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Unveiling the link between chronic inflammation and cancer

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ABSTRACT

The highly nuanced transition from an inflammatory process to tumorigenesis is of great scientific interest. While it is well known that environmental stimuli can cause inflammation, less is known about the oncogenic modifications that chronic inflammation in the tissue microenvironment can bring about, as well as how these modifications can set off pro-tumorigenic processes. It is clear that no matter where the environmental factors come from, maintaining an inflammatory microenvironment encourages carcinogenesis. In addition to encouraging angiogenesis and metastatic processes, sustaining the survival and proliferation of malignant transformed cells, and possibly altering the efficacy of therapeutic agents, inflammation can negatively regulate the antitumoral adaptive and innate immune responses. Because chronic inflammation has multiple pathways involved in tumorigenesis and metastasis, it has gained recognition as a marker of cancer and a desirable target for cancer therapy. Recent advances in our knowledge of the molecular mechanisms that drive cancer's progression demonstrate that inflammation promotes tumorigenesis and metastasis while suppressing anti-tumor immunity. In many solid tumor types, including breast, lung, and liver cancer, inflammation stimulates the activation of oncogenes and impairs the body's defenses against the tumor. Additionally, it alters the microenvironment of the tumor. As a tactical approach to cancer treatment, these findings have underscored the importance of targeting inflammatory pathways. This review highlights the role of inflammation in cancer development and metastasis, focusing on its impact on tumor progression, immune suppression, and therapy resistance. It examines current anti-inflammatory strategies, including NSAIDs, cytokine modulators, and STAT3 inhibitors, while addressing their potential and limitations. The review emphasizes the need for further research to unravel the complex mechanisms linking inflammation to cancer progression and identify molecular targets for specific cancer subtypes.

1. Introduction

The body uses inflammation, the immune system's response to damaging stimuli, to help remove the source of the injury and heal damaged tissue [1]. Immune cell activation and ongoing inflammatory stimulation both lead to chronic inflammation, and they both need recurring tissue death and regeneration over time. There have been theories linking chronic inflammation to cancer dating back to the seventeenth century. German physician Rudolf Virchow postulated in 1863 that tumor formation is the consequence of recurring inflammatory responses after seeing immune cells penetrate cancerous tissue [2]. Based on Virchow's findings, Japanese physician Katsusaburo Yamagiwa showed in 1915 that artificially generated chronic inflammation may promote tumor formation in an animal model [3]. Many scientists released research papers supporting Virchow's idea throughout the twentieth century. For instance, in the 1970s, there was a belief that nonsteroidal anti-inflammatory medications (NSAIDs) may reduce inflammation and so stop or limit the development of cancer [4]. According to Harold F. Dvorak, tumors are "wounds that do not heal," and the same molecular pathways that promote wound healing and tissue regeneration after damage may also be responsible for the genesis of tumors [5,6]. Knowledge about the identification of inflammation as a characteristic and cause of cancer has generally increased over the previous 20 years [7]. The cellular and molecular architecture of inflammation in cancer has been better understood because of developments in molecular biology and the creation of genetically engineered mice. In addition to the many tasks carried out by distinct immune cell subtypes, this also involves intricate signaling route networks controlled by an extensive range of cytokines, chemokines, and growth factors [8]. Furthermore, previously unidentified inflammatory

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aspects of cancer have been uncovered by breakthroughs in comprehensive analysis, such as single-cell technologies and next-generation sequencing (NGS) [9–11].

Most solid and hematopoietic cancers include inflammation as a part of their etiology. Consequently, understanding the molecular pathways relating inflammation to the development and advancement of cancer is necessary to develop viable treatment options. This study assesses the correlation between several cancer types and inflammation, examining the processes and latest data that support each.

2. Similarities between "inflammation in cancer" and "normal" inflammatory responses

The capacity to repair damage, regenerate tissue, and react to infections is more positively selected for evolution than the capacity to stop tumor development, which often happens after a person reaches reproductive age. Thus, inflammatory processes offer an acceptable evolutionary "trade-off" as they are necessary for normal tissue regeneration but may potentially induce cancer (Fig. 1). Inflammation defends and reacts to potential shocks (stresses, infections, tissue injury, metabolic abnormalities, and other homeostasis-related disturbances) within the context of tissue homeostasis in order to maintain tissue function and restore balance [12]. A modified tissue's low-level homeostatic inflammatory response [13]. In reaction to changes in the tissue, major tissue sentinels and tissue-associated macrophages maintain the stem cell niche, regulate immunological responses and barrier functions, and eliminate dead cells (apoptotic cell clearance). They also produce chemotactic molecules when needed to entice certain cell types. At least three primary and perhaps interconnected mechanisms may be involved in the initiation and persistence of tissue inflammatory responses. If the original damage was not severe enough, local tissue macrophages and dendritic cells (DCs) may initially multiply to increase their numbers locally. In a similar manner, immune cells originating from secondary lymphoid organs (lymphoid cells) and bone marrow (monocytes, neutrophils, and monocyte-derived cells) would deploy in response to significant disturbances in tissue homeostasis. Following their uptake of signals from the microenvironment, recruited or locally amplified inflammatory cells proceed through a phase of local activation, differentiation, and polarization [12,14].

In addition, an increase of fibroblasts and macrophages two essential "tissue blocks" connected to epithelial tissues may result from homeostatic responses set off by the hyperproliferation of epithelial cells in the context of cancer. Signaling circuits comprised of many growth factors and chemokines, produced by one kind of cell and absorbed by another via reciprocal connections, enable this [15]. This process most likely won't alter in reaction to tumor growth, limited tissue repair after damage or infection, or tissue multiplication in response to organism expansion. Thus, the simple multiplication of malignant tissue and epithelial cells initiates the predefined process of aggregating additional fibroblasts and macrophages inside the tissue. According to research, local tissue macrophage migration and proliferation may account for the majority of tumor-associated macrophages if the initial degree of stress, hypoxia, and other tumor-specific insults is not substantial [16,17].

Growth tumors are characterized by a sustained combination of microbial signals, oncogene-derived stress, and cell death that feed into a feedback loop of inflammatory cell recruitment and inflammation-induced signaling. Conversely, infections and wound healing disappear with the expansion of epithelial cells and the recruitment of immune cells (Fig. 1). Because there are no local antecedents in the tissue, during tumor growth and progression, the migration of hematopoietic-derived (spleen, blood, and bone marrow) cellular precursors promotes the production of monocyte-derived cells, including subsets of DCs, monocytes themselves, and neutrophils. Although the exact transcriptional programs causing the tumors' systemic and local myeloid cell multiplication are yet unknown, it is likely that growth factors like colony-stimulating factor-1 (CSF-1) and chemokine induction are what cause the former.

3. Inflammation triggers during tumorigenesis

Germline mutations account for just 10 % of cancer instances; acquired variables, such as environmental cues, or chronic inflammation, are responsible for the majority of cancer cases [8]. Crucially, tumor-intrinsic factors may potentially be able to start the tumor-promoting inflammatory cycle in addition to tumor-extrinsic proteins [18]. We will look at a few inflammatory mediators that might show up when the cancer grows.

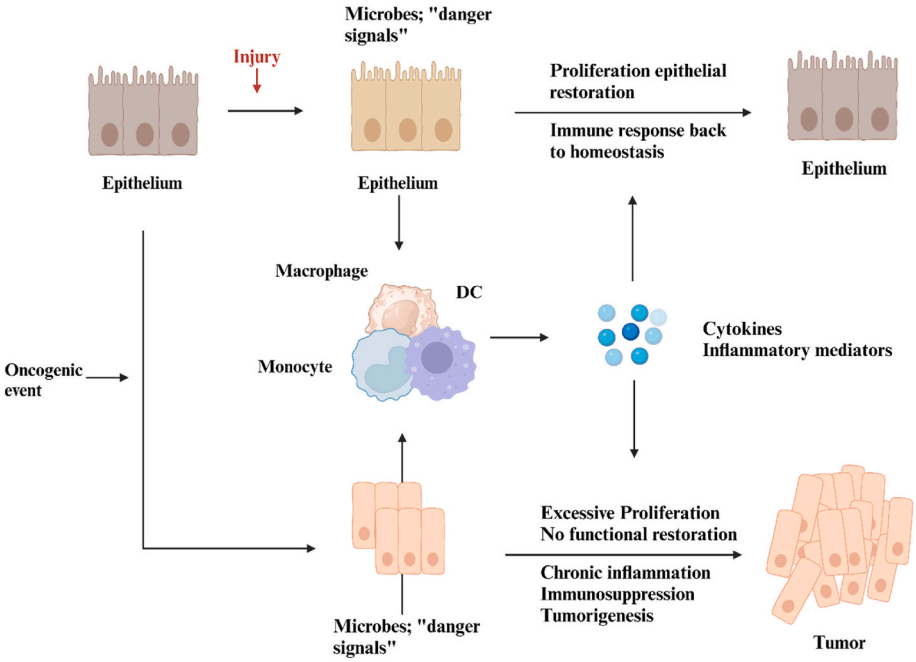

Fig. 1. Development and function-related differences and similarities between inflammation during infection, malignancy, and tissue regeneration.

3.1. Inflammation caused by chronic infection and autoimmunity

According to studies, chronic infections including gastritis brought on by *Helicobacter pylori* and hepatitis B/C virus (HBV or HCV)-induced hepatitis account for 20 % of cancer cases [8]. In addition, these infections raise the risk of hepatocellular carcinoma (HCC) and gastric cancer (GC) [19]. The host's immune system ought should be capable of quickly eliminating invaders, such as bacteria and viruses. Unfortunately, tumorigenic infections often succeed in evading the host's defenses and causing a protracted infection that results in chronic inflammation, which fuels the formation of tumors.

The autoimmune illnesses' chronic inflammation raises the possibility of cancer. For instance, the pro-neoplastic effects of chronic intestinal inflammation increase the risk of colorectal cancer (CRC) in individuals with inflammatory bowel disease (IBD) [20]. Two research groups from Japan found that the inflammatory epithelium of patients preferentially creates cell clones that had mutations related to the interleukin (IL)-17A signaling gene, shielding them from the harmful effects of inflammation [21,22]. The absence of these somatic mutations in CRC tissues is an indication of negative selection.

Interestingly enough, there isn't always a link between chronic inflammatory diseases and the chance of getting cancer. It is important to consider the tissue or organ in which inflammatory reactions take place; for example, inflammation in the joints or muscles is seldom linked to the development of cancer [8].

3.2. Inflammation associated with aging

Aging, also called "inflammaging," is a low-grade, systemic, chronic inflammatory process that raises the morbidity rate of cancer in the elderly [23]. Long-term lifestyle choices, immunosenescence, and cellular senescence are a few of the many variables linked to inflammation associated with aging and, ultimately, the emergence of cancer. Senescence-associated secretory phenotype, or (SASP), components include inflammatory chemicals like IL-6 and IL-8 that may promote the growth of malignancies when senescent cells proliferate with age [24,25]. A recent study suggests that targeting senescent cells with chimeric antigen receptor (CAR) T cells might be a helpful cancer treatment approach [26].

Surprisingly, comprehensive genomic research found that changes in cancer driver genes promote the age-related growth of cell clones in physiologically normal esophageal epithelia [27]. According to this study, inflammation may accelerate the remodeling of the esophagus epithelia associated with aging, which may contribute to esophageal cancer. Other contributing causes to this remodeling include excessive drinking and smoking.

