 2023
	Colon cancer	Inhibit	Inhibits growth and metastasis when combined with SU6668 and 5-FU	Du Z et al., 2003
			Inhibits the progress of chemically induced colon tumor	Li W et al., 2005
	Bladder cancer	Inhibit	Inhibits tumor growth by regulating MMP, VEGF and inducing apoptosis	Du Z et al., 2003
			Inhibits angiogenesis	Wu T et al., 2020
	Liver cancer	Inhibit	Inhibits tumor growth when combined with IL12	Wang X et al., 2005
	Breast cancer	Inhibit	Inhibits tumor growth by inhibiting angiogenesis and increasing apoptosis	Liby K et al., 2003
	Lung cancer	Inhibit	Inhibits growth and induces apoptosis by down-regulating Bcl-2 expression	Cheng X et al., 2008
			Inhibits proliferation and angiogenesis, and suppresses tumor growth	Luo X et al., 2014
	Oral squamous cell carcinoma	Inhibit	Delays tumor growth and lymphatic metastasis	Chung I et al., 2008
Tumstatin	Breast cancer	Inhibit	Inhibits cell growth of breast cancer	Zhong Q et al., 2011
	Ovarian cancer	Inhibit	Promotes apoptosis	Wang M et al., 2011

Table 8 (continued)

ECM proteins	Cancer types	Promote/inhibit	Mechanisms	References
			Inhibits tumor growth by reducing angiogenesis and angiogenic factors	Zhang G et al., 2008
	Laryngocarcinoma	Inhibit	Induces apoptosis through mitochondrial apoptosis pathway	Wang L et al., 2016
	Bladder cancer	Inhibit	Inhibits cell proliferation and induces apoptosis	Li Z et al., 2011
	Liver cancer	Inhibit	Inhibits cell proliferation and induces apoptosis through PTEN/PI3K/Akt signaling when combined with Ginsenoside Rg3	Yi T et al., 2020
	Cervical cancer	Inhibit	Inhibits tumor growth by inhibiting angiogenesis and angiogenic factors	Zhang G et al., 2007
	Prostate cancer	Inhibit	Inhibits cell proliferation and tumor growth through apoptosis and anti-angiogenesis effects	Zhang X et al., 2011
	Hypervascular hepatocellular carcinoma	Inhibit	Inhibits vascular endothelial cells	Li C et al., 2017
	Glioma	Inhibit	Inhibits proliferation and migration by down-regulating stem cell maintenance factors	Yu W et al., 2021
	Colon cancer, Lewis lung cancer	Inhibit	Inhibits tumor growth by inhibiting angiogenesis and enhancing apoptosis when being combined with gemcitabine	Yao B et al., 2005
	Non-small cell lung cancer	Inhibit	Enhances the sensitivity of cells to cisplatin; promotes apoptosis and inhibits proliferation by inactivating Akt and ERK pathways	Wang W et al., 2010
	Gastric cancer	Inhibit	Inhibits proliferation, induces apoptosis and inhibits tumor growth	Li Y et al., 2009
			Inhibits proliferation and metastasis by inducing apoptosis through anoikis and PTEN/Akt pathway	He Y et al., 2010
	Hepatocellular carc Inoma	Inhibit	Inhibits tumor growth by inhibiting angiogenesis	Goto T et al., 2008
	Non-small cell lung cancer	Inhibit	Induces apoptosis, inhibits proliferation, enhances the sensitivity of cells to cisplatin by inactivating AKT pathway	Wang W et al., 2015
	Melanoma	Inhibit	Inhibits tumor progression by triggering intracellular transduction pathway	Sylvie B et al., 2004
Canstatin	Colon cancer	Inhibit	Delays tumor growth without obvious adverse reactions	Wang L et al., 2009
	Lewis lung cancer	Inhibit	Inhibits metastasis, angiogenesis and tumor growth by mediating the expression of somatostatin	Lu W et al., 2011
	Gastric cancer	Inhibit	Induces apoptosis through the mitochondrial apoptotic pathway	Xing Y et al., 2019
	Pancreatic cancer	Inhibit	Delays tumor growth by inhibiting angiogenesis	He X et al., 2006
	Glioma	Inhibit	Inhibits tumor growth by inhibiting the formation of VM-like structure	Ma Y et al., 2021
	Liver cancer	Inhibit	Inhibits tumor growth and angiogenesis by reducing the expression of Flk-1	Qi M et al., 2009
	Primary oral squamous cell carcinoma	Inhibit	Inhibits tumor growth	Hwang-Bo J et al., 2010
	Esophageal cancer	Inhibit	Inhibits angiogenesis and tumor growth by down-regulating Flk-1	Zheng X et al., 2009

Table 8 (continued)

ECM proteins	Cancer types	Promote/inhibit	Mechanisms	References
	Hepatocellular carcinoma	Inhibit	Inhibits proliferation, migration and adhesion,promotes apoptosis and inhibits tumor growth when combined with arsenic trioxide	Zhang F et al., 2020
	Pancreatic cancer	Inhibit	Decreases microvessel density and increases apoptosis; has synergistic effects of oncolytic therapy and antiangiogenic therapy in a CRAd-Cans form	He X et al., 2009
	Lewis lung cancer	Inhibit	Inhibits tumor growth and metastasis	Lu W et al., 2006
	Ovarian cancer	Inhibit	Delays tumor growth by inhibiting angiogenesis	Zhu B et al., 2009
Arresten	Colon cancer	Inhibit	Inhibits metastasis by suppressing angiogenesis	Long M et al., 2008
	Gastric adenocarcinoma	Inhibit	Inhibits the proliferation of tumor vascular endothelial cells	Lu C et al., 2005
	Lung cancer	Inhibit	Treats cancer in a CRAd-arresten-TRAIL form	Li S et al., 2015
	Squamous cell carcinoma	Inhibit	Inhibits invasion by suppressing collagen-derived angiogenesis	Mari A et al., 2012
Hexastatin	Melanoma and lung cancer	Inhibit	Inhibits tumor growth and suppresses cell proliferation of melanoma	Wen L et al., 2009
Versican	Lymph node negative breast cancer	Promote	Promotes local invasion and metastasis by tumor remodeling of extracellular matrix through increasing versican deposition	Ricciardelli C et al., 2002
	Breast cancer	Promote	Promotes tumor progression and metastasis	dos Reis D et al., 2019
			Enhances the self-renewal of breast cancer through EGFR/AKT/GSK-3β (S9P) signaling, and endows it with resistance to chemotherapy drugs	Du W et al., 2013
			Enhances bone metastasis by promoting migration, invasion and survival of cells	Du W et al., 2023
			Promotes invasion, enhances cell viability, proliferation, migration and local tumor growth, enhances vascular endothelial proliferation, migration and angiogenesis	Yee A et al., 2007
			Promotes invasion and metastasis through EGFR signaling	Du W et al., 2010
	Cervical cancer	Promote	Enhances local invasion and decreases CD8 positive T cells	Gorter A et al., 2010
	Ovarian cancer	Promote	Promotes tumor growth	Voutilainen K et al., 2003
			Increases metastasis by obtaining matrix around HA/versican cells	Miranda P et al., 2011
			Changes tumor microenvironment and promotes tumor cancer invasion	Yeung, T et al., 2011
	Prostatic cancer	Promote	Promotes the metastasis and spread of clinical prostate cancer	Ricciardelli C et al., 2007
	Hepatocellular carcinoma	Promote	Promotes tumor development by regulating miRNA activity	Fang L et al., 2013
			Promotes proliferation and metastasis by activating EGFR-PI3K-AKT pathway	Zhang Y et al., 2020
	Gastric cancer	Promote	Promotes the progress of gastric cancer caused by IL-11	Zhang Z et al., 2012

Table 8 (continued)