3.3. Environmental and lifestyle factors that cause inflammation

Many environmental variables may cause chronic inflammation in people, usually in trace quantities [8]. For example, breathing in particulate matter from tobacco smoke, silica, and asbestos irritates the airways and induces lung inflammation, increasing the risk of lung cancer and mesothelioma [28,29]. Excessive lipid buildup linked to obesity and an elevated risk of several cancer types indicate that poor eating habits and other lifestyle variables may also play a role in the chronic inflammation that fosters tumor development [30,31]. Through disruption of the gut barrier and gut microbial dysbiosis, high-fat diets (HFDs) and obesity increase the incidence of gastrointestinal malignancies and aggravate chronic low-grade inflammation [32]. According to one research, consuming too much fructose lowers the intestinal barrier, which makes it possible for endotoxins produced by gut bacteria to enter the circulation. This leaking exposes the patient to HCC risk in addition to serving as an inflammatory trigger for hepatosteatosis and nonalcoholic steatohepatitis (NASH) [33,34]. There will be more worries about nutritional and food-related cancer as the Western diet spreads across the world. This suggests that inflammation may increase the remodeling of esophageal epithelia with aging, which might lead to esophageal cancer. Other contributing causes to this remodeling include excessive drinking and smoking.

3.4. Cancer-induced inflammation

"Cancer-elicited inflammation (CEI)" happens after the tumor starts to grow, in contrast to other types of inflammation that happen before the tumor develops [18]. For example, only 2 % of colorectal malignancies (CRCs) involve intestinal inflammation, such as IBD; yet, most CRC tissues that arise sporadically have significant immune cell infiltration and elevated production of inflammatory cytokines and chemokines [18]. The many internal components of the tumor constitute the root cause of CEI. In addition to directly affecting cancer cells, the activation of oncogenes such as Kirsten rat sarcoma viral oncogene homolog (KRAS) and Myelocytomatosis oncogene (MYC) and the inactivation of tumor suppressors such as tumor suppressor (TP53) initiate transcriptional programs that lead to the creation of a microenvironment that promotes tumor growth by attracting immune cells, promoting angiogenesis, and producing pro-inflammatory cytokines and chemokines [35–37]. Tumor-Associated Macrophages (TAMs) release IL-1β when p53-deficient breast cancer cells generate WNT ligands, which leads to the spread of cancer and systemic neutrophilic inflammation [38].

Abnormal angiogenesis, which exposes tumor cells to unfavorable microenvironments such as hypoxia and nutritional deprivation and causes significant necrotic cell death in the tumor cells, is a common characteristic of solid tumors [39]. Damage-associated molecular patterns (DAMPs) including ATP, IL-1α, and HMGB1 are released by necrotic tumor cells and may act as mediators of inflammation [40]. DAMPs trigger the innate immune response and encourage the growth of malignancies via their interactions with Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs). The phrase "sterile inflammation" describes certain forms of CEI that take place in the absence of a pathogenic infection.

However, infections caused by bacteria and their metabolites may also lead to CEI. For example, loss of the adenomatous polyposis coli (APC) gene impairs the intestinal barrier in colorectal malignancies (CRCs), enabling microbes to penetrate the tumor bed and cause inflammatory responses that accelerate the tumor's development [41]. Hence, one of the main causes of CEIs is the loss of tissue structure brought on by malignant transformation.

3.5. Inflammation from cancer treatment

As strange as it seems, there are circumstances in which removing tumor cells might trigger inflammatory reactions that encourage the development of new cancers. Malignancies proliferate, angiogenesis, and spread due in part to the secretion of pro-inflammatory cytokines by immune cells in response to DAMP molecules or tumor cell debris. Other important causes include radiation and chemotherapy-induced necrotic cell death [42,43]. This technique is most likely analogous to natural tissues' capacity to regenerate damaged tissue and heal wounds. Anti-cancer medications worsen inflammation, which increases a patient's resistance to treatment. While neutralizing cytokines such as IL-17A improve response to therapy, 5-fluorouracil (5-FU) administration, for example, causes inflammatory responses that encourage tumor development [44]. Most notably, intestinal barrier failure-induced bacterial translocation may cause systemic inflammation, which in turn promotes the formation of malignancies. Chemotherapy also destroys healthy organs like the intestines. Therefore, cytotoxic cancer treatment is a two-edged sword.

However, when anti-cancer treatment leads to cancer cell death, tumor antigen release often rises, potentially enhancing anti-tumor immune responses [8]. It is thus debatable whether therapy-induced

inflammation encourages the growth of tumors; other variables, such as the kind of cancer cell and the usage of anti-cancer drugs, could be involved. It matters how cells die; compared to apoptosis and autophagic cell death, necrosis, and necroptosis, which generate DAMPs, are stronger inducers of inflammation [45,46].

4. Histone modifications as key players in cancer epigenetics

Without changing the DNA sequence, histone modifications are post-translational alterations to histone proteins that control chromatin structure and gene expression [47]. Because they change chromatin accessibility, these modifications which include acetylation, methylation, and phosphorylation play crucial roles in gene regulation [48]. Apoptosis, DNA repair, and cell cycle control genes are dysregulated by aberrant histone modifications, which are commonly seen in cancer and aid in tumorigenesis [49].

4.1. Different kinds of histone modifications and how they affect cancer

4.1.1. Histone acetylation

Mechanism: Higher gene expression and an open chromatin structure result from the reduction of histone-DNA interaction caused by the addition of acetyl groups to lysine residues on histone tails [50].

Role in Cancer: Abnormal acetylation patterns have a role in cancer by either activating oncogenes or silencing tumor suppressor genes, which can impact DNA repair and cell cycle regulation [51].

4.1.2. Histone Methylation

Mechanism: Depending on the site of methylation, adding one, two, or three methyl groups to particular histone residues can either activate or repress gene expression [52].

Role in Cancer: Mistakes in methylation patterns can cause tumor suppressor gene silencing or oncogene activation, which can accelerate the development of cancer [53].

4.1.3. Histone phosphorylation

Mechanism: Cellular signals cause histones to become phosphorylated, which in turn affects transcription and chromatin remodeling by influencing other histone modifications [54].

Role in Cancer: Histone phosphorylation can change acetylation and methylation patterns in cancer cells, which can result in dysregulated gene expression [55].

4.2. Influence of cytokines on histone modifications in cancer

By affecting histone modifications, cytokines small signaling proteins involved in inflammation and immune responses play a crucial part in the development of cancer [56]. Inflammation and epigenetic regulation in cancer are linked by this interaction [57].

4.2.1. Histone modifications induced by cytokine

Histone Acetylation: Pro-inflammatory cytokines such as Tumor necrosis factor (TNF-α) and IL-1β encourage histone acetylation, which activates genes linked to the development and spread of tumors [58].

Histone Methylation: Cytokines change the methylation patterns that control genes linked to cancer by modulating histone methyltransferases and demethylases [56].

4.2.2. Interaction between epigenetics and cytokines

Histone-modifying enzymes are attracted to particular genomic loci by cytokine signaling pathways, which changes chromatin structure and gene expression [59].

This establishes a feedback loop in which inflammatory genes are activated by cytokine-induced histone modifications, thereby sustaining chronic inflammation and encouraging the development of tumors [60].

4.3. Chronic inflammation and cancer: the role of histone modifications and cytokines

One known contributing factor to the onset and spread of cancer is chronic inflammation [61]. Cytokines and histone alterations are important mediators of the link between inflammation and cancer [62].

4.3.1. Mechanisms connecting cancer and inflammation

Intrinsic Pathway: When cancer cells undergo genetic mutations, inflammatory programs are triggered, resulting in a microenvironment that promotes tumor growth [63].

Extrinsic Pathway: By attracting inflammatory cells and mediators, pre-existing inflammatory conditions make tissues more vulnerable to cancer [64].

4.3.2. Histone modifications' role

Histone modifications and other epigenetic alterations brought on by chronic inflammation dysregulate genes implicated in the development of cancer [56].

Histone-modifying enzymes are influenced by inflammatory cytokines, which change chromatin structure and encourage carcinogenesis [65].

4.3.3. Cytokines' function

Pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, promote angiogenesis, tissue remodeling, and leukocyte recruitment, all of which contribute to the development of tumors [66].

Cytokines alter the transcriptional regulation of genes involved in the survival and proliferation of cancer cells by modulating histone modifications [67].

5. Cell types involved in cancer-related inflammation

The development and spread of cancer are fueled by a complex, self-reinforcing network of cytokines, chronic inflammation, and altered histones. Long-term inflammation intensifies epigenetic changes, especially histone modifications like methylation and acetylation, which can either activate oncogenes or silence tumor suppressor genes [68]. Histone methyltransferase Enhancer of zeste homolog 2 (EZH2), for example, is frequently overexpressed in a variety of cancers, which raises H3K27me3 levels and subsequently suppresses tumor suppressor genes [69]. On the other hand, oncogenes involved in cell cycle regulation and apoptosis can be activated by histone acetylation, which is controlled by Histone acetyltransferases (HATs) and histone deacetylases (HDACs) [70]. The inflammatory environment maintains and intensifies these epigenetic modifications, resulting in a vicious cycle that promotes carcinogenesis [68]. The tumor microenvironment (TME), which is made up of stromal cells (like endothelial cells and fibroblasts), immune cells, and cancerous cells, is shaped by the interaction of inflammation and epigenetic changes. Through direct contact or the release of soluble factors such as cytokines, growth factors, and chemokines, these TME components dynamically interact to create an inflammatory environment that promotes tumor growth and metastasis [71]. For instance, extracellular matrix proteins and cytokines secreted by cancer-associated fibroblasts (CAFs), which are controlled by epigenetic modifications, can foster an immunosuppressive environment [72]. Similarly, epigenetic changes can cause tumor-associated macrophages (TAMs) to change from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, which further reduces the anti-tumor immune response [72]. Gaining knowledge of these complex relationships between inflammation, the TME, and histone modifications paves the way for the creation of specialized treatments that break this cycle and enhance the effectiveness of cancer treatment. The traits and roles of each TMEcomponent will be covered in more detail in the section that follows, along with how they support the inflammatory microenvironment and aid in the growth of tumors.

5.1. Cancer-associated fibroblasts

In the microenvironment of many solid cancers, Cancer-Associated Fibroblasts (CAFs) are the most common type of stromal cells. During the transition from normal fibroblasts, they become active due to reciprocal tumor stroma signaling. Multiple mechanisms, including growth factor secretion, angiogenesis, extracellular matrix remodeling, and the production of tumor-promoting inflammation via cytokine and chemokine release, are known to be involved in the encouragement of tumor development by CAFs. In the end, these pathways aid in the recruitment of immune cells and the effective control of the TME [73]. In CAFs, activation of the NLRP3 inflammasome results in the production of IL-1β, which facilitates the growth of breast cancer and lung metastases [74]. Pro-inflammatory cytokines that induce cellular senescence in CAFs include TNF, IL-1α, and IL-1β. As a result, the downregulation of EZH2 by senescent CAFs promotes H3K27me3 demethylation, maintaining high levels of GC peritoneal dispersion and IL-6 production [75]. For GC patients who also have increased levels of these pro-inflammatory cytokines simultaneously, the prognosis is worse [76]. Research has shown that the heterogeneous cell population known as CAFs is made up of several cell subsets with different roles [77–79]. Öhlund et al. identified two unique CAF populations: inflammatory (iCAFs) and myofibroblastic (myCAFs) [80]. iCAFs have low expression of Alpha-smooth muscle actin (α-SMA) and high expression of inflammatory mediators such as IL-6, IL-11, and Leukemia inhibitory factor (LIF), while myCAFs have the opposite properties. For this reason, a variety of solid tumors may benefit from therapy that specifically targets pro-tumorigenic CAF subpopulations.