ECM proteins	Cancer types	Promote/inhibit	Mechanisms	References
			Promotes proliferation, migration and invasion by overexpressing VCAN	Zhai L et al., 2012
	Skin cancer	Promote	Promotes tumor development	Kunisada M et al., 2012
	Melanoma	Promote	Promotes proliferation and migration, inhibits adhesion to type I collagen, laminin and fibronectin	Hernandez D et al., 2011
		Inhibit	Reduces tumorigenecity	Miquel-Serra L et al., 2005
Tenascin	Prostate cancer	Promote	Is up-regulated in cancer tissue and relates to glucose uptake, lactic acid production and glycolytic enzyme expression	Qian Y et al., 2022
			Promotes tumor progression, enhances adhesion and colony formation through integrin α 9 β 1	Martin R et al., 2017
	Breast cancer	Promote	Supports the tumor initiation ability through transfer niche	Hassan F et al., 2016
			Up-regulates the expression of growth-related genes, increases cell migration, mitosis and growth factor-dependent endothelial cell germination and elongation	Jones P et al., 2000
			Promotes tumor progress by immobilizing infiltrating T lymphocytes through CXCL12	Jones F et al., 2000
			Contributes to the invasion behavior of tumor cells	Scherberich A et al., 2005
			Promotes therapy-resistant metastasis	Insua-Rodriguez J et al., 2018
			Increases invasion by promoting Tenascin C inclusion in extracellular vesicles	Campos A et al., 2023
			Mediates lung metastasis	Taraseviciute A et al., 2006
			Promotes invasion and proliferation	Alcock R et al., 2005
			Promotes cell proliferation	Swierczynski S et al., 2011
			Promotes invasion and proliferation	Alcock R et al., 2005
	Colon cancer	Promote	Promotes tumorigenesis by activating matrix fibroblasts based on 1- integrin activation	Fujita M et al., 2019
			Promotes invasion through EMT regulation and acts as a specific new indicator	Takahashi Y et al., 2013
			Promotes EMT-like changes and proliferation and leads to poor prognosis	Yang Z et al., 2018
			Drives tumor progression and participates in CSC characteristics through HH signaling	Yang Z et al., 2020
	Gastric cancer	Promote	Inhibits the angiogenesis simulation by suppressing ERK-triggered EMT	Xing K et al., 2021
	Oral squamous cell carcinoma	Promote	Promotes metastasis by enhancing the immunosuppressive lymphatic matrix through CCL21/CCR7 signaling	Caroline S et al., 2020
	Triple negative breast cancer	Promote	Promotes the resistance to T cell-mediated cytotoxicity by blocking the degradation of Tenin C	Li Z et al., 2020
	Endometrium cancer	Promote	Promotes tumor progress by immobilizing infiltrating T lymphocytes through CXCL12	Murdamoothoo D et al., 1996
	Ovarian cancer	Promote	Promotes patients' survival and supports spheroids formation and tumor progression	Roders A et al., 2024

Table 8 (continued)

ECM proteins	Cancer types	Promote/inhibit	Mechanisms	References
	Glioblastoma	Promote	Promotes invasion of glioblastoma	Hirata E et al., 2009
			Induces excessive proliferation of glioblastoma cells	Fujita M et al., 2019
	Laryngocarcinoma	Promote	Promotes proliferation and migration in an autocrine way	Toshimichi Y et al., 1999
	Osteosarcoma	Promote	Promotes distant metastasis of osteosarcoma	Tanaka M et al., 2000
	Pancreatic ductal adenocarcinoma	Promote	Hedgehog signaling stimulates Tenascin C to promote invasion through Annexin A2	Foley K et al., 2017
	Squamous cell carcinoma of head and neck	Promote	Migration of cancer cells is dependent on tenascin-C expression	Thomas C et al., 2016
	Esophageal squamous cell carcinoma	Promote	Enhances the dry-like characteristics of cancer and promotes EMT-like changes through Akt/HIF1α axis	Yang Z et al., 2019
	Neuroendocrine tumor	Promote	Down-regulation of DKK1 is an important mechanism for TNC to enhance tumor progression by providing tumor microenvironment that promotes angiogenesis	Falk S et al., 2014
	Pancreatic cancer	Promote	Suppresses apoptosis through activation of ERK/NF-κB pathway	Shi M et al., 2015
			Promotes tumor progress	Chen J et al., 2009
			Promotes the diffusion and metastasis by affecting the proliferation, migration and adhesion	Berchtold S et al., 2011
	Bladder cancer	Promote	Mediates malignant behavior through syndecan-4 and NF-κB signaling	Guan Z et al., 2022
Matrikines	Melanoma	Promote	Up-regulates migration and promotes chemotaxis, mitosis and metastasis	Tran K et al.,2005

instance, siltuximab, an IL-6 inhibitor, is being tested to prevent severe irAEs during the rechallenge of ICIs in patients with advanced cancer (NCT06470971). Additionally, drugs used in chemokine modulation therapy, such as celecoxib, recombinant interferon alfa-2b, and rintatolimod, have been combined with pembrolizumab in the treatment of metastatic triple-negative breast cancer (NCT03599453). Further investigation is needed to fully evaluate the clinical utility and identify the patient subgroups that are most likely to benefit from the combination of anti-inflammatory agents with ICIs. More information about the clinical trials of these cytokines or their antibody or their derivatives is summarized in Table 11.

The application of artificial intelligence (AI) in inflammation-related cancer for cancer chemoprevention

In recent years, AI has gained significant popularity. With the advancement of deep learning and the availability of extensive imaging databases, AI-based computer-aided diagnostic (CAD) systems—which incorporate machine learning (ML), deep learning (DL), and artificial neural networks (ANN)—are increasingly being used to standardize and improve the evaluation of medical imaging.

AI models have been used to identify inflammatory and immune cells in cancer tissues. For instance, deep learning techniques have been employed to detect tumor-infiltrating lymphocytes (TILs), which could serve as a potential prognostic marker for testicular germ cell tumors [439]. Deep convolutional neural networks based on supervised learning have been used to quantify the biomarkers of immune cells in the lung cancer microenvironment [440]. TILs densities and spatial structures can be analyzed using deep learning on pathology images, providing insights into the tumor-immune microenvironment [441]. Deep learning supervised by antibodies was utilized to quantify tumor-infiltrating immune cells, an emerging prognostic biomarker in breast cancer samples [442]. AI-based pathology served as a biomarker for progression-free survival in patients treated with atezolizumab and bevacizumab for hepatocellular carcinoma [443]. Identifying PLA2G1B, a gene crucial for lipid metabolism and inflammation, suggests it may serve as a

Table 9 Mechanisms underlying anti-tumor properties of non-steroidal anti-inflammatory drugs

Drugs	Cancer types	Mechanisms	References
Salicylates			
Dexamethasone	Colon cancer	Inhibits AKT and ERK phosphorylation, decreases CYR61 expression and blocks TGF-β1-induced migration	Han, S et al., 2016
		Induces apoptosis through TGF-β1/Smad2 pathway	Du, C et al., 2020
	Prostate cancer	Decreases ERK1/2 activity and cyclin D1 expression	Gao, Q et al., 2006
Aspirin	Lung cancer	Blockades growth by suppressing PD-L1 through regulating the transcriptional coactivator of TAZ	Zhang, Y et al., 2020
	Esophageal cancer	Induces apoptosis by inhibiting COX-2 enzymatic activity	Du, C et al., 2020
	Pancreatic cancer	Decreases the expression of cyclin D1 and inactivates GSK-3/3 but not the p38 MAPK pathway	Nakabayashi, R et al., 2022
	Bladder cancer	Identifies GSK3B, CDC20, TPX2, AURKA and CCNE1 as potential therapeutic targets	Li, X et al., 2022
	Ovarian cancer	Inhibits cell viability by blocking phosphorylation of AKTand ERK activated by EGF	Cho, M et al., 2013
	Cervical cancer	Induces apoptosis and inhibits proliferation via suppressing ErbB2 downstream cell survival signaling pathways	Sun, Z et al., 2023;
		Induces apoptosis and inhibits proliferation	Wang, B et al., 2014
	Endometrial cancer	Improves survival outcomes of patients	Matsuo, K et al., 2016
Lysine Acetylsalicylate	Colon cancer	Inhibits cell proliferation	Wang, B et al., 2007
Acetic Acid			
Indomethacin	Colon cancer	Down-regulates CDK2 and CDK4 and up-regulates p21WAF1/PIC1	Xu, M et al., 2005
		Regulates the focal complexes formation and attenuates EGF-mediated Ca2 + influx	Guo, Y et al., 2016
	Gastric cancer	Induces apoptosis through AKT/GSK3β/NAG −1 pathway	Pang, R et al., 2011
	Endometrial cancer	Reduces platelet aggregation and TxB2 level when combined with leukinferon	Mistakopulo, N et al.,1992
	Laryngeal cancer	Inhibits cell proliferation and viability and decreases LPS- induced cell iNOS activity	Zhang, L et al., 2008
	Lung cancer	Inhibits tumor growth and promotes apoptosis when combined with cisplatin	Gao, J et al., 2013
Diclofenac	Colon cancer	Inhibits PI3K/AKT axis through dephosphorylating PTEN, PDK, AKT	Arisan, E et al., 2018
		Promotes apoptosis	Arisan, E et al., 2018
	Breast cancer	Enhances the anti-proliferative and apoptotic effects when combined with diclofenac, piperine, and D-limonene than each individually used	Sankar, S et al., 2023
	Pancreatic cancer	Blocks cancer cell proliferation	Choi, S et al., 2022