5.2. Lymphocytes

T lymphocytes are immune cells that often enter the TME. The differentiation of T lymphocytes into αβ and γδ T cells is based on the expression of T cell receptors. The majority of T cells are classified as αβ T cells, which are further divided into $CD8^+$ cytotoxic T cells and $CD4^+$ helper T (Th) cells, which comprise Th1, Th2, Th9, Th17, Th22, Tfh, and regulatory T (Treg) cells [81]. $CD8^+$ T and Th1 cells perform critical roles in anti-tumor immunity by eradicating tumor cells. However, throughout the course of intestinal cancer development, Th17 and Th22 cells are necessary for the generation of the pro-tumorigenic cytokines IL-17 and IL-22 [82,83]. A subset of T cells known as "Treg cells" inhibit the immune system, making anti-tumor responses less efficient and promoting the growth of malignancies [84]. However, in some clinical contexts, Tregs may transform into an inflammatory phenotype akin to Th17 and Th22, which facilitates the formation of cancers [85,86]. Recent studies on the involvement of $CD4^+$ T cells in inflammation suggest that they may play a role in age-dependent carcinogenesis [87,88].

Innate lymphoid cells (ILCs) are a subpopulation of innate lymphocytes that control inflammation, carcinogenesis, tumor monitoring, and tissue homeostasis [89–92]. NK cells and ILC3s make up group 3, LTi cells and ILC2s make up group 2, while NK cells and ILC1s make up group 1. Group 1 ILCs are mostly anti-tumorigenic, while groups 2 and 3 ILCs are primarily pro-tumorigenic [89]. Despite the wealth of data connecting NK cells to cancer, less is known about the roles that other ILC subsets—metastasis, inflammation-induced carcinogenesis, and anti-cancer immunity play in the illness.

5.3. Myeloid cells

One of the most common immune cell subgroups in the tumor microenvironment (TME) is TAMs, and they play a significant role in producing pro-inflammatory cytokines that fuel cancer-related inflammation [93]. One of the distinguishing features of this cell population is its functional "polarization," which is exclusive to the M1 and M2 subtypes and is dependent on external inputs. Among the pro-inflammatory cytokines released by these cytotoxic and pro-inflammatory M1-type macrophages are nitric oxide (NO), tumor necrosis factor (TNF), IL-1, IL-6, and IL-12. M2-type macrophages are crucial for resolving inflammatory responses because they express chemicals related to immunosuppression (IL-10, TGF-β, PGE2, and arginase-1), angiogenesis (IL-8, VEGF-A, and MMP-9), and cell proliferation and tissue repair (IGF-1 and amphiregulin) [94]. According to current theories, the majority of TAMs are associated with the M2 subtype, which stimulates angiogenesis and tumor development. Tumor materials produced by the Warburg effect, such as lactic acid, polarize macrophages in the TME in an M2-like way [95]. In contrast, the primary source of inflammatory cytokines that stimulate tumor development in TME is "M1-cytokines" produced by TAMs. Even while the general classification of M1 and M2 macrophages is based on gene expression patterns, TAMs may express genes related to both M1 and M2, requiring a unique approach to TAM functional categorization [63]. This is because the M1/M2 paradigm breaks down under complex situations like the TME. Surprisingly, recent research has shown that tumor-educated macrophages produce pyrimidine nucleotides that provide pancreatic cancer cells gemcitabine resistance, suggesting a novel function for TAMs [96].

Renal-associated neutrophils (TANs), important participants in acute inflammation, could also be engaged in chronic inflammation subsequent to malignancy. High systemic neutrophil-to-lymphocyte ratios (NLRs) are linked to a poor prognosis in the majority of human epithelial tumor types [97], and systemic neutrophilic inflammation in cancer patients promotes the spread of cancer cells [98,99]. Noteworthy, research has revealed that neutrophils that concentrate in humans and animals with tumors are "pathologically activated," which may promote the growth of tumors by impeding the immune system's capacity to fight cancer and resulting in the formation of premetastatic or metastatic niches [99,100]. This group of neutrophils is known as "polymorphonuclear myeloid-derived suppressor cells" (PMN-MDSCs); high MDSC levels in cancer patients may be a sign of poor prognosis and resistance to cancer therapy [101]. Remarkably, recent studies have shown that neutrophil functional reprogramming in the TME is regulated by the endoplasmic reticulum (ER) stress response and cellular lipid accumulation [102,103]. Apart from PMN-MDSCs, another subtype of MDSCs seen in tumor-bearing hosts are monocytic MDSCs, which have an appearance similar to monocytes. According to a study by Kwak et al., M-MDSCs may develop into S100A9-expressing tumor-promoting macrophages [104].

Within the tumor microenvironment (TME), dendritic cells (DCs) are the most effective antigen-presenting cells that have the potential to trigger T-cell responses specific to cancers. However, they are an uncommon kind of immune cell. However, the TME often erodes these anti-tumor characteristics, polarizing them into phenotypes that encourage the formation of tumors [105].

5.4. Tumor endothelial cells

Tumor endothelial cells, or TECs, are the cells that line tumor blood vessels and contribute to the formation of tumors by functioning as conduits for the dissemination of cancer cells and supplying nutrients and oxygen [106]. Angiogenesis is the process of generating new blood vessels, and angiogenesis is a hallmark of cancer [7]. Hypoxia is the primary cause of tumor angiogenesis, and hypoxia-inducible factor 1 (HIF-1) is a crucial regulator of this process [107]. Tumor angiogenesis requires pro-angiogenic molecules like Vascular endothelial growth factor (VEGF-A), which TAMs produce in response to hypoxic stimuli [108]. It is noteworthy that the interaction between TECs and tumor cells via inflammatory mediators has the potential to modify the ways in which metastatic cancer cells invade and spread [109,110].

6. Multifaceted role of inflammation during tumorigenesis

Prolonged inflammation has an impact on all stages of the

development of cancer, including the start, growth, and spread of tumors. Here, we discuss the several functions that inflammation performs throughout a tumor's whole developmental stage (Fig. 2).

Long-term exposure to substances known to induce tumors, such as infectious viruses and gut bacteria, often triggers inflammatory signaling that results in chronic inflammation, which fuels the development of tumors.

Inflammatory cells that are proliferating release growth factors, reactive oxygen species (ROS), and cytokines such as IL-1, IL-6, and TNF. These are inflammatory mediators that promote tumor growth and may have a direct or indirect role in the overall development of the tumor. Tumor cells are one item that intensifies this inflammatory cycle. For instance, increased production of chemokines and cytokines due to cancer-associated gene deregulation draws and activates a significant number of immune cells (dashed arrows).

6.1. The role of inflammation in tumor initiation

Genes linked to cancer in normal cells must accrue genetic mutations, epigenetic changes, or both before tumors develop. This mechanism requires the existence of an inflammatory microenvironment. Proliferating inflammatory cells like neutrophils and macrophages are the main source of ROS and reactive nitrogen intermediates (RNIs), which cause genomic instability and damage to DNA. Canli et al.'s study indicates that ROS produced by myeloid cells alters the epithelial cells' genome, which promotes the malignant growth of the cells [111]. By raising intracellular ROS and RNI in premalignant cells, cytokines secreted by inflammatory cells aid in the process of mutagenesis. Numerous significant genes linked to cancer, including the tumor suppressor TP53 and the mismatch repair (MMR) response genes, have been linked to this kind of inflammation-induced mutagenesis [8]. Extended inflammation may also impact the functions of the epigenetic machinery, including microRNA, long non-coding RNA (lncRNA), and enzymes that modify DNA and histones. Also, it may result in chromosomal instability. Tumor development is one outcome of these pathways that may occur.

On the other hand, inflammation might arise from damage to genomic DNA. For instance, innate immune DNA sensing system activation brought on by carcinogen-induced genotoxic stress results in inflammation-induced skin carcinogenesis [112,113]. Wilson et al. describe colibactin as a gut bacterial genotoxin that alkylates DNA in vivo and may have a role in the development of colorectal cancer (CRC) [114].

In addition to providing habitats for tumor-initiating cells to survive and proliferate, chronic inflammation also increases the number of sites available for mutagenesis and gives premalignant cells properties similar to those of stem cells [8].

6.2. The role of inflammation in tumor progression and metastasis

When tumor cells exhibit malignant traits, namely the capacity to proliferate, it may result in unpredictably hazardous situations. One of the most significant events in this phase is the epithelial-mesenchymal transition (EMT), which occurs when epithelial cancer cells take on mesenchymal characteristics such as increased cell motility and migratory activity [115,116]. EMT happens not just during wound healing and tissue fibrosis after damage, but also during the start and progression of cancer. Numerous inflammatory mediators, including as TNF, IL-1β, IL-6, IL-11, and IL-8, are known to be able to initiate EMT [117]. Inflammation is a component of tumor stroma remodeling, which is required for cancer cells to migrate and invade effectively. For example, TAMs generate Matrix metalloproteinases (MMPs) that break down cell-cell adhesions and extracellular matrix, promoting the growth of cancer cells [118]. Furthermore, chemokine gradients produced inside the TME and recognized by chemokine receptors regulate tumor cell migration and metastases to specific distant organs, much like leukocyte trafficking [119]. Within the TME, pro-inflammatory cytokines TNF and IL-1β induce the synthesis of chemokines, such as CXCL1 (keratinocyte-derived chemokines), CXCL5, CXCL8 (IL-8), CCL2 (MCP-1), and CCL5 (RANTES) [120,121].

Cancer cells may spread via lymphatic and blood channels [8]. One of the chemicals produced by activated macrophages to promote angiogenesis and lymphangiogenesis is VEGF. In order to help metastatic cancer cells survive and colonize their target organ when they reach the bloodstream, immune cells create inflammatory mediators. Albrengues et al. report that in mice subjected to long-term experimental lung inflammation caused by tobacco smoke or lipopolysaccharide (LPS) and the creation of neutrophil extracellular traps (NETs), latent cancer

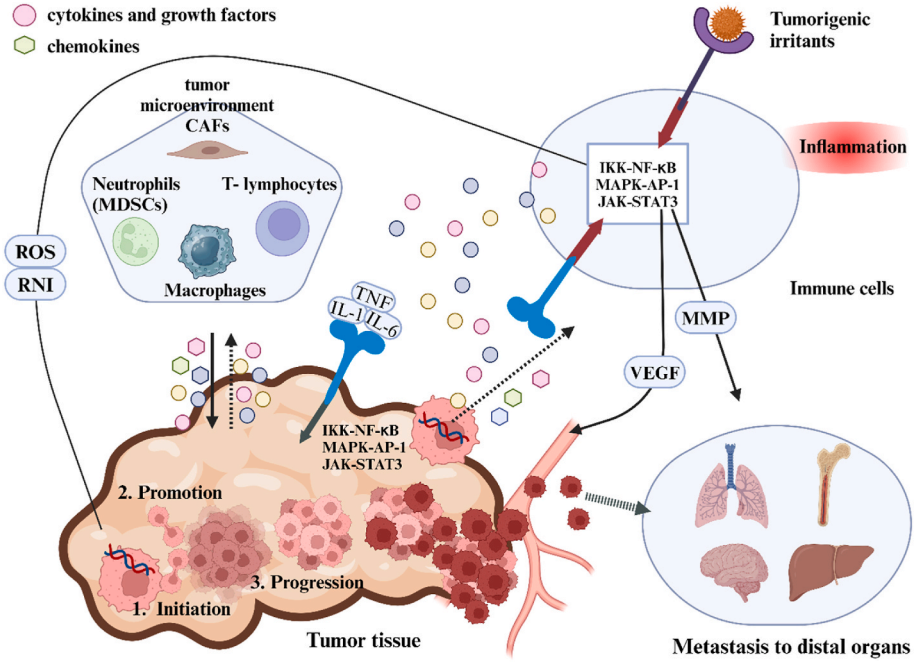

Fig. 2. Extended inflammation causes tumors to develop more quickly.

cells become rapidly spreading metastases [122].

6.3. The role of inflammation in tumor promotion

Malignant-transformed cells proliferate abnormally to create the main tumor during tumor promotion. Currently, inflammatory cells play a vital role in providing growth factors and cytokines that support the survival and multiplication of tumor cells. In some cancer models, tumor development is suppressed by myeloid cell-specific inhibition of IKK-nuclear factor-κB (NF-κB) signaling, a key pathway of pro-inflammatory cytokine production [123,124]. The role of these substances in tumor promotion was further shown by the studies conducted on mice whose genes for different cytokines or cytokine receptors were knocked out [125]. In addition to tumor cells, inflammatory signals affect immune cells, fibroblasts, endothelial cells, and other components of the tumor stroma. These cells also form the tumor microenvironment (TME), which promotes the growth of the tumor [8].

7. Tumor-promoting inflammatory signaling

Growth factors, chemokines, and cytokines play a major role in the development of the inflammatory milieu inside the tumor microenvironment (TME). Then, this environment affects other components of the TME or directly promotes the growth of tumors on tumor cells. A multitude of transcription factors and signaling molecules regulate complex signaling networks, which are essential for the synthesis and operation of a wide range of inflammatory mediators. Numerous significant players are involved in the process, such as the Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3), the mitogen-activated protein kinase (MAPK)-activator protein-1 (AP-1) axis, and NF-κB [8,126,127].

Close cooperation exists between the transcription factor NF-κB, which binds DNA, and the nuclear factor-kB kinase subunit β (IKKβ) [126]. The IKK-NF-κB axis controls the expression of several genes that are associated with inflammation and cancer, including TNF, IL1B, and IL6, growth factors (CSF2 (GM-CSF), SPP1 (osteopontin), and VEGFA), chemokines (CXCL8 (IL-8), CXCL1, CXCL2, CCL2 (MCP-1), and CCL5 (RANTES), MMPs, and pro-inflammatory enzymes (PTGS2 (cyclo-oxygenase-2 (COX-2) and NOS2). Numerous cancer forms exhibit constitutive activation of the IKK-NF-κB axis in both the cancer cells and the surrounding tissues. Two types of PRRs that employ the downstream signal transduction route to activate NF-κB are TLRs and Nod-like receptors. Through PRR activation, DAMPs, pathogens, and gut microorganisms all induce NF-κB-dependent gene expression. Pro-inflammatory cytokines like TNF and IL-1 may activate NF-κB via cognate receptors, creating a positive feedback loop [126].

Early studies on IL-6-stimulated hepatocytes revealed that STAT3 may bind DNA [127]. STAT3 hyperactivation in malignant and non-cancerous cells inside the tumor microenvironment (TME) of most human malignancies has been linked to poor patient outcomes [128, 129]. Platelet-derived growth factor (PDGF), epidermal growth factor (EGF), cytokines from the IL-6 family (IL-6, IL-11, LIF, and oncostatin M), IL-22, and IL-23 are growth factors that mainly activate STAT3 via their associated receptors. STAT3 may then connect to the target region and initiate transcription after JAK phosphorylates it [128,130]. STAT3 activates a large number of NF-κB targets and genes linked to the growth of tumors [126]. Dimeric AP-1, a DNA-binding transcription factor, functions indirectly via MAPK signaling. The MAPK-AP-1 axis, like NF-κB, activates target genes by stimulating downstream PRRs and inflammatory cytokine receptors (TNF and IL-1).

Only AP-1, STAT3, and NF-κB are able to regulate the patterns of gene expression that drive tumor development and inflammation. Working together and interacting with other transcription factors and associated signaling cascades, including p53, HIF-1α, and WNT-β-catenin, is essential [126,131]. Interestingly, cytokines of the IL-6 family also activate Yes-associated protein (YAP) and downstream Notch signaling via their shared receptor glycoprotein 130 (gp130)/IL6ST in gastrointestinal cancers, in addition to activating the JAK-STAT3 pathway. Since YAP and Notch are transcriptional regulators that govern tissue development and regeneration, Gp130 signaling connects cancer-associated inflammation with tissue regeneration [132–134].

8. Plasticity and inflammation in the tumor microenvironment

Tumor heterogeneity is one recent development in oncogenesis research. In addition to the well-known genetic and epigenetic heterogeneity of cancer cells, tumors vary significantly in terms of the quantity and phenotype of the immune and stromal cells involved in recruitment. As a consequence, the TME possesses a high level of cellular plasticity (Fig. 3). Different transcriptional processes initially induce distinct types of cell polarization in order to illustrate this adaptability. This enables cells to carry out functions that are required for tissue regeneration or tumor formation but that these cells would not typically be able to execute. Second, cells may shift between many states during processes such as cell migration, metastasis, epithelial-mesenchymal transition (EMT), and mesenchymal-epithelial transition (MET) as a result of spatiotemporal cellular plasticity. Subtypes and types previously assigned to distinct cell types or phases of terminal differentiation within the TME most likely reflect these differentiation and activation stages. These states could experience further phenotypic and functional changes as a result of cell plasticity. Different cell types may be flexible during different stages of a tumor's development. Barker et al. suggest that stem cells might be the cause of intestinal cancers in their early stages [135]. On the other hand, NF-κB-triggered inflammatory signaling may cause mutant epithelium and transient-amplifying cells to dedifferentiate and become plastic, culminating in the acquisition of a phenotype similar to cancer stem cells [136]. Cancer cells may go through many EMT and MET phases [137–139]. The most well-known application of cancer cell plasticity is the restoration of the cancer stem cell pool after treatment or metastasis [140,141]. Growth factors, cytokines, and inflammation are significant regulators and impacts on all of these processes. That being said, not all cancer cells possess plasticity. Nearly all other cell types in the TME use reciprocal activation, inhibition, and differentiation signals to influence and foster plasticity. For example, cancer cells may alter the plasticity of dendritic cells and ultimately affect T-cell responses by supplying them with antigens and signals generated by tumors [142]. Alexander and Cukierman have shown that cancer cells have the ability to induce fibroblasts to differentiate into states that facilitate the formation of tumors and immunosuppression [143]. On the other hand, immune cell-produced cytokines like IL-6 or IL-17 may also cause fibroblast activation [144,145]. Cancer-associated fibroblasts (CAFs) exhibit pro- or anti-tumorigenic behavior according to inflammatory stimuli [146]. Depending on their proximity to cancer cells and their response to TGF-β activation or IL-1R engagement, they may develop into either inflammatory CAFs (iCAFs) or myofibroblasts (myCAFs) [147,148]. CAFs supply cancer cells with differentiation, growth factors, survival, and metabolic cues that promote metastasis, growth, and resistance to therapy in return for protecting the cancer stem cell niche [149–153]. Additionally, CAFs may regulate the infiltration of T and myeloid cells and produce molecules that regulate the proliferation, adaptability, and immunosuppressive properties of immune cells [154–156]. Research conducted by Özdemir et al. and Pallangyo et al. has shown that CAFs or the inflammatory signals they generate may possess tumor-suppressive qualities based on the circumstances [157,158]. Furthermore, TME-regulated plasticity is highly present in myeloid cells [159–161]. TGF-β, dead cell products, and other cytokines polarize adjacent macrophages or incoming monocytes toward a more "tissue repair" subtype, which is defined by a decrease in genes involved in antigen presentation and the induction of antigen-dependent immune responses and an increase in growth factors and tissue-protective factors [162–164]. In vivo, the expression of genes belonging to the "former M1" and "former M2" groups is possible in

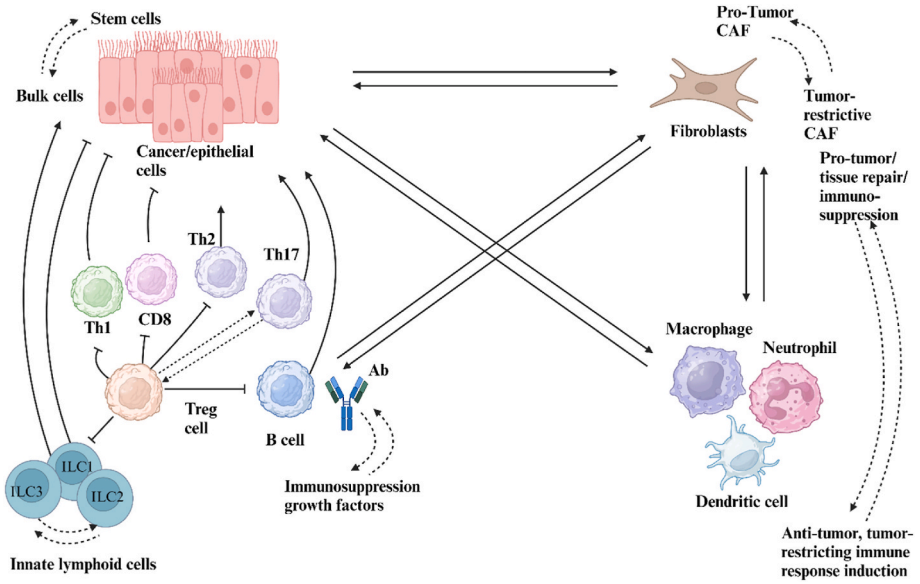

Fig. 3. Increased cell plasticity within the tumor microenvironment (TME).

these macrophages. However, it is now evident that the complex background of the TME does not allow for such a differentiation. Adaptive immunity cells, such as T helper 2 (Th2) cells [165], B cells [166], or T regulatory cells [167,168], may also provide the direction signals for macrophage polarization. These cells can penetrate cancers that are bacterially rich [169]. Tumor-associated macrophages (TAMs) may, however, be polarized toward a functional phenotype described as "tumor-ignorant" TAMs by Th1 and $CD8^+$ T cells. Increased phagocytosis, antigen presentation, and cross-presentation, together with the absence of growth factor production, define this subgroup of TAMs. Thus, this phenotype may elicit immune responses against malignancies, particularly in cases where pathways reliant on interferon-γ (IFN-γ) are implicated [168,170]. Curiously, each tumor types seem to teach their specific macrophages, leading to tumor-associated macrophage (TAM) profiles that are exclusive to each tumor [163]. Moreover, macrophage reprogramming might result from activating their integrins and surface receptors, such as CD11b [171]. Similar to monocytes and macrophages, the TME imprints tumor-associated neutrophils with a notable degree of plasticity through metabolism regulation or cytokine signaling, further shaping them into being anti-tumorigenic and antigen-presenting [172, 173], immunosuppressive [103,174], or directly tumor-promoting [175, 176].