Table 9 (continued)

Drugs	Cancer types	Mechanisms	References
Propionic Acid			
Ibuprofen	Colon, breast, cervical, gastric, lung cancer, and head and neck cancer	Reduces HDACs and histone demethylase (KDM6A/B) expression, and suppresses gene expression via a COX2-dependent way	Shen, W et al., 2020
	Colon cancer	Suppresses nuclear translocation of β-catenin	Ouyang, N et al., 2013
		Induces apoptosis when combined with TRAIL	Todo, M et al., 2013
		Reverse the effect of ADMA in vitro and in vivo by blocking COX −2 and providing an arginine source	Ahmetaj-Shala, B et al., 2017
	Non-small cell lung cancer. breast cancer	Inhibits cell proliferation and metastasis by decreasing survivin expression level and increasing E-cadherin expression level	Zhu, L et al., 2015
	Prostate cancer	Induces apoptosis and oxidative stress via mediating pro-apoptotic signaling by regulating ceramide synthesis when combined with EGCG	Kim, M et al., 2007;
		Induces apoptosis	Andrews, J et al., 2002
	Lung cancer	Enhances sensitivity to cisplatin by enhancing apoptosis at several stages of the mitochondrial cascade	Endo, H et al., 2014
	Liver cancer	Regulates β-catenin signaling and downstream target gene transcription	Ma, J et al., 2009
Ketoprofen	Breast cancer	Induces apoptosis through intrinsic pathway and diminishes the phosphorylation of JAK2 and STAT	Noori, S et al., 2021
		Induces apoptosis and inhibits autophagy through the extrinsic apoptotic pathway and inhibition of the JAK/STAT signaling	Patra, I et al., 2023
		Inhibits the migration and invasion through PI3K/AKT/mTOR signaling	Nan, Z et al., 2017
	Gastric cancer	Inhibits cell proliferation	Akrami, H et al., 2018
		Enhances anti-proliferative effects on cells rich in progesterone receptors	Saha, D et al., 2001
	Colon cancer	Inhibits proliferation through prostaglandin H synthase and prostaglandin production	Sánchez, T et al.,1999
		Induces apoptosis through inhibition of PUM1	Gor, R et al., 2023
	Colon cancer and melanoma	Exhibits high cytostatic activity	Buzharevski, A et al., 2019
	Leukemia and Ovarian Cancer	Diminishes cell viability through cAMP/PKA signaling through inhibiting PDE1 and CaM	Afshari, H et al., 2023
	Colon and cervix cancer	Inhibits cell proliferation through transcription factor NF-κB	Damnjanovic, I et al., 2015
Loxoprofen sodium	Lung cancer	Inhibits tumor growth, while didn't affect cell proliferation and viability, decreases intratumoral vessel density, suppresses both intratumoral and systemic VEGF protein and inhibits tubular formation by suppressing VEGF; decreases the plasma VEGF level in patients	Kanda, A et al., 2003

Table 9 (continued)

Drugs	Cancer types	Mechanisms	References
Naproxen	Prostate and Breast cancer	Shows high anticancer activity, but less toxic against healthy cells	Pedro-Hernandez, L et al., 2022
	Bladder cancer	Inhibits the COX-2 enzyme	Han, M et al., 2022
		Induces apoptosis and inhibits AKT phosphorylation	Kim, M et al., 2014
	Bladder, colon cancer	Prolongs tumor latency and inhibits tumor growth	Grubbs, C et al., 2009
	Colon cancer	Shows chemo-preventive activity partly due to the inhibition of the transcriptional activation of TCF4	Pedro-Hernandez, L et al., 2022
	Liver cancer	Induces apoptosis and cell arrest in the G2/M phase	Lavasani, R et al., 2023
Phospho-naproxen (P-N)	Colon cancer	Inhibits NF-κB activity in a concentration-dependent manner	Patel, L et al., 2023
Oxicam			
Meloxicam	Bladder cancer	Increases cytotoxicity of sunitinib malate through DNA damage	Arantes-Rodrigues, R et al., 2013
	Gastric cancer	Inhibits proliferation through the down-regulation of COX-2 expression	Li, J et al., 2009
	Liver cancer	Inhibits cell proliferation, reduces microvessel density and up-regulates the expression of Bax when combined with anti-angiogenic therapy	Jiang, X et al., 2010
	Colon cancer	Inhibits proliferation and migration by up-regulating the expression of PTEN	Zhou, M et al., 2016
	Prostate cancer	Prolongs tumor latency and inhibits tumor growth	Montejo, C et al., 2010
	Lung and colon cancer	Increases the intracellular accumulation of doxorubicin and enhances doxorubicin-induced cytotoxicity by inhibiting MRP1 and MRP4	Chen, S et al., 2016
	Colon adenocarcinoma cancer	Meloxicam-loaded NPs shows cytotoxic effects on cells	Sengel-Turk, C et al., 2012
	Liver cancer	Inhibits tumor progression and enhances the sensitivity of immuno-therapy via the microRNA-200/PD-L1 pathway	Montejo, C et al., 2010
Piroxicam	Prostate cancer	Shows cytotoxic effects and induces apoptosis	Kisla, C et al., 2023
	Breast cancer	Kills cells and induces apoptosis	Peng, X et al., 2012
	Oral cancer	Selectively inhibits cell growth via regulating the S phase of the cell cycle	Ding, HM et al., 2003
Fenamic Acid			
Mefenamic acid	Colon cancer and breast cancer	Shows anticancer activity against cancer cells	Castillo-Rodriguez, I et al., 2023
	Prostate cancer	Prolongs tumor latency and inhibits tumor growth	Melnikov, V et al., 2021
	Lung cancer	Overcomes drug resistance by controlling biological function of AKR1C	Shiiba, M et al., 2017
	Liver cancer	Blocks PARP-1 cleavage activity and protects against MEF-induced apoptotic cell death	Woo, D et al., 2004

Table 9 (continued)

Drugs	Cancer types	Mechanisms	References
Aryl Acetic Acid			
Sulindac	Colon cancer	Increases the nuclear level of activated aryl hydrocarbon receptor and mediates CYP expression	Ciolino, H et al., 2008
		Prolongs tumor latency and inhibits tumor growth	Ohishi, T et.al., 2002
		Induces apoptosis	Shi, J et al., 2009
		Down-regulates Sp proteins by up-regulating the Sp-repressor ZBTB10	Li, X et al., 2016
		Decrease Fas Ligand expression and induces apoptosis of lymphocyte	Wu, Z et al., 2005
		Negatively regulates the function of VDAC1 and VDAC2	Aono, Y et al., 2018
		Induces apoptosis and inhibits the Wnt/β-catenin signaling	Tai, W et al., 2014
	Pharyngeal cancer	Increases VEGF-R2 and decreases ADAMTS1 levels	Agdas, F et al., 2021
	Lung cancer	Augments apoptotic activity and intracellular ROS production when combined with simvastatin	Kim, Y et al., 2015
	Liver, colon and breast cancer	Suppresses β-catenin signaling	Han, A et al., 2008
	Sinonasal cancer	Prolongs tumor latency and inhibits tumor growth	Kim, C et al., 2005
	Liver cancer	Inhibits cell proliferation	Deng, X et al., 2015
	Gastric Cancer	Suppresses proliferation, induces apoptosis and reduces angiogenesis	Wang, X et al., 2008
Formic Acid			
Meclofenamic acid	Prostate cancer	Inhibits tumor aggression, increases fibrosis, reduces cell proliferation and tumor vascularity	Delgado-Enciso, I et al., 2015
		Attenuates insulin-like growth factor 1-induced Akt activation when combined with simvastatin	Sekine, Y et al., 2018
Non-acid			
Nimesulide	Gastric cancer	Inhibits the activation of COX-2 and influences cell cycle	Xu, M et al., 2003
		Induces apoptosis	Zhang, Y et al., 2010
		Enhances gammadelta T cell-mediated killing effect	Liu, J et al., 2010
		Down-regulates the protein level of P-STAT3, CyclinD1 and Bcl-2	Chen, M et al., 2008
		Inhibits cell growth and induces apoptosis by enhancing Bax-to-Bcl-2 ratio and decreases COX-2 mRNA level	Zhang, L et al., 2005
		Blocks the activation of protein kinase B	Hu, G et al., 2004