T and B cells form the adaptive immune arm in the fight against cancer, and they are also very malleable within the TME. How B cells recruited into tumors regulate anti-cancer immune responses, directly contribute to tumor promotion, or modify the myeloid cell response depends on the signals that B cells receive from TME and the kinds of ligands that their B cell receptors (BCRs) recognize [177–180]. Though essential for tumor immune surveillance, γδ T cells may also exhibit tumor-promoting traits associated with cytokine production in the tumor microenvironment (TME) or perhaps operate as a negative regulator of T cell activation in pancreatic cancer [181]. T lymphocytes with αβ have exceptional flexibility in the TME, where they undergo priming, and in the secondary lymphoid organs, where they undergo impact. Inflammatory cytokine IFN-γ triggers the PD-L1-PD-1 pathway, which cancer cells may use to communicate and eventually eliminate $CD8^+$ and $CD4^+$ T cells [182]. According to Clever et al., Eil et al., and Johnson et al., metabolic products of TME such as glutamine, potassium ions, or hypoxia, as well as regulatory T cells, may impose comparable processes. In response to inflammatory and microbiological cytokine signaling, FoxP3+ Tregs, which are normally anti-inflammatory and immunosuppressive, may co-express the transcription factor RORγt [183–185]. This produces a pro-inflammatory regulatory plastic T cell lineage that may produce the cytokines IL-17 and IL-22 that promote tumor growth but are generally suppressive for anti-cancer immunity [186].

9. The role of inflammation in cancer types

9.1. Liver cancer

With almost 70 % of cases, intrahepatic cholangiocarcinoma (ICC) is the second most frequent kind of liver cancer [187]. Alcohol use, nonalcoholic fatty liver disease (NAFLD), and hepatitis virus infection (HCV or HBV) are three known risk factors for HCC [188]. Obesity and type 2 diabetes are strongly linked to NASH-related HCC, which is becoming more commonplace globally, particularly in developed nations, albeit its precise causes are still unknown [189]. While the exact cause of most ICCs remains unknown, certain risk factors have been found, such as liver flukes, hepato-choledocholithiasis, and chronic inflammation of the liver caused by primary sclerosing cholangitis [156]. Remarkably, chronic inflammation is thought to be the cause of 80–90 % of cases of both forms of liver cancer [190].

Chronic inflammation initiates the process of cell death and regeneration, which leads to liver carcinogenesis. This cycle then produces signals for cell survival and proliferation, which in turn stimulates the development of dysplasia, cancer, and regenerative nodules [191,192]. Prolonged cytokine production is linked to the development of cancer and activates several types of liver cells via a variety of unique and repetitive interactions. IL-4, IL-5, IL-8, and IL-10 are examples of Th2-like cytokines, which are more common in the microenvironment than Th1-like cytokines [193].

TNF increases NF-κB and stops converted hepatocytes from going through apoptosis in conjunction with other growth factors and cytokines generated during inflammation [126,194–196]. When an immune cell has chronic hepatitis, it generates TNF, which activates IKK and NF-κB. This leads to the production of proliferative genes like CCND1 and anti-apoptotic genes like BCL2L1 as well as TNF gene [194]. However, prior studies using a synthetic animal model of HCC found that IKKβ ablation specific to hepatocytes sped up the progression of the illness [191]. IL-6 is another important regulator of the development of HCC. Immune cells called Kupffer cells and macrophages secrete IL-6, which activates the JAK-STAT signaling pathway and promotes cell proliferation and survival [192,197]. However, human ICC has

significant levels of IL-6 expression, which improves cell survival via a STAT3-dependent mechanism. Furthermore, in a subset of human ICC, the IL-6-STAT3 signaling pathway is linked to a pattern of gene expression [198,199]. Because it cooperates with STAT3 to regulate the activation of several genes related to cell survival and proliferation, inhibiting IL-22, a cytokine that has the ability to regenerate hepatocytes, aids in the reduction of HCC [200].

Hepatitis is a major and secondary cause of HCC development, and HBV causes hepatitis. Covalently closed circular DNA (HBV cccDNA) from HBV integrates with the host genome early in the formation of clonal tumors, causing genomic instability and direct insertional mutagenesis of several genes associated with cancer [201]. The HBx regulatory protein is necessary for viral replication, but it may also have a role in HBV oncogenicity [202]. In addition to being required for viral replication, HBx also attracts chromatin-modifying proteins such as HDAC1, activates transcription factors via the Ras-Raf-MAPK and NF-κB pathways, and results in genomic instability, all of which contribute to the development of HCC [203]. HBV-related HCCs are genetically distinct from other forms of HCCs due to their high prevalence of chromosomal abnormalities, TP53 inactivation, and overexpression of genes associated with fetal liver progenitor cells [204]. Chronic HCV infection causes HCC via overlapping host metabolic bystander effect, indirect host-related inflammatory response, and direct virus-induced cellular programming [205,206].

The immunological milieu of HCC promotes both immunogenic and tolerogenic immune responses [207]. Enhancing immune tolerance, HCCs generate IL-10 and TGF-β. Tumor cells and TILs express immunosuppressive regulators, including PD-1, PD-L1, and CTLA4, that promote the growth and spread of cancers [208,209]. Despite the fact that immunotherapy has shown efficacy [210], further research in this area is required to completely comprehend the liver TME and create efficient anti-cancer immunotherapy.

9.3. Breast cancer

The relationship between inflammation and breast cancer has been the subject of several investigations. This section will cover current developments in the area, with a focus on the pathophysiology of inflammatory breast cancer (IBC) and the role inflammation plays in the development of obesity-related breast cancer.

IBC is an uncommon subtype of breast cancer, accounting for just 3 % of occurrences. However, it is known to be aggressive, and it accounts for 7–10 % of breast cancer deaths. Given that individuals with IBC often outlast those without the disease in terms of age, it is essential to understand the underlying processes and develop specifically tailored therapies for IBC [238]. The two ways that IBC differs from non-IBC are dermal-lymphatic invasion and intralymphatic tumor emboli [239]. Moreover, despite the discovery that ALDH1 [240] and E-cadherin [241] are indicators of a poor prognosis, the categorization of IBC and non-IBC based on genetic characterization has not yet been shown to be beneficial [238]. IBC has been associated with a number of inflammatory pathways, although there are currently no clear markers. IBC is associated with elevated levels of cytokines, including IL-6 [242] and IFNα [243]. By inhibiting IL-6 with a neutralizing antibody or statin medication, it could be feasible to stop the development of cancers, indicating that the TME has changed. In addition to the JAK-STAT signaling cascade, other pathways implicated in the development of IBC include COX-2 and EGFR. Phase II therapeutic studies with anti-EGFR antibodies are promising [244]. Furthermore, JAK2-STAT3 hyperactivation may be the cause of therapy resistance in IBC [245]. This technique may also aid in the survival of cancer stem-like cells in breast cancer instances [246,247]. Empirical data suggests that COX-2-induced inflammation accelerates the growth of many malignancies, including IBC [248]. Extended inflammation in IBC may increase COX-2 and EGFR signaling, which may work together to maintain cancer cells' stem-like properties [249]. Furthermore, understanding the pathophysiology of IBC requires knowledge of the immune cell composition [238]. Although DCs, T cells, MSCs, and TAMs have been shown to play important roles in IBC, more compelling evidence is required to designate these immune cell types as prospective therapeutic targets [242].

Adipocytes and breast cancer cells interact to regulate the course of the illness and the degree of chemoresistance [250]. White adipose tissue (WAT) adipocytes, which are prevalent in obese individuals, are linked to these processes and chronic inflammation [251]. WAT-produced free fatty acids attach to TLR4, activating NF-κB and releasing pro-inflammatory cytokines such as TNF and IL-1β [252]. Adipocytes also suppress COX-2 and sex hormones, which increases aromatase activity and speeds up androstenedione's enzymatic conversion to estrone [253,254]. In order to trigger the production of PGE2 from malignant epithelial cells or to activate aromatase, adipocytes also increase insulin levels [255].

There have been a lot of studies on the relationship between the adipokines leptin and breast cancer. Overexpressed leptin interacts with leptin receptors (LEPRs) in peritumoral fat and breast cancer cells to activate many signaling cascades that promote tumor formation and survival, including the PI3K-AKT-mTOR and JAK2-STAT3 pathways [253,256]. Cytosolic signaling events may trigger NF-κB and HIF-1α, which in turn can stimulate VEGF-A [257]. mTOR signaling promotes the production of TNF, IL-1, and IL-6, among other pro-inflammatory cytokines [256]. Moreover, leptin-LEPR signaling improves the motility, invasion, proliferation, and self-renewal capacities of breast cancer stem cells in addition to working with EGFR, Notch, IL-1, and the estrogen receptor [258,259]. Due to the fact that leptin, IGF-1, adipocytokines, and hormones associated with obesity are key factors in the etiology of breast cancer, it is now feasible to prevent the illness through lifestyle changes and signaling suppression [255,260].

Furthermore associated with treatment resistance in cancer [261], particularly in breast cancer patients [262], are fat cells and adipocytes. A major contributing factor to obesity-associated chemoresistance is changes in the lipid metabolism of TME. Chemoresistance and leptin-LEPR signaling have been linked to the control of fatty acid oxidation [263]. Because of increased HIF production, adipocytes and myeloid cells in obese individuals release more IL-6 [264,265], which further defines breast cancer and increases resistance to anti-VEGF-A treatment. Inflammasome activation is one kind of inflammatory response that promotes tumor development; new research has shown their role in the pathophysiology of breast cancer [266]. Obesity-related TME triggers NLRC4 inflammasomes in tumor-infiltrating myeloid cells via adipocyte-mediated VEGFA production and angiogenesis, which ultimately results in IL-1β activation and disease progression [267]. Furthermore, obesity modifies the composition of immune cells, which promotes the development or metastasis of tumors [268]. An interesting study found that obesity enhanced the CXCR2-mediated accumulation of FasL + granulocytic MDSCs, which in turn increased the resistance to immunotherapy and the death rate of $CD8^+$ T cells that were able to infiltrate tumors [269].

Even in cases when inflammation associated with obesity is not present, the immune microenvironment plays a significant role in the development of breast cancer. A poor prognosis and CCL2 expression are associated with metastatic human breast cancer, as is the presence of inflammatory macrophages that express CCR2 [270]. While inhibiting the CCL2-CCR2 signaling axis seems to be an effective therapy, quitting it may result in the VEGF-A and IL-6-dependent disease returning [271]. IL-1β from tumors stimulates γδ T cells, which then generate IL-17, according to a study [99]. Consequently, neutrophils multiply and acquire a functional polarization, displaying a phenotype that requires G-CSF to inhibit $CD8^+$ T cells. This promotes the growth of metastases in other organs. Table 1 outlines the role that inflammation plays in breast, lung, and liver cancer.

Recent studies have connected inflammation to breast cancer's initiation, growth, and metastasis. It is unclear, therefore, exactly how

Table 1
Summarizes the involvement of inflammation in liver cancer, lung cancer, and breast cancer.

Cancer Types	Characteristics	References
Liver Cancer	Th2-like cytokines—including IL-4, IL-5, IL-8, and IL-10—have been linked to a more aggressive and metastatic form of HCC.	[275]
	IL-22 regulates the expression of several genes involved in the survival and proliferation of HCC cells.	[276]
	Macrophages become M1-type during inhibition of IL-6 signaling, which also decreases the growth of HCC tumors.	[277]
	Inhibiting HCC cell growth directly is miR-451's way of suppressing IKKβ.	[278]
	Immune cells like macrophages and Kupffer cells produce IL-6, which stimulates NF-κB and JAK–STAT3 inflammatory signaling pathways in hepatocytes to increase cell division.	[192]
Lung Cancer	Lesions from stage I lung cancer already have markedly changed NK and T cell compartments.	[215]
	Through a process reliant on immunological checkpoint activation, CAFs facilitate T-cell suppression inside the tumor microenvironment.	[222]
	Over a range of cell types and species, stable production of HIF-1α protein prevents TGF-β-stimulated EMT phenotypes from emerging.	[223]
	Immune escape occurs in the TME as a result of tumor-promoting inflammation and immune regulation brought on by the KRAS mutation.	[37]
	In EGFR-mutant lung tumors, NF-κB may be a possible companion therapeutic target in addition to EGFR.	[230]
Breast Cancer	By reprogramming the protein synthesis machinery for enhanced translation, eIF4GI helps to boost the survival of IBC tumor cells and the development of tumor emboli.	[279]
	The JAK2–STAT3 signaling pathway is required for the growth of CD44+CD24- stem cell-like breast cancer cells in human tumors.	[280]
	A diet that mimics fasting encourages tumor regression that lasts for a long time and reverses acquired medication resistance.	[281]
	Obesity-related BC patients had higher systemic levels of IL-6 and/or FGF-2, and the tumor vasculature was less responsive to anti-VEGF-A therapy.	[282]
	In a mouse model, inhibiting CCL2-CCR2 signaling prevents the recruitment of inflammatory monocytes and prevents breast cancers from metastasizing.	[283]

inflammation causes breast cancer. Reducing WNT release in TP53-deficient breast cancer cells may inhibit the spread of the disease by decreasing the invasion of neutrophils and the IL-1β produced by macrophages [272]. IL-1β prevents E-cadherin-positive cells that initiate metastases from multiplying into highly proliferative cells, which explains why patients with high protein expression levels had better overall survival and distant metastasis-free survival [273]. In conclusion, more study is necessary to create medications that target inflammation in breast cancer and to determine whether or not to employ them in clinical settings [274].

9.2. Lung cancer

Lung cancer continues to be the most prevalent cause of death among all cancers and has taken the lives of the largest number of Americans since the 1950s, according to the American Cancer Society 2020 Cancer Facts & Figures. Even with recent advancements in treatment, such as immune checkpoint inhibitors (ICIs) and molecularly targeted drugs against particular oncogenic mutations, the 5-year relative survival rate for lung cancer in the United States remains at 19 %. In the first half of this century, there will probably be a global increase in the incidence of lung cancer, since there is evidence that tobacco use has increased the number of smoking-related lung cancer fatalities worldwide [211]. It has long been known that inflammation plays a significant role in the development of lung cancer [212], as tobacco smoking accounts for about 80 % of instances of lung cancer and chronic obstructive pulmonary disease is independently connected to the development of lung cancer [213].

Lung cancer research has accelerated due to new technology in the field of cancer immunology. The extracellular matrix (ECM) enclosing the alveoli, the lymphocytes, TAMs, and MDSCs that permeate the tissue, and the CAFs encircling the alveoli are a few of the many essential components that make up the lung cancer microenvironment [214,215].

Among the cytokines secreted by lung cancer cells that stimulate CAFs include TGF-β, PDGF, and FGF-2 [216]. CAFs alter the shape of the tissue by stiffening it and producing collagen. One way that autophagy and metabolic regulation influence CAF activity is by potentially increasing the synthesis of collagen [217]. The remodeling process produces TGF-β, which contributes to the immunosuppression of the TME [218]. CAFs may affect lung cancer cells by interacting with TGF-β, ROS, and IGF-2/IGF-1R/Nanog paracrine signaling [219,220]. It's intriguing to consider that CAFs may control immune cell activity. For example, CAFs suppress $CD8^+$ T cell activation and promote the induction of Tregs by expressing PD-L1, PD-L2, and the Fas ligand [221,222].

Collagen, glycoproteins, and proteoglycans/glycosaminoglycans are the three primary forms of extracellular matrix. Every one of them contains many constituents that interact differently with the growth and metastasis of lung cancer [216,223]. People with idiopathic pulmonary fibrosis are more likely to develop lung cancer because breathing continuously stresses the pulmonary extracellular matrix (ECM), which may enhance the production of TGF-β [224]. This creates a setting that suppresses the immune system.

Lung cancer's immune cell composition has been the subject of several investigations [214]. Unfortunately, studies have not shown that widely used immunological markers, such as MDSC levels and the Treg: CD8 ratio [225], are accurate markers of lung cancer. A bigger sample size and a more comprehensive analysis, such as immune profiling based on the distinct genetic mutation pattern of each lung cancer patient, may be the causes of this. The influence of gene mutation patterns on the immunological characteristics of lung malignancies is becoming more apparent. Tumor suppressor liver kinase B1 (LKB1) inactivation may reduce T cell infiltration and activity by enhancing neutrophil recruitment and producing pro-inflammatory cytokines [226]. Moreover, mutations in KRAS, a crucial driver mutation in non-small cell lung cancer (NSCLC), are associated with heightened pro-inflammatory circumstances that promote an immune-suppressive environment [37,227]. Furthermore, recent research found that the co-occurrence of mutations in the LKB1, MYC, KEAP1, and TP53 genes has a substantial influence on the immunological landscape of lung cancer with a KRAS mutation [228]. Most remarkably, a genetic mutation modifies the TME, resulting in a distinct reaction to cancer therapy.

Finally, we examine two critical regulators of inflammation: NF-κB and COX-2. NF-κB signaling has a major function in lung cancer and other malignancies [229,230]. Tobacco smoke may induce lung cancer because it causes inflammation that is dependent on JNK1 and IKKβ [231]. The cause of lung fibrosis is smoking-induced chronic inflammation of the lung epithelial cells, which triggers downstream noncanonical NF-κB signaling and the activation of the lymphotoxin β-receptor (LTβR) [232]. NF-κB reduces anti-tumor immunity by upregulating the expression of PD-L1 in cancer cells. Compared to NSCLCs with wild-type EGFR, those with mutant EGFR had a higher prevalence of PD-L1. Inhibiting this route in an NF-κB-dependent manner is possible using the EGFR-tyrosine kinase inhibitor gefitinib [233,234].

Key components in the development of the immune environment that fosters lung cancer are COX-2 and PGE2, an enzymatic byproduct of COX-2. For example, PGE2 enhances the activation of Foxp3+ Treg [221]. Furthermore, a prior study found that COX-2-PGE2 diminishes antitumor immunity, which encourages the growth of cancer. PGE2

from tumors selectively activates myeloid cells to produce pro-cancerous inflammatory mediators such as IL-6, CXCL1, and G-CSF while inhibiting type I immune responses that are antitumor [235]. This study also demonstrates the complementary roles that anti-PD-1 blocking and COX inhibition play. The idea that aspirin and other COX-2-PGE2 axis inhibitors may actually lower the incidence of lung cancer has generated much discussion [236]. Surprisingly, aspirin inhibits the platelet-derived COX-1 thromboxane A2 (TXA2), which may prevent the lung from developing intravascular metastatic habitats [237].

10. Therapeutic strategies tackling inflammation in cancer

Both a promoter and a suppressor of tumor growth, inflammation has a complicated and multidimensional role in cancer [284]. Researchers have created a variety of methods to target inflammation in cancer treatment in recognition of this dual nature. In order to prevent tumor growth, increase the effectiveness of current treatments, and enhance patient outcomes, these strategies seek to modify the inflammatory response. Inflammatory processes facilitate the development of cancer through a number of mechanisms, such as the activation of transcription factors that encourage tumor growth and metastasis [285]. The relationship between inflammation and cancer is complex.

10.1. Targeted anti-inflammatory medications in cancer therapy

One promising approach to treating cancer is the use of targeted anti-inflammatory drugs to lessen inflammation linked to tumors [286]. Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are two of these that have demonstrated a great deal of promise in enhancing patient outcomes [287].

10.1.1. Inhibitors of COX-2 in cancer treatment

A COX-2 inhibitor called celecoxib has shown significant advantages for patients with particular genetic mutations, such as PIK3CA mutations in colon cancer [288].

Celecoxib's therapeutic potential was highlighted by a study that found patients who took it after surgery had longer disease-free and overall survival times [289].

10.1.2. NSAIDs and the recurrence of cancer

NSAIDs have been linked to a preventative effect against the recurrence of cancer [290]. For example, NSAID use was associated with a lower incidence of second cancers in patients with breast cancer, according to a Taiwanese population-based cohort study [291].

This implies that NSAIDs might help lower the chance of cancer recurrence and enhance long-term results.

These results highlight the potential of anti-inflammatory drugs, especially NSAIDs and COX-2 inhibitors, as supplemental therapies in the treatment of cancer, providing advantages for survival as well as protection against recurrence.

10.2. Emerging anti-inflammatory drugs in cancer treatment

The creation of innovative anti-inflammatory medications is demonstrating great promise for improving the results of cancer treatment. The potential of these medications to enhance the efficacy of conventional therapies and supplement them is being researched.

10.2.1. L-NMMA: an inhibitor of nitric oxide synthase

Mechanism: Nitric oxide (NO), a molecule linked to angiogenesis and tumor growth, is inhibited by L-NMMA [292].

Clinical Outcomes: When combined with chemotherapy, L-NMMA showed promising results in clinical trials. In patients with breast cancer, for example, tumor shrinkage was seen in roughly half of the cases, and some patients experienced complete remission [292].

Significance: These results demonstrate how L-NMMA may improve chemotherapy's effectiveness and open up a new treatment option for nitric oxide signaling-related cancers.

10.2.2. Inhibitors of STAT3

Mechanism: The STAT3 protein, a crucial component of inflammatory signaling pathways that encourage tumor growth and immune evasion, is the target of STAT3 inhibitors [293].

Potential Advantages: These medications may improve the immune system's capacity to eradicate tumor cells and stop the spread of tumors by blocking STAT3 [293].

Therapeutic Implications: One promising tactic to stop the inflammatory processes that promote the growth and spread of cancer is to use STAT3 inhibitors [294].

These developments show how anti-inflammatory medications, like L-NMMA and STAT3 inhibitors, can be used in addition to conventional cancer treatments, giving patients new hope for better results.

10.3. Combination treatments: enhancing cancer therapy by targeting inflammation

Combination therapies are a major step forward in the fight against inflammation linked to cancer. Researchers hope to increase the effectiveness of current methods and improve treatment outcomes by combining anti-inflammatory medications with conventional cancer therapies.

10.3.1. Chemotherapy combined with anti-inflammatory medications

Example: the addition of L-NMMA, a nitric oxide synthase inhibitor, to chemotherapy, showed increased efficacy in patients with breast cancer [292]. This implies that lowering inflammation may enhance chemotherapy's therapeutic benefits.

10.3.2. Immunotherapy combined with anti-inflammatory medications

Example: Immunotherapy may be more effective if immune checkpoint inhibitors and JAK inhibitors, which target inflammatory pathways, are combined [295]. These combinations may improve the immune system's capacity to fight tumors by lowering chronic inflammation.