Table 9 (continued)

Drugs	Cancer types	Mechanisms	References
		Induces apoptosis by up-regulating c-myc expression, down-regulating Bcl-2 expression and activating caspase-3	Song, J et al., 2002
	Liver cancer	Exhibits lethal effect when combined with mDRA-6	Liu, Y et al., 2008
	Colon cancer	Blocks cell cycle progression and down-regulates the release of VEGF	Fei, S et al., 2006
		Inhibits COX-2 activity and PGE2 synthesis and blocks the progression of cell cycle	Chen, G et al., 2005
		Inhibits cell growth which overexpressing COX-2 protein, and up-regulates the expression of E-cadherin	Liu, W et al., 2004
	Breast cancer	Reverses multi-drug resistance by down-regulating P-170 and GST-pi expression	Guo, Y et al., 2008
		Inhibits IFN-γ-induced PD-L1 surface expression	Liang, M et al., 2009
		Enhances chemotherapy sensitivity and stimulates apoptosis	Tian, B et al., 2010
	Small cell lung cancer cell	Inhibits cell proliferation	Liu, Y et al., 2006
	Endometrial cancer	Induces apoptosis by activating caspase-3	Ozalp, SS et al., 2012
	Ladder cancer	Inhibits the growth of T24 cell	Wang, Q et al., 2007
	Pancreatic cancer	Enhances TRAIL-induced apoptosis by promoting clustering of DR5	Vunnam, N et al., 2023
		Induces apoptosis and inhibits cell growth by enhancing PTEN expression level	Chu, M et al., 2018
	Breast and ovarian cancer	Induces apoptosis	Jaragh, A et al., 2022
	Head and neck cancer	Inhibits the expression of Ets-1 and Ets-2	Lamm, W et al., 2005
	Esophageal cancer	Inhibits cell proliferation and VEGF expression when combined with 5-FU	Li, M et al., 2010
	Colorectal cancer	Improves selectivity through HA/CD44 receptor interactions	Jian, Y et al., 2017
Nabumetone	Colon cancer	Induces glycogen synthase kinase-3β	Roy, H et.al., 1999
	Intestinal tumorigenesis	Induces apoptosis and down-regulates Bcl-2	Roy, H et al., 2001
Etoricoxib			
Celecoxib	Pancreatic cancer	Attenuates invasion and migration	Gu, Z et al., 2015
	Breast cancer	Enhances the anti-tumor effect by down-regulating expressions of VEGF and MMP-2 when combined with p65miRNA	Wang, L et al., 2012
		Inhibits cell growth	Li, Y et al., 2008

Table 9 (continued)

Drugs	Cancer types	Mechanisms	References
	Gallbladder cancer	Inhibits cell growth by inducing apoptosis	Wang, Y et al., 2005
	Non-small cell lung cancer	Triggers ER stress and induces apoptosis through both non-classical caspase-4 and GRP78	Kim, B et al., 2017
	Colon cancer	Suppresses Wnt/β-catenin signaling but not COX-2	Egashira, I et al., 2017
		Induces the various phosphorylation sites of p53 and activates p53-PUMA pathway	Liu, H et al., 2008
	Cervical cancer	Down-regulates the expression of caveolin-1 and inhibits the activation of downstream signaling molecules when combined with Lovastatin	Chen, L et al., 2016
Etoricoxib	Colon cancer	Modulates the Delta Psi(M)	Tanwar, L et al., 2010
Parecoxib Sodium	Thyroid cancer	Improves functional neck lymph node dissection	Peng, Y et al., 2013
	Colon cancer	Provides good postoperative analgesic effect	Xie, H et al., 2011
		Inhibits EMT and metastasis by down-regulating β-catenin	Wang, C et al., 2022
	Breast cancer	Inhibits proliferation and migration by up—regulating the expression of microRNA-199a /b-3p and blocks cell cycle when combined with adriamycin	Wang, J et al., 2018
Rofecoxib	Gastric cancer	Enhances anti-proliferation effect when combined with octreotide	Liu, C et al., 2004
	Pancreatic cancer	Improves inhibitory effects when combined with octreotide	Zhou, X et al., 2003
		Inhibits not only ERK-1/ ERK-2 and c-Fos expressions but also AP-1 binding activity	Zhou, X et al., 2005
		Changes gene expression which favors cell cycle arrest	Tseng, W et al., 2002
	Triple-negative breast cancer	Induces apoptosis by suppressing the expression of Bcl-2 family	Zhao, Y et al., 2016
	NSCLC	Increases apoptosis	Alam, M et al., 2007
	Gastric cancer	Sensitizes chemotherapeutic effect of various anticancer agents	Zhu, F et al., 2010
		Prolongs tumor latency and inhibits tumor growth	Zhu, F et al., 2007
	Lung cancer	Inhibit tumor growth and prevents recurrences	Tanaka, T et al., 2005
	Colorectal cancer	Negatively regulates angiogenesis	Fenwick, S et al., 2023
	Cervical cancer	Prolongs tumor latency and inhibits tumor growth	Jung, Y et al., 2009

Table 9 (continued)

Drugs	Cancer types	Mechanisms	References
Imrecoxib	Lung cancer	Up-regulates PTEN and down-regulates cortactin	Wang, L et al., 2017
		Inhibits tumor growth and lymph node metastasis via down-regulating ezrin and up-regulating E-cadherin when combined with lobaphatin	Wang, D et al., 2013
	Colon cancer	Induces apoptosis by regulating the expression of Survivin and Caspase-3, and enhances the anti-tumor effect of oxaliplatin	Wang, X et al., 2020

Table 10 Mechanisms underlying anti-tumor properties of steroidal anti-inflammatory drugs

Drug	Cancer Types	Mechanisms	References
Hydrocortisone	Breast cancer	Reduces colony formation, inhibits migration, induces cell cycle arrest in the SubG1 phase, induces apoptosis via caspase-3, inhibits migration and down-regulates Bcl-2	Msalbi, D et al., 2023
	Colon cancer	Entrap docetaxel and complexed with anti-tumor plasmid DNA for enhanced killing of cancer cells	Sridharan, K et al., 2021
	Melanomas, sarcomas, and colon tumors	Inhibit cell viability selectively in colon cancer cells	KERN, D et al., 1984
Prednisone	Non-small cell lung cancer	Induces a shutdown of bypass RTK signaling and inhibits key resistance signals	Gong, K et al., 2021

preventive marker for lung cancer through bioinformatics and machine learning methods [444].

Artificial intelligence has recently emerged as a powerful and promising tool for developing anti-tumor medications more quickly, affordably, and effectively [445]. Due to the crucial role of TLR4 in pro-inflammatory responses, and considering the costly, time-consuming, and labor-intensive nature of traditional drug design approaches, novel TLR4 modulators identified through artificial intelligence and computer-assisted drug design show great promise and have demonstrated positive results [446]. Due to their high selectivity and low toxicity, anti-inflammatory peptides (AIPs) have shown greater therapeutic potential against inflammatory diseases compared to small compounds. Additionally, machine learning plays a crucial role in predicting peptides [447].

Artificial intelligence solutions for endoscopy-based cancer evaluation hold great promise for the future. However, the application of these models in clinical practice faces several challenges, including the need for more robust validation studies and overcoming regulatory hurdles. At the same time, AI facilitates data-driven decision-making, helping to expedite drug discovery and development while reducing failure rates. Additionally, AI-powered precision medicine allows doctors to tailor early therapies to the individual needs of each patient.

Open questions/Future perspective

It is now evident that inflammatory cells and related inflammatory pathways significantly influence tumor growth. However, several issues still need to be addressed. 1) In the absence of an external carcinogenic agent, can inflammation itself lead to neoplasia? While various studies have suggested that inflammation can cause cancer without the presence of exogenous carcinogens, evidence shows that more DNA mutations were observed in a mouse model of bowel inflammation lacking IL-10 when exposed to external carcinogens [448], and more powerful proof is required to make such a disclosure. 2) Due to the dual role of inflammatory molecules, such as inflammasomes and interleukins, in cancer development and progression, it is important to consider the question about whether we can suppress tumor growth by shifting the balance between "bad" inflammation and "good" inflammation? The adaptive, humoral, and innate immune systems all play integral roles in the complex relationship between local and systemic inflammation and tumor growth. Therefore, triggering an effective anti-tumor adaptive immune response is crucial and requires careful attention. Recently, the use of bromodomain and extra-terminal domain (BET) protein inhibitors (iBET) has been reported to induce cell death and reduce the aggressiveness of oral squamous cell carcinoma (OSCC) [449]. iBET protects mice from

Table 11 Summary of pharmacological strategies direct targeting inflammatory molecules for cancer therapy in clinical trials (information was obtained fromhttps://www.clinicaltrials.gov/)

Identifier	Phase	Drug	Cancer types	Treatment	Status	References
NCT01943422	Phase 1	IFNα2b	Advanced melanoma	Combined BRAF inhibitor Vemurafenib and high-dose interferon α−2b	Terminated	N/A
NCT00913913	Phase 2	IFNα2b	Metastatic renal cell carcinoma	Bevacizumab, autologous tumor/DC Vaccine, IL-2 and IFNα−2b	Completed	N/A
NCT00871533	Early Phase 1	IFNα2b	Melanoma	IFNα2b/ PEG- IFNα2b	Terminated With Results	N/A
NCT05870475	Phase 2	IFNα2b	Hydroxyurea-resistant/intolerant PV	Pegylated interferon α−2b in combination with Ruxolitinib	Recruiting	N/A
NCT02339324	Phase 1	IFNα2b	Locally/regionally advanced/recurrent melanoma	Standard-dose interferon α−2b (HDI) and anti-PD1 monoclonal antibody	Completed	N/A
NCT05756166	Phase 1 Phase 2	IFNα2b	Metastatic or unresectable triple negative breast cancer	Rintatolimod, celecoxib and interferon α−2b with pembrolizumab	Recruiting	N/A
NCT02086721	Phase 1	IL-2	Oligometastatic solid tumor	Combining L19-IL2 with SABR	Completed	Relinde, I et al., 2020
NCT00590824	Phase 2	IL-2	Resectable recurrent stage III or stage IV melanoma	Pilot hu14.18-IL2	Completed	Albertini, M et al., 2018
NCT05829057	Phase 1	IL-2	Bladder, esophagus, liver, ovarian and small-cell lung cancer	The IIT study of evaluation of P-IL-2	Recruiting	N/A
NCT05471271	Not Applicable	IL-2	Metastatic solid tumor	IL-2	Recruiting	N/A
NCT05307874	Phase 1 Phase 2	IL-2	Advanced solid tumors	ICT01 plus low dose SC IL-2	Recruiting	N/A
NCT02306954	Phase 2	IL-2	Metastatic renal cancer	High dose interleukin-2 (IL-2) and stereotactic body radiation (SBRT)	Active, not recruiting	Steven, K et al., 2012
NCT00100906	Phase 2	IL-2	Metastatic renal cell cancer	Sequential ATRA then IL-2 for modulation	Completed	N/A
NCT00003842	Phase 1	IL-4	Recurrent malignant astrocytoma	IL-4(38–37)-PE38KDEL immunotoxin	Unknown Status	N/A
NCT00923910	Phase 1 Phase 2	IL-4	Cancers of the blood	WT1 peptide-pulsed dendritic cells, donor lymphocytes, IL-4	Completed	N/A
NCT00039052	Phase 1	IL-4	Recurrent or metastatic kidney cancer, non-small cell lung cancer, or breast cancer	Intravenous interleukin-4 PE38KDEL cytotoxin	Completed	Yan, L et al., 2018
NCT02858895	Phase 2	IL-4	Recurrent or progressive glioblastoma	MDNA55 (IL-4)	Completed	N/A
NCT00001564	Phase 2	IL-4	Recurrent pediatric sarcomas	Tumor-specific peptide vaccination and IL-2 with or without autologous T cell transplantation	Completed	N/A
NCT02494206	Not Applicable	IL-4	Breast cancer related upper extremity lymphedema	QBX258 (IL-4)	Completed	Mehrara, B et al., 2021
NCT00000769	Phase 1	IL-4	AIDS and Kaposi's sarcoma	Interleukin-4 (IL-4)	Completed	N/A
NCT04253080	Not Applicable	IL-4	Cutaneous melanoma	IL-4	Recruiting	N/A
NCT00014677	Phase 2	IL-4	Recurrent glioblastoma multiforme	NBI-3001	Completed	N/A
NCT04903197	Phase 1	IL-4	Non-hodgkin lymphoma	VAY736	Recruiting	N/A
NCT06191887	Phase 1	IL-4	Relapsed or refractory B-cell hematologic malignancies	Bendamustine	Recruiting	N/A
NCT01368107	Phase 2	IL-7	Metastatic breast cancer	IL-7	Completed	N/A
NCT06204991	Phase 1	IL-7	Locally advanced or metastatic melanoma	ADP-TILIL7	Not yet recruiting	N/A
NCT06221553	Phase 1	IL-7	Diffuse intrinsic pontine glioma	IL-7Ra	Recruiting	N/A

Table 11 (continued)

Identifier	Phase	Drug	Cancer types	Treatment	Status	References
NCT03932565	Phase 1	IL-7	Malignant solid tumors	Fourth-generation CAR-T	Unknown status	N/A
NCT03941769	Phase 1 Phase 2	IL-7	Acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia, or myeoproliferative disease after a haploidentical or cord blood stem cell transplant	2018–0674—IL-7	Completed	N/A
NCT03198546	Phase 1	IL-7	Cancer with GPC3 expression	GPC3 and/or TGFβ	Recruiting	N/A
NCT05659628	Phase 1	IL-7	RR-DLBCL	CD19 CAR-T	Recruiting	N/A
NCT05378464	Phase 1	IL-7	Metastatic HER2 + breast cancer	Adoptive T cell therapy following HER2-pulsed dendritic cell vaccine & pepinemab /trastuzumab	Recruiting	N/A
NCT04381741	Phase 1	IL-7	Relapsed or refractory diffuse large B cell lymphoma	CD19 CAR-T expressing IL7 and CCL19 combined with PD1 mAb	Enrolling by invitation	N/A
NCT04588038	Phase 1	IL-7	Recurrent squamous cell carcinoma of head and neck	NT-I7 (IL-7)	Recruiting	N/A
NCT05465954	Phase 2	IL-7	Recurrent glioblastoma	Efineptakin alfa and Pembrolizumab	Recruiting	N/A
NCT03513952	Phase 2	IL-7	Locally advanced, inoperable, or metastatic urothelial carcinoma	Atezolizumab and CYT107	Completed	N/A
NCT00091338	Phase 1	IL-7	Metastatic melanoma	Interleukin-7 and vaccine	Completed	N/A
NCT03239392	Phase 1 Phase 2	IL-9	LGL leukemia or refractory CTCL	IV BNZ-1	Completed	N/A
NCT01035697	Observational	IL-9	Cerebral palsy	IL-9	Completed	N/A
NCT05991583	Phase 1 Phase 2	IL-10	Advanced malignant tumors	IBB0979	Recruiting	N/A
NCT05396339	Phase 1 Phase 2	IL-10	Advanced malignant solid tumors	IAE0972	Recruiting	N/A
NCT06468358	Phase 1 Phase 2	IL-10	Advanced or metastatic solid tumors	LB1410 in Combination With LB4330	Recruiting	N/A
NCT05704985	Phase 1	IL-10	Locally advanced or metastatic EGFR + tumors	Using DK210	Recruiting	N/A
NCT02009449	Phase 1	IL-10	Advanced solid tumors(IVY)	LY3500518	Active, not recruiting	N/A
NCT00433446	Phase 2	IL-6	Metastatic prostate cancer	S0354, Anti-IL-6 chimeric monoclonal Antibody	Completed	N/A
NCT00841191	Phase 1 Phase 2	IL-6	Solid tumors	Siltuximab (CNTO 328)	Completed	N/A
NCT05704634	Phase 1	IL-6	Non-small cell lung cancer	IL6-receptor antibody Sarilumab in combination with anti-PD1 antibody Cemiplimab	Recruiting	N/A
NCT01219010	Phase 1	IL-6	Undetermined significance, smoldering multiple myeloma, or indolent multiple myeloma	Siltuximab	Completed	Thomas, S et al., 2014
NCT00955812	Phase 1	IL-6	Solid tumors	STAT3 inhibitor	Completed	N/A
NCT04641910	Observational	IL-6	Acute myeloid leukemia	FLt3 ligand plasma concentration kinetic profile and IL-6 concentration	Recruiting	N/A
NCT01417546	Phase 1	IL-12	Solid tumors	NHS-IL12	Completed	Nicole, J et al., 2023
NCT02483312	Phase 1	IL-12	Acute myelogenous leukemia	IL-12	Recruiting	N/A
NCT04471987	Phase 1	IL-12	Advanced solid tumor, metastatic solid tumor	IL12-L19	Recruiting	N/A