10.3.3. Combination therapies' synergistic effects

Anti-inflammatory drugs that are combined with immunotherapy or chemotherapy target the tumor as well as the inflammatory milieu around it [296]. This dual strategy improves overall results by reducing the pro-tumorigenic effects of chronic inflammation in addition to targeting cancer cells [297].

These results demonstrate how combination therapies, which take advantage of the interaction between inflammation and tumor growth, have the potential to completely transform the treatment of cancer.

10.4. Targeting the tumor microenvironment in anti-inflammatory cancer therapy

Addressing the tumor microenvironment (TME), which is crucial for tumor progression, immunological evasion, and therapy resistance, is a crucial part of anti-inflammatory cancer treatment strategies. Therapies seek to break down the barriers that protect tumors and increase the efficacy of cancer treatments by focusing on the inflammatory conditions within the TME [298].

10.4.1. Dismantling barriers to inflammation

L-NMMA: This treatment targets cancer cells by reducing the protective inflammatory barriers that surround tumors. This makes it easier for immune cells to enter the TME. L-NMMA improves immune cell access and activity by modulating the inflammatory microenvironment by lowering nitric oxide synthesis [299].

10.4.2. Nanomedicine for accurate administration

Nanomedicine Techniques: New methods for delivering anti-inflammatory drugs straight to the tumor microenvironment are being developed. Through precise targeting of the TME and the reduction of systemic side effects, these nanotechnology-based techniques seek to alter local inflammatory conditions, increasing the efficacy of cancer immunotherapy [300].

10.4.3. Therapeutic consequences

By emphasizing the dynamic interactions between cancer cells, immune cells, and inflammatory mediators within the tumor microenvironment, the TME-centric approach marks a change in the way cancer is treated.

These tactics seek to enhance therapeutic results and get past resistance to conventional treatments by addressing the inflammatory TME. This emphasis on the tumor microenvironment emphasizes how crucial it is to incorporate anti-inflammatory treatments into cancer treatment plans, providing fresh chances to boost immune responses and halt the growth of tumors [301].

10.5. Personalized medicine in anti-inflammatory cancer treatment

Anti-inflammatory cancer treatment is increasingly incorporating personalized medicine techniques, which provide individualized strategies based on each patient's unique genetic and molecular profile. This tactic highlights how crucial it is to tailor therapies in order to increase their effectiveness and improve patient outcomes.

10.5.1. Genetic markers directing therapy

Celecoxib and PIK3CA Mutations: Research has demonstrated that the COX-2 inhibitor celecoxib is highly beneficial for colon cancer patients with PIK3CA mutations [288]. Compared to patients without the mutation, those who took celecoxib following surgery had longer durations of overall and disease-free survival [302]. This demonstrates how anti-inflammatory treatment plans may be guided by genetic markers.

10.5.2. The function of molecular diagnostics and genomic profiling

Clinicians can find particular genetic mutations or biomarkers linked to inflammation and the advancement of cancer by integrating genomic profiling and molecular diagnostics into treatment planning [303]. Clinicians can create more individualized and efficient strategies to address inflammation linked to cancer by customizing treatments to the molecular features of a patient's tumor [303].

10.5.3. Progressing with precision health care

In order to address the heterogeneity of cancer, personalized medicine in anti-inflammatory cancer therapy is a major advancement. Celecoxib and other treatments can be tailored for particular patient subgroups by utilizing genetic insights, which will improve results and minimize needless side effects [304].

This strategy emphasizes how precision medicine, which tailors treatments to the particular genetic and molecular makeup of each patient's illness, is becoming increasingly important in the treatment of cancer.

10.6. Emerging therapeutic agents targeting cancer-associated inflammation

An intriguing field of study is the creation of new therapeutic agents that target inflammation in relation to cancer. Natural substances, cytokine and chemokine modulators, and novel medications with anti-inflammatory and anti-tumor effects are some examples of these strategies.

10.6.1. Natural compounds with anti-inflammatory effects

Phytochemicals: Natural compounds such as resveratrol and curcumin have demonstrated potential in modifying important inflammatory pathways linked to cancer [305]. These substances are appealing candidates for cancer prevention and treatment because they not only have anti-inflammatory properties but also offer a host of other health advantages.

Mechanism: By targeting pathways implicated in inflammation and tumor progression, curcumin and resveratrol may lower the risk of cancer and enhance the effectiveness of treatment [306].

10.6.2. Modulators of cytokine and chemokine

Targeting Inflammatory Mediators: One of the main goals of developing medications that reduce inflammation that promotes tumor growth is to modify cytokines and chemokines [307]. The inflammatory signaling that promotes tumor growth and immune evasion is what these drugs seek to interfere with.

10.6.3. Innovative anti-inflammatory medication

Selinexor: This medication is being researched for its potential to treat cancer and inflammatory diseases because it has anti-inflammatory and anti-tumor effects. Selinexor is a potentially effective dual-action medication that fights tumor cells directly while also addressing inflammation [307].

10.6.4. NSAID-based preventive techniques

Long-Term NSAID Use: Research indicates that using NSAIDs for an extended period of time may reduce the risk of developing some types of cancer, especially in high-risk groups. NSAIDs, for instance, have been linked to a lower incidence of breast and colorectal cancers [290].

Preventive measures include NSAIDs as part of a comprehensive cancer prevention plan and lifestyle changes like anti-inflammatory foods and habits that may help lower the risk of cancer.

10.6.5. Including anti-inflammatory substances in the prevention of cancer

Lifestyle and Diet: A comprehensive strategy for lowering the risk of cancer is provided by anti-inflammatory foods and behaviors, natural substances, and preventative drugs.

Personalized Prevention: The efficacy of preventive measures can be increased by customizing them according to each person's unique risk factors and genetic predispositions.

The growing potential of addressing inflammation as a crucial element of cancer treatment and prevention is highlighted by these new therapeutic agents and preventative measures. By targeting the inflammatory mechanisms that propel tumor growth, these strategies provide fresh hope for enhancing patient outcomes and lowering the risk of cancer.

These treatment approaches are probably going to get more complex and essential to all-encompassing cancer care as our knowledge of the connection between inflammation and cancer keeps expanding. Larger-scale clinical trials to confirm the effectiveness of promising anti-inflammatory treatments, more accurate techniques to target inflammatory pathways unique to cancer, and an examination of the long-term impacts of anti-inflammatory interventions on cancer outcomes and patient health, in general, should be the main goals of future research. Anti-inflammatory strategies combined with current cancer treatments have the potential to significantly enhance treatment results and cancer patients' quality of life, opening the door to future cancer care that is more efficient and individualized.

11. Inflammatory biomarkers in cancer: insights into development, progression, and treatment

Because they are quantifiable indicators of biological processes, conditions, or diseases within the body, biomarkers are essential to the understanding and treatment of cancer. Biomarkers offer important

information about the course of the disease, the effectiveness of treatment, and patient outcomes in the context of inflammation and cancer. These molecular signatures come in a variety of forms, such as circulating molecules, protein expressions, and genetic mutations, and each one provides a distinct viewpoint on the intricate relationship between inflammation and cancer [308].

Inflammation and cancer have a complex and multidimensional relationship. Because it can cause epigenetic alterations that aid in tumorigenesis, chronic inflammation is known to be a substantial risk factor for the onset and spread of cancer. Without changing the DNA sequence itself, epigenetic processes like DNA methylation, histone modification, and non-coding RNA expression control the expression of genes. Cancer frequently disrupts these processes, which can result in the silencing of tumor suppressor genes or the activation of oncogenes. Research has shown that certain epigenetic changes in inflammatory diseases can result in cancer, underscoring the significance of comprehending these molecular alterations [57].

C-reactive protein (CRP) is one of the most extensively researched and used inflammatory biomarkers in clinical practice [309]. The liver produces CRP, an acute-phase protein, in reaction to inflammation, and cancer can cause a marked increase in its levels [310]. Although CRP is useful for assessing the severity and course of the disease, the type of cancer can affect its sensitivity and specificity [311]. Despite being widely used, CRP is nonspecific and cannot be used to diagnose cancer because it can be elevated in a variety of inflammatory conditions [311]. Another class of inflammatory biomarkers linked to cancer are interleukins, specifically interleukin-6 (IL-6). A cytokine that affects inflammation and the immune system, IL-6 can increase the synthesis of CRP [312]. Increased IL-6 levels are believed to aid in tumor growth and metastasis and have been connected to a number of cancers [313].

Our knowledge of inflammatory biomarkers in particular cancer types has grown as a result of recent research. For example, prediagnostic levels of TNF-α, IL-6, and IL-10 have been linked to higher all-cause and breast cancer-specific mortality in cases of breast cancer, especially in postmenopausal women [314]. Additionally, systemic inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been shown to predict survival and chemotherapeutic outcomes in a variety of cancers, including breast cancer [315]. These results highlight how inflammatory biomarkers can be used to inform treatment choices and track treatment outcomes, enabling oncologists to customize treatments according to a patient's inflammatory profile. Inflammatory biomarkers in cancer have clinical significance that goes beyond prognosis and diagnosis. Since elevated levels of CRP and specific cytokines are associated with a higher incidence of cancer, these biomarkers can be used as non-invasive tools for early cancer detection [316]. Inflammatory biomarkers have the potential to increase the effectiveness of interventions by guiding therapeutic decisions and tracking treatment responses. For instance, in luminal breast cancers, the presence of specific inflammatory markers may suggest a poor response to endocrine therapy, which could impact the treatment strategy selection [317].

New inflammatory biomarkers and their uses in cancer treatment are still being discovered by emerging research. The development of novel biomarkers that can forecast the effectiveness of cancer immunotherapy across a range of cancer types has been made easier by advances in bioinformatics and sequencing technologies, including bulk RNA-Seq and scRNA-Seq [318]. It has also drawn attention to how the gut microbiota affects the effectiveness of immunotherapies and modifies the cancer microenvironment. For example, the presence of intratumoral tertiary lymphoid structures in patients with hepatocellular carcinoma has been linked to the enrichment of specific gut bacteria, such as Lachnoclostridium, indicating a possible connection between gut microbiota and inflammation related to cancer [319].

A more thorough evaluation of a patient's inflammatory status and its relationship to the prognosis of cancer is provided by the incorporation of multiple biomarkers into composite inflammatory scores. These biomarkers have the potential to improve patient outcomes, advance personalized medicine strategies, and lower healthcare costs by minimizing needless treatments as our knowledge of the molecular mechanisms underlying inflammation and cancer advances. Our knowledge and treatment of cancer are improved by the new biomarkers and therapeutic targets that are being found by the ongoing research in this area [320].

In conclusion, one of the most active and exciting areas of oncology is the investigation of biomarkers linked to inflammation in cancer. These biomarkers, which range from well-known indicators like CRP and interleukins to newly discovered genetic and epigenetic signatures, provide important information about the onset, course, and response to treatment of cancer. As studies progress, the use of inflammatory biomarkers in clinical practice could transform cancer treatment by offering more specialized and tailored treatment, which would ultimately benefit cancer patients.

12. Controversies in inflammation and cancer research: complexities and debates

12.1. The two-sided character of cancer inflammation

The dual role of inflammation in cancer is one of the main points of contention in this field. It is commonly acknowledged that chronic inflammation plays a major role in the development and spread of cancer. It is still up for debate, though, to what degree inflammation plays a role in each stage of cancer development. While some scientists contend that inflammation plays a more significant role in the early phases of cancer development, others highlight its significance in the later stages, especially in metastasis [285].