Table 11 (continued)

Identifier	Phase	Drug	Cancer types	Treatment	Status	References
NCT04708470	Phase 1 Phase 2	IL-12	Advanced cancers including HPV-associated malignancies, small bowel, and colon cancers	Bintrafusp alfa, NHS-IL12, Entinostat	Recruiting	N/A
NCT00005604	Phase 1	IL-12	Advanced solid tumors	Interleukin-12 plus interleukin-2	Completed	N/A
NCT02531425	Phase 1	IL-12	TNBC	IT-pIL12-EP	Completed	N/A
NCT00015977	Phase 2	IL-12	Metastatic prostate cancer	Vaccine therapy plus interleukin-12	Completed	N/A
NCT00004074	Phase 1	IL-12	Cancer that has high levels of HER2/Neu	Interleukin-12 and Trastuzumab	Completed	N/A
NCT00323206	Not Applicable	IL-12	Malignant melanoma	Phase I trial of intratumoral pIL-12 electroporation	Completed	N/A
NCT00406939	Phase 1	IL-12	Prostate cancer	IL-12	Completed	N/A
NCT03281382	Phase 1	IL-12	Metastatic pancreatic cancer	Interleukin 12	Completed	Barton, K et al., 2021
NCT02960594	Phase 1	IL-12	Solid tumors at high risk of relapse	hTERT immunotherapy alone or in combination with IL-12 DNA	Completed	N/A
NCT00016289	Phase 2	IL-12	Ovarian epithelial cancer or primary peritoneal cancer	Interleukin-12	Completed	N/A
NCT01440816	Phase 2	IL-12	Merkel cell cancer	IL-12	Completed	N/A
NCT05756907	Phase 1 Phase 2	IL-12	Platinum-resistant ovarian cancer	Combination of SON-1010 (IL12-FHAB) and Atezolizumab	Recruiting	N/A
NCT05788926	Phase 1	IL-12	Metastatic non-small cell lung cancer	TG6050	Recruiting	N/A
NCT01118052	Phase 2	IL-12	Persistent or recurrent ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer	EGEN-001	Completed	Alvarez, R et al., 2014
NCT00028535	Phase 1	IL-12	Solid tumors	Interleukin-12	Completed	N/A
NCT02395822	Phase 2	IL-15	Relapsed or refractory AML	Haplo NK With SQ IL-15	Completed	N/A
NCT01021059	Phase 1	IL-15	Refractory metastatic malignant melanoma and metastatic renal cell cancer	Intravenous recombinant human IL-15	Completed	N/A
NCT02689453	Phase 1	IL-15	Refractory or relapsed chronic and acute adult T-cell leukemia	Subcutaneous recombinant human IL-15 (s.c. rhIL-15) and Alemtuzumab	Completed	N/A
NCT03669172	Phase 1 Phase 2	IL-15	Acute leukemia	IL-15	Completed	N/A
NCT05110742	Phase 1 Phase 2	IL-15	Relapsed/refractory hematological malignances	CD5 CAR engineered IL15-transduced	Recruiting	N/A
NCT00107718	Phase 2	IL-18	Previously untreated metastatic melanoma	SB-485232	Completed	N/A
NCT00659178	Phase 1	IL-18	Advanced stage epithelial ovarian cancer	SB-485232 (Interleukin 18)	Completed	N/A
NCT01768338	Phase 1	IL-18	Lymphoma	Recombinant human IL-18 and ofatumumab	Completed	N/A
NCT02277392	Phase 1	IL-18	Recurrent ovarian, fallopian tube or primary peritoneal cancer	Recombinant human interleukin-18 (Sb-485232) combined with adoptive transfer of vaccine-primed CD3/CD28-costimulated autologous T-cells	Withdrawn	N/A
NCT05914376	Phase 1	IL-21	Advanced tumors	Recombinant human IL-21 oncolytic vaccinia virus injection (hV01)	Recruiting	N/A
NCT06198296	Phase 1	IL-21	GPC3-positive solid tumors	IL-15 and IL-21 armored GPC3-CAR T cells	Not yet recruiting	N/A
NCT00617253	Phase 2	IL-21	Stage IV renal cell carcinoma	Recombinant human IL-21 (rIL-21) and sunitinib	Completed	N/A

Table 11 (continued)

Identifier	Phase	Drug	Cancer types	Treatment	Status	References
NCT00336986	Phase 2	IL-21	Metastatic melanoma	IL-21	Completed	N/A
NCT02809092	Phase 1 Phase 2	IL-21	Acute myeloid leukemia	Interleukin-21	Unknown status	N/A
NCT04715191	Phase 1	IL-21	Pediatric solid tumors	Interleukin-15 and −21 armored glypican-3-specific chimeric antigen receptor	Not yet recruiting	N/A
NCT01629758	Phase 1	IL-21	Solid tumors	IL-21/anti-PD-1 combination	Completed	N/A
NCT01489059	Phase 1	IL-21	Melanoma	IL-21/Ipilimumab combination	Completed	N/A
NCT00514085	Phase 2	IL-21	Metastatic or recurrent malignant melanoma	Interleukin-21	Completed	N/A
NCT04220684	Phase 1	IL-21	Relapsed/refractory acute myeloid leukemia	IL-21	Recruiting	N/A
NCT04729543	Phase 1 Phase 2	IL-21	Melanoma and head and neck cancer (MC2TCR)	MAGE-C2/HLA-A2 TCR T cells	Recruiting	N/A
NCT00095108	Phase 1	IL-21	Metastatic malignant melanoma and metastatic kidney cancer	Interleukin-21	Completed	N/A
NCT00523380	Phase 2	IL-21	Ovarian cancer	Recombinant interleukin-21	Completed	N/A
NCT02858895	Phase 2	IL-4R	Recurrent or progressive glioblastoma	MDNA55	Completed	N/A
NCT00019032	Phase 1	IL-2R	Chronic lymphocytic leukemia	Monoclonal antibody	Completed	N/A
NCT00076180	Phase 1	IL-2R	T-Cell large granular lymphocytic leukemia	Hu-Mik-beta1	Completed	N/A
NCT00001249	Phase 1	IL-2R	Cutaneous T-Cell lymphoma (CTCL) and adult T-Cell leukemia (ATL)	Yttrium-90 radiolabeled anti-Tac	Completed	N/A
NCT00072969	Phase 2	IL-2R	Cytopenia of myelodysplastic syndrome (MDS)	Recombinant humanized anti-IL-2 receptor Antibody (Daclizumab) versus Antithymocyte globulin (ATG)	Completed	N/A
NCT05200559	Phase 1 Phase 2	IL-2R	Recurrent or metastatic solid tumors	E7777 combined with pembrolizumab	Recruiting	N/A
NCT00001567	Phase 2	IL-2R	Hairy cell leukemia	Roferon-A	Completed	N/A
NCT05699811	Phase 1 Phase 2	IFNα	Locally advanced/metastatic solid tumors	IFNα	Recruiting	N/A
NCT02151448	Phase 1 Phase 2	IFNα	Peritoneal surface malignancies	αDC1 vaccine + chemokine modulatory regimen (CKM)	Completed	N/A
NCT02923466	Phase 1	IFNβ	Refractory solid tumors	Ph1 administration of VSV-IFNβ-NIS monotherapy and in combination with avelumab	Completed	N/A
NCT03647163	Phase 1 Phase 2	IFNβ	Select solid tumors	Systemic VSV-IFNβ-NIS in Combination with checkpoint inhibitor therapy	Completed	N/A
NCT04291105	Phase 2	IFNβ	Select solid tumors	Voyager V1	Recruiting	N/A
NCT05076760	Phase 1	IFNβ	Solid tumors including non-small cell lung cancer	MEM-288 oncolytic virus alone and in combination with nivolumab	Recruiting	N/A
NCT04695327	Phase 1	TNFα	Oncolytic adenovirus TILT-123	TNFα and IL-2	Recruiting	N/A
NCT02076620	Phase 1	TNFα	Advanced solid tumours	L19 TNFα	Completed	N/A
NCT03259230	Observational	IFNγ	Malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH)	Interferon γ and other inflammatory mediators	Completed	N/A

Table 11 (continued)

Identifier	Phase	Drug	Cancer types	Treatment	Status	References
NCT06344052	Phase 2	IFNγ	Locally advanced basal cell carcinoma	SP-002 with vismodegib	Recruiting	N/A
NCT06430788	Phase 2	IFNγ	Pediatric aplastic anemia	Emapalumab	Recruiting	N/A
NCT06052839	Phase 2	IFNγ	Recurrent/metastatic HNSCC	Pulsed dose chemotherapy plus pembrolizumab	Recruiting	N/A
NCT00004016	Phase 1	IFNγ	Recurrent or metastatic melanoma or other solid tumors	Interferon γ	Completed	N/A
NCT02614456	Phase 1	IFNγ	Advanced solid tumors	Combination of interferon-γ and nivolumab	Completed	Zibelman, M et al., 2023
NCT01957709	Early Phase 1	IFNγ	Soft tissue sarcoma	Recombinant interferon γ	Terminated (Enough samples were collected for data analysis)	N/A
NCT00059878	Phase 2	IFNγ	Aspergillosis or other fungal infections	Voriconazole with or without interferon γ	Completed	N/A
NCT00004032	Phase 1	IFNγ	Refractory epithelial ovarian cancer	Tumor vaccine and interferon γ	Completed	N/A
NCT02197169	Phase 1	IFNγ	Recurrent glioblastoma or gliosarcoma brain tumors (TARGET-I)	DNX-2401 With Interferon Gamma (IFN-γ)	Completed	N/A
NCT06371482	Phase 2	IFNγ	Limited stage small cell lung cancer (Camel-01)	Durvalumab combined with chemoradiotherapy	Recruiting	N/A
NCT05156541	Phase 3	IFNγ	Anogenital warts (ING-HPV-1)	Drug Ingaron (Interferon-γ)	Completed	N/A
NCT00786643	Phase 2	IFNγ	Metastatic colorectal carcinoma	Interferon γ	Completed	N/A
NCT03112590	Phase 1 Phase 2	IFNγ	HER-2 positive breast cancer	Interferon γ	Completed	N/A
NCT00616720	Phase 2	IFNγ	Multiple myeloma	Interferon γ or aldesleukin and vaccine	Completed	N/A
NCT02550678	Phase 1 Phase 2	IFNγ	Low-risk nodular basal cell carcinoma (ASN-002–001)	ASN-002, 5-FU	Completed	N/A
NCT03063632	Phase 2	IFNγ	Mycosis Fungoides and Sézary Syndrome and Advanced Synovial Sarcoma	Combination of two experimental drugs MK-3475 (Pembrolizumab) and interferon-γ	Completed	N/A
NCT00070187	Phase 2 Phase 3	IFNγ	Refractory or relapsed Hodgkin's lymphoma	Cyclosporine, Interferon γ, and Interleukin-2 after high-dose myeloablative chemotherapy	Completed	N/A
NCT04628338	Early Phase 1	IFNγ	Acute myeloid leukemia and myelodysplastic syndrome	IFN-γ	Completed	N/A

pancreatic inflammation caused by LPS and the resulting cytokine storm, while also inhibiting cell proliferation in pancreatic cancer [450]. Another promising approach is to restore a balanced host response by normalizing the inflammatory network. This involves reducing high levels of pro-inflammatory cytokines and other tumor-promoting characteristics of infiltrating cells while increasing the levels of anti-inflammatory cytokines. 3) Do sex steroid hormones play a role in the interplay between inflammation and cancer? The occurrence of tumors varies between genders due to differing sex hormones. Analyzing the interaction between these hormones and inflammation in cancer development could enhance the treatment of hormone-related cancers, such as breast, lung, ovarian, cervical, and prostate cancers. Recent studies have shown that Treg cells, which play a crucial role in managing immune responses and reducing tissue inflammation, are more abundant in male visceral adipose tissue (VAT) compared to females. These differences in Treg cell populations are influenced by the tissue environment and shaped by sex hormones, which help to decrease inflammation in adipose tissue [451]. Considering the widespread use of selective androgen receptor modulators and selective estrogen receptor modulators like tamoxifen, understanding the interaction between sex hormones, inflammation, and cancer will significantly influence the clinical treatment of cancer.

Discussion

Cancer is still the second leading cause of death after cardiovascular disease in the world, the main reason is that about 50% of cancers are diagnosed at a late stage. The limited efficacy of existing treatment methods and the high failure rate in drug development make the situation more complex, and there is an urgent need for a better understanding of disease mechanisms, the development of early detection technology, and cancer chemoprevention strategies. Here, we systematically analyzed the role of inflammation and its related molecules in tumors. We expect that a substantial amount of information and intricacies continually uncovered in the area will eventually be condensed into a few key principles that regulate the molecular and cellular processes underpinning inflammation that promote tumor growth.

The role of inflammatory molecules in cancer has attracted the researchers' attention during the past decades. New insights into the pro- or anti-tumor effect in the tumor and its microenvironment have given impetus to drug discovery and patient evaluation of inflammation-directed strategies. For example, as the most effective and widely distributed family of cytokines, IFN-Is, or type I interferons, are essential for launching a successful anti-tumor response. Antigen-presenting cells require interferon-alpha to trigger T cell responses; additionally, IFN-Is directly boost CD8 + T cell activity and cytotoxicity, stimulate CD4 + Th1 cell development, augment cytotoxicity from natural killer cells, and limit regulatory T cells. However, IFN-Is induce the expression of negative regulatory molecules, which can reduce immunological responses and induce fatigue, thus facilitating the growth of tumors. Besides, other inflammatory molecules such as interleukins, tumor necrosis factors, colony-stimulating factors, chemokines, and inflammasomes also showed multifaceted effects in cancer. The two-side effect may depend on the cancer type, time, cells present, total IFN-I signal levels, and others. Therefore, further studies are needed to dissect the dual role of these inflammatory molecules in different cancer models, which will enable the identification of novel molecular and immunological targets and lead to the development of novel therapeutic strategies. Recently, researchers created a portable smart blue-light controlled (PSLC) gadget based on optogenetic technology. The findings demonstrate that blue light can efficiently control pro-inflammatory cytokine expression in both in vitro and in vivo settings, which offers a unique strategy for cytokine therapy [452].