Depending on the situation, the inflammatory microenvironment can either encourage or prevent the development of cancer. For both researchers and clinicians, this dichotomy poses a serious problem. On the one hand, inflammation may trigger the onset of cancer by causing DNA damage, genomic instability, and oncogene activation. However, the body's immune response against cancer cells also depends on inflammation. It is challenging to create targeted treatments that can successfully reduce inflammation without jeopardizing the body's defenses against cancer because of this intricate interaction [321].

12.2. Epidemiological study interpretation

Another hotly debated topic is how epidemiological research that links inflammation to cancer risk should be interpreted. Although inflammatory markers and cancer risk have been linked in a number of studies, Conflicting interpretations have resulted from the variability in study results. Variations in the study design, the population's demographics, and the particular inflammatory markers under investigation can all be blamed for this discrepancy. Differentiating between correlation and causation is one of the main difficulties in interpreting these studies. Some studies have found weaker or non-significant associations between chronic inflammation and an increased risk of cancer, while other studies have found a strong correlation. This variation calls into question the actual nature of the connection between inflammation and cancer and emphasizes the need for more exacting and uniform research procedures [322].

12.3. Particular inflammatory biomarkers' function

There is continuous discussion regarding the significance of particular inflammatory biomarkers, such as interleukin-6 (IL-6) and C-reactive protein (CRP), in the prognosis of cancer. These markers have been linked in some studies to a poor prognosis for a variety of cancers, but other studies have produced contradictory findings [323]. High CRP levels, for example, have been connected to increased tumor size, metastasis, and mortality in colorectal cancer. The relationship between

CRP levels and cancer risk in breast cancer is still debatable, though, as some research has found no meaningful correlation. The role of IL-6 as a prognostic marker varies depending on the type of cancer, but it has been linked to poor survival in melanoma patients receiving immune checkpoint inhibitors. These contradictory results emphasize the difficulty of utilizing inflammatory biomarkers in cancer prognosis and the demand for more focused studies that take into account the particular cancer type, stage, and treatment setting [324].

12.4. Anti-inflammatory medication for the prevention and treatment of cancer

Another highly contentious topic is the use of anti-inflammatory medications, especially nonsteroidal anti-inflammatory drugs (NSAIDs), in the prevention and treatment of cancer. Although some research indicates that NSAIDs may lower the risk of some cancers, including colorectal and gastric cancers, the data is not universal across all cancer types or studies [325].

It's also up for debate how NSAIDs might prevent or treat cancer. Although it is well known that NSAIDs inhibit the COX-2 enzyme, they may also function via mechanisms that are not dependent on COX-2. Additionally, the possible advantages of NSAIDs in the prevention and treatment of cancer must be balanced against the possible risks and adverse effects of long-term use, such as cardiovascular risks and gastrointestinal bleeding [290].

12.5. The Microbiome's effect on cancer and inflammation

A new field of study that has generated a lot of discussion is how the microbiota affects inflammation and how that affects the risk of cancer. Although there is strong evidence that the microbiome affects inflammation and cancer, there are many disagreements in the field about causality, the effect of outside variables, and the possibility of therapeutic interventions [326]. The question of whether alterations in the microbiome cause or result from cancer is one of the main points of contention. Certain microbial profiles may raise the risk of cancer, according to some research, but other studies show that cancer itself can change the makeup of the microbiome. The development of microbiome-based cancer prevention and treatment strategies is hampered by this chicken-and-egg conundrum [327].

12.6. Targeting inflammation with ethical considerations

There has also been discussion about the moral ramifications of using inflammation-targeting cancer treatments. Among these factors is weighing the possible advantages of anti-inflammatory therapies against the dangers of inhibiting healthy inflammatory reactions that are essential for battling infections and other illnesses. Another crucial ethical issue is maintaining patient autonomy and informed consent in the face of developing research and possible long-term consequences [328].

The fair distribution of novel anti-inflammatory cancer treatments is another topic of discussion. There is an ethical duty to guarantee that all populations, irrespective of socioeconomic background or geographic location, can profit from these developments as these treatments become more complex and possibly more costly.

In conclusion, there are a lot of ongoing discussions and controversies in the field of inflammation and cancer research. These cover everything from basic inquiries into the nature of the connection between inflammation and cancer to pragmatic issues regarding the application of anti-inflammatory medications in the prevention and treatment of cancer. It is essential to approach these disputes critically and nuancedly as research in this area develops, acknowledging the intricate interactions between biological, clinical, and ethical considerations. More thorough study designs, extensive clinical trials, and interdisciplinary approaches that can offer a more thorough understanding of the role of inflammation in cancer should be the main focus of future research in order to resolve these controversies.

13. Inflammation's relevance to pediatric cancer: A comprehensive overview and comparison with adult cancers

13.1. Development and etiology

Chronic inflammation is commonly acknowledged as a major precursor and contributing factor to the development of adult cancers. Numerous things, such as infectious agents, physical or chemical irritants, and lifestyle choices, can contribute to this chronic inflammatory state. Adults' protracted inflammatory response contributes to the pathophysiology of many cancers by fostering a tumor-promoting environment [329].

On the other hand, chronic inflammation has a less significant role in the etiology of pediatric cancers. Unlike adult cancers, which are more frequently caused by the accumulation of genetic mutations over time, these cancers frequently result from developmental processes. The lower frequency of chronic inflammation linked to pediatric cancers may be explained by the basic difference in origin. Developmental processes are frequently connected to pediatric tumors, and some genetic modules linked to pediatric tumor histotypes are functionally connected to these processes [330].

13.2. The inflammatory microclimate

Compared to adult cancers, pediatric cancers exhibit a very different inflammatory microenvironment. A wide variety of tumor-associated leukocytes (TALs), such as T cells, natural killer cells, macrophages, and a sizable number of dendritic cells, which are usually located at the edges of tumor islands, are characteristics of adult tumors. This intricate inflammatory environment can either stimulate or inhibit the growth of tumors, contingent on the particular signaling pathways and context [331].

Pediatric cancers, on the other hand, like blastomas and sarcomas, show a distinct immune milieu. They have a notably low number of dendritic cells and are primarily infiltrated by macrophages. This unique inflammatory profile points to various tumor-immune interaction mechanisms in pediatric cancers, which could affect tumor behavior and treatment response [332].

13.3. Molecular and genetic features

In contrast to adult cancers, pediatric cancers frequently exhibit distinct molecular and genetic processes. Compared to adult tumors, these tumors typically have a lower mutational burden, which could affect the type and intensity of the inflammatory response. Compared to adult cancers, pediatric cancers have fewer genomic alterations and are characterized by genomic simplicity. This includes fewer copy number alterations (CNAs), mutations, and other genomic alterations [333].

Despite this genomic simplicity, single genetic events which are frequently specific to each case can be the cause of pediatric tumors. They are therefore "N of 1″ studies in which distinct molecular drivers can be found through genome-wide analysis. Understanding the unique molecular mechanisms and mutational signatures that distinguish different pediatric cancers from adult cancers is essential for comprehending tumor biology [334].

13.4. Inflammation's contribution to the development of cancer

Chronic inflammation is a known factor in the development of cancer in adults, but its function in pediatric cancers is unclear and seems to be less closely related to the onset of cancer. Recent research, however, has shown that inflammation continues to be a critical factor in the initiation and spread of some childhood cancers, especially those with

developmental origins [335].

Inflammation plays a role in childhood cancer through a number of intricate molecular and genetic processes. Reactive oxygen species and cytokines are produced as a result of inflammation, and these substances have the potential to damage DNA and increase genomic instability, which can aid in the development of cancer. Furthermore, inflammation can change the tumor microenvironment by influencing the interactions between immune cells and cancer cells, which can either encourage or inhibit the growth of the tumor [336].

13.5. Particular studies and examples

Recent studies have shed light on how inflammation contributes to particular childhood cancers:

The impact of persistent inflammation on TP53-mutant hematopoietic stem cells, which are linked to the emergence of aggressive leukemia, was investigated in a study that was published. According to the study, inflammation encourages the growth of TP53-mutant cells, which aid in the development of cancer because they are resistant to cell death [337].

Chronic inflammation in children with pediatric-onset inflammatory bowel disease (IBD) increases the risk of gastrointestinal and extra-intestinal cancers. IBD's inflammatory milieu can result in epigenetic alterations and genetic mutations that raise the risk of cancer [338].

Studies on recessive dystrophic epidermolysis bullosa (RDEB), a rare skin condition, have demonstrated that long-term skin inflammation can result in mutations that cause cancer via different pathways than those triggered by UV light. This demonstrates how children with specific genetic disorders may develop cancer as a result of chronic inflammation [339].

13.6. Treatment and research implications

Treatment and research are significantly impacted by the unique features of inflammation in pediatric cancers.

13.6.1. Targeted therapies

Creating targeted therapies requires an understanding of the distinct molecular and genetic mechanisms underlying pediatric cancers. Whole-exome sequencing (WES) and RNA sequencing are two examples of high-throughput molecular profiling that has been used in pediatric oncology to find actionable results and possible treatment targets [339].

13.6.2. Immunotherapies

How pediatric and adult cancers react to immunotherapies that take advantage of inflammatory processes may be influenced by the variations in their inflammatory responses. Creating age-appropriate treatment plans is essential to enhancing the prognosis of young cancer patients [332].

13.6.3. Personalized medicine

Due to the high level of molecular heterogeneity in pediatric tumors, treatment must be tailored to the individual patient, with each tumor profiled to find possible therapeutic targets [340].

13.6.4. Combination therapies

By focusing on the tumor microenvironment and inflammatory pathways, new treatments that enhance the prognosis of children with cancer may be developed. Immunotherapies may improve therapeutic effects and provide promising approaches to the management of cancers driven by inflammation when combined with other treatment modalities [332]. In summary, inflammation is important in both childhood and adult cancers, but its significance and effects vary greatly between the two. In contrast to adult cancers, pediatric cancers have unique inflammatory profiles, genetic traits, and developmental origins. Comprehending these distinctions is essential to creating efficacious therapies and enhancing the results for children with cancer. Subsequent investigations ought to concentrate on clarifying the distinct features of inflammation in pediatric cancers and converting these discoveries into tailored treatment plans and targeted therapies.

13.7. Conclusions and perspective

More than a century ago, Katsusaburo Yamagiwa purposefully created cancer in his research. Later studies have uncovered the molecular pathways through which inflammation encourages the growth and metastasis of cancer. As previously stated, some processes are specific to a given type of cancer, while others are universal. There is mounting evidence that chronic inflammation and pro-inflammatory signaling pathways are promising targets for cancer prevention and treatment. Pro-inflammatory cytokines (such as TNF and IL-6), inflammation-related kinases (like IKKβ and JAK), and transcriptional factors (like NF-κB and STAT3) are possible targets for cancer treatment. On the other hand, due to the physiological effects of these substances, long-term suppression of inflammation and the chemicals associated with it results in immunosuppression, which increases the risk of serious infection. Reduced inflammation may also impact the immune system's capacity to combat cancer and encourage the regeneration and repair of damaged tissue. It is crucial to recognize and target significant chemicals specific to particular cancer types as well as inflammation linked to cancer in order to prevent side effects. To accomplish this, more research on inflammation and cancer is required.

CRediT authorship contribution statement

Siddhant Tripathi: Writing – original draft. **Yashika Sharma:** Writing – original draft. **Dileep Kumar:** Conceptualization.

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