FDA-approved non-anticancer drugs- "old medicine", have obvious advantages in anti-tumor treatment—"new use", because FDA-approved drug applications could better avoid numerous obstacles and uncertainties in every step of converting drugs into clinical applications. This suggests that the application of non-anticancer drugs may be a promising strategy for cancer chemoprevention. The evident role of inflammation in cancer development and progression prompted the application of anti-inflammatory medications as a therapeutic strategy. While the application of anti-inflammatory drugs in clinical antitumor therapy still needs to overcome several obstacles. 1) Targeted delivery to the cancerous cell. Although the anti-inflammatory medications now approved by the FDA are undoubtedly effective, their off-target effects and toxicities make them less desirable options for cancer therapy when taken at the current dosages and frequency. Rather, to improve drug targetability and reduce off-target adverse effects, recent developments in nanotechnology have facilitated a paradigm shift away from traditional anti-inflammatory medications and toward anti-inflammatory nano-therapeutics in cancer therapy. However, the field of anti-inflammatory nanomedicines is still in its infancy with little commercial application, and there is a great need to consider and identify the issues with nano-inflammatory therapies to aid in the practical clinical translation of commercially available anti-inflammatory nanotherapeutics. 2) Tumor cells have different or even opposite responses to these anti-inflammatory drugs. Abundant evidence indicates that

anti-inflammation drugs are promising candidates for preventing carcinogenesis and cancer recurrence because of their availability and relatively low occurrence of side effects compared to other chemotherapeutic drugs. Nevertheless, due to the paucity of information and the complexity of carcinogenesis, these anti-inflammation drugs showed different or even inverse effects. Well-designed, long-term clinical trials are required to ascertain the clinical application potential of these medications, and additional trials are required to investigate the doses, kinds, and length of response of these drugs. 3) The side effects after long-term use. Although the FDA-approved anti-inflammatory drugs have far fewer side effects than chemotherapeutics, some anti-inflammatory drugs, such as aspirin, also showed obvious side effects after long-term use. The main side effects of NSAIDs are cardiovascular (CV) and renal adverse effects. While the main side effects of seroidal anti-inflammatory drugs such as glucocorticoids (GRs) are diabetes, glaucoma, and suppression of the hypothalamic–pituitary–adrenal axis, among others. NSAIDs cause cell death by directly targeting mitochondria, while NSAIDs have been shown to enhance mitochondrial health in dose-dependent ways [453], which suggesting that future research should focus on comparing equipotent dosages of these drugs. Additionally, it's important to assess the alleviation of symptoms. There are ongoing efforts to develop selective GR agonists (SEGRAs) with the hypothesis that they are safer than traditional glucocorticoids. To support this hypothesis, appropriate in vitro and in vivo studies are needed to provide reliable experimental results. 4) Patients continue to experience other thromboembolic events despite aspirin therapy, which is known as aspirin resistance (AR). Besides, anti-inflammatory drugs may lead to a degree of drug resistance. For example, dexamethasone can increase the resistance of human tumor cells to ionizing radiation and chemotherapy [454].

Hence, larger-scale adoption of the chemoprevention strategy is likely to require improved identification of individuals for whom the protective benefits outweigh the harms. Such a precision medicine approach may emerge through further clarification of these anti-inflammatory drugs' mechanism of action.

Abbreviations

IL	Interleukin
TNF-α	Tumor necrosis factor alpha
NF-κB	Nuclear factor-κB
STAT3	Signal transducer and activator of transcription 3
NSAIDs	Nonsteroidal anti-inflammatory drugs
CRC	Colorectal cancer
USPSTF	US Preventive Services Task Force
DR5	Death receptor 5
FDA	Food and Drug Administration
TLRs	Toll-like receptors
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
LAP	LC3-associated phagocytosis
LANDO	LC3-associated endocytosis
Ab	Beta-amyloid
IFN	Interferon
ROS	Reactive oxygen species
IKK	IκB kinase
IRGM	Immunity-related GTPase M
AIM 2	Absent in melanoma 2
FUNDC1	FUN14 domain-containing 1
MMPs	Matrix metalloproteinases
COX	Cyclooxygenase
PIK3CA	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform
AKT	Protein kinase B
PTEN	Phosphatase and tensin homolog
Wnt	Wingless-type MMTV integration site family
Fc–IL-4	Interleukin-4 fusion protein
AA	African American
EA	European American
CLSs	Crown-like structures
Tregs	T regulatory cells
NK cells	Natural killer cells
ICIs	Checkpoint inhibitors
irAEs	Immune-related adverse events
MSI-H	High microsatellite instability
PPARα	Peroxisome proliferator-activated receptor alpha
MetS	Metabolic syndrome
3-MA	Methyladenine
TLR	Toll-like receptor
NLRP3	Nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain-containing receptor
TGF-β	Transforming growth factor beta
ECs	Endothelial cells
VEGF	Vascular endothelial growth factor
BDNF	Brain-derived neurotrophic factor
TrkB	Tropomyosin receptor kinase B
CXCR	C-X-C chemokine receptor
CXCL	(C-X-C motif) ligand
CX3CR1	CX3Chemokine receptor 1
CCR1	CC-chemokine receptor 1
EMT	Epithelial-mesenchymal transition
DDR	DNA damage response
IFN-γ	Interferon gamma
STAT6	Signal transducer and activator of transcription 6
EGCG	Epigallocatechin-3-gallate
ICB	Immune checkpoint blockade
CD	Crohn's disease
UC	Ulcerative colitis
IBD	Inflammatory bowel disease
RA	Rheumatoid arthritis
NMSC	Nonmelanoma skin cancer
HPV	Human papillomavirus
H. pylori	Helicobacter pylori
HBV	Hepatitis B virus
HCV	Hepatitis C virus
NAFLD	Nonalcoholic fatty liver disease
MYC	Myelocytomatosis oncogene
RAS	Rats arcomaviral oncogene homolog
KRAS	Kristen rats arcomaviral oncogene homolog
NSCLC	Non-small cell lung cancer
VHL	Von Hippel-Lindau
JAK	Janus kinase
ISGF3	IFN-stimulated gene (ISG) factor 3
RIG-I	Retinoic acid-inducible gene I
cGAMP	Cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP)
cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
IOD	Indoleamine-2,3-dioxygenase
GM-CSF	Granulocyte/macrophage colony-stimulating factor

M-CSF	Macrophage colony-stimulating factor
G-CSF	Granulocyte colony-stimulating factor
GPCRs	Gai-protein-coupled seven-transmembrane-spanning receptor
TME	Tumor microenvironment
LRR	Leucine rich repeat
PYD	Pyrin domain
NLRP1	Pyrin domain (PYD) domain-containing protein 1
NLRC4	NLR family caspase activation and recruitment domain-containing protein 4
NLRP6	NOD-like receptor family pyrin domain containing 6
ASC	Apoptosis-associated speck-like protein containing caspase activation and recruitment domain
DSS	Dextran sulfate sodium
AOM	Azoxymethane
CARD	C-terminal caspase recruitment domain
FIIND	Function to find domain
DPP	Dipeptidyl protease
LT	Lethal toxin
LUAD	Lung adenocarcinoma
PAAD	Pancreatic adenocarcinoma
TRX	Thioredoxin
NBD	Nucleotide-binding domain
HD1	Helical domain 1
WHD	Winged helix domain (WHD)
HD2	Helical domain 2
T4SS	Type IV secretion system
T3SS	Type III secretion system
IRF	Interferon regulatory factor
NASH	Nonalcoholic steatohepatitis
AH	Alcoholic hepatitis
GC	Gastric cancer
SCLC	Small cell lung cancer
ALRs	AIM2-like receptors
POP3	PYD-only protein 3
HCMV	Human cytomegalovirus
HSV-1	Herpes simplex virus-1
HbeAG	Hepatitis B e-antigen
TMS1	Target of methylation-induced silencing-1
TSLP	Thymic stromal lymphopoietin
CAFs	Cancer-associated fibroblasts
ECM	Extracellular metrix
TNC	Tenascin-C
PSA	Prostate-specific antigen
RECIST	Response evaluation criteria in solid tumors
CR	Complete response
MSS	Metastatic microsatellite stable
dMMR	Mismatch repair-deficient
AI	Artificial intelligence
CAD	Computer-aided diagnostic
ML	Machine learning
DL	Deep learning
ANN	Artificial neural networks
TILs	Tumor-infiltrating lymphocytes
AIPs	Anti-inflammatory peptides
BET	Bromodomain and extra-terminal domain
iBET	Bromodomain and extra-terminal domain (BET) protein inhibitors
OSCC	Oral squamous cell carcinoma
VAT	Visceral adipose tissue
PSLC	Portable smart blue-light controlled
CV	Cardiovascular
GRs	Glucocorticoids
SEGRAs	Selective GR agonists
AR	Aspirin resistance

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Authors' contributions
All authors have contributed to the article and approved its publication. Y.X., F.L., designed and wrote the manuscript. Y.W. and Y.Z., prepared the figures. Y.J. and Q.W., modified the language. Z.D. and K.L., reviewed and edited the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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