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Targeting inflammatory microenvironments: overcoming therapy resistance and immunosuppression

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Abstract

Chronic inflammation within the tumor microenvironment (TME) is a critical driver of immune evasion, resistance to therapy, and progression of cancer, while epidemiological and immunological evidence indicates that allergic inflammation is also associated with the risk of several cancer types. Key pro-inflammatory cytokines: IL-6, IL-1β, TNF-α, and TGF-β activate key signaling pathways such as STAT3, NF-κB, and HIF-1α which create a self-amplifying cycle fostering angiogenesis, epithelial–mesenchymal transition, and immunosuppression. The accumulation of regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages additionally promotes an immunologically "cold" TME limiting the efficacy of immune checkpoint blockade, chemotherapy, and radiotherapy. Recent advances have elucidated on how inflammatory signaling dynamically changes cellular and metabolic states fostering resistance. Targeting these inflammatory signaling axes has demonstrated promising therapeutic efficacy: IL-6R and IL-1β neutralization, JAK/STAT3 and NF-κB inhibition, TGF-β blockade, and CXCR2 targeted strategies all have demonstrated the ability to restore anti-tumor immunity. Rationally designed combination therapies utilizing cytokine inhibition in combination with checkpoint blockades or anti-angiogenic agents are beginning to convert refractory tumors to responsive tumors. Herein we review mechanistic insights linking chronic inflammation to immunosuppression and treatment failure across multiple cancer types and discuss the translational promise of inflammation-targeted treatments. Targeting the TME through multi-variate inhibition of inflammatory pathways may be able to allow durable therapeutic responses to be achieved in tumors previously resistant to conventional and immune-based therapies.

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Keywords Tumor microenvironment, Chronic inflammation, Immunosuppression, Therapy resistance, Regulatory t cells, Myeloid-derived suppressor cells, Tumor-associated macrophages, Cytokines, Immune checkpoint blockade, Combination therapy

Background

The development and progression of tumors depend tremendously upon the surrounding microenvironment, which contains not only cancer cells, but also immune cells, stromal cells, blood vessels, and a rich background of cytokines and growth factors [1]. The development of an inflammatory tumor microenvironment (TME) is a hallmark of many advanced cancers, which paradoxically causes immune evasion rather than efficacy in antitumor immunity [2, 3]. Indeed, chronic or persistent inflammation is a recognized enabling trait of cancer, which contributes to multiple stages of tumorigenesis and metastasis. The presence of inflammatory cytokines such as IL-6, IL-1β, and TNF-α within tumors can lead to activation of such transcription factors as nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3), which lead in turn to the activation of a large number of genes enabling cancer cell survival, growth, invasion, and angiogenesis [3]. Increasing amounts of evidence have established that these same inflammatory signals will also shape an immunosuppressive microenvironment which diminishes the efficacy of nearly all major modalities of cancer therapy, from immune checkpoint inhibition to chemotherapy and radiotherapy [3, 4].

A key insight is that the immune contexture of tumors, such as the type, density and functional orientation of immune cells that reside in the TME, correlate significantly with therapeutic outcome. "Hot" tumors which exhibit abundant cytotoxic T lymphocytes (CTLs) and Th1-type cytokines often exhibit a good response to immunotherapy whereas "cold" tumors with few T-cells and a preponderance of immunosuppressive cells have poor responses [5, 6]. Chronic inflammation can contribute towards the establishment of this cold, immunologically excluded TMEs. For example, high systemic concentrations of the inflammatory chemokine IL-8 (CXCL8) have been identified as a biomarker of resistance to PD-1/PD-L1 checkpoint blockade across multiple cancers as a consequence of IL-8-mediated recruitment of neutrophils and MDSCs that inhibit T-cell infiltration [7]. In a similar manner chronic TNF-α signaling in tumors can result in activation of NF-κB dependent survival pathways as well as promoting the accumulation of suppressive myeloid cells, leading to generalized resistance to therapy [8, 9]. These findings highlight that inflammation-driven immunosuppression is an important barrier to effective therapy.

This review highlights the role of inflammatory microenvironments in therapy resistance and immune evasion and examines current and future strategies to circumvent these difficulties. Utilizing recent primary studies and clinical trials, we explain how targeting different cellular components, soluble factors and signaling pathways of the TME might recapture immune surveillance and enhance therapeutic responses. Importantly we examine several cancer types to elucidate the fact that whilst specifics differ, the fundamental principles of inflammatory microenvironment induced therapy resistance are broadly applicable. In contrast to recent reviews that primarily catalog inflammatory mediators or therapeutic agents, this review adopts a tumor microenvironment–centric framework to dissect how inflammation-driven cellular interactions actively shape immunosuppression and therapeutic resistance, and to highlight emerging strategies aimed at reprogramming these inflammatory niches. The understanding, but more importantly the targeting, of tumor and inflammatory microenvironment interaction provides hope for sensitization of refractory tumors to therapy and therefore more durable cancer control.

Inflammation-induced immunosuppression in the tumor microenvironment

Chronic inflammation in the TME often leads to a state of immunosuppression via a complex interplay of immune cell types, stromal elements and cytokine networks. This state is defined by the accumulation of immune cell types that suppress anti-tumor immunity and the presence of immunosuppressive cytokines and metabolites. In parallel, pro-inflammatory signaling pathways become persistently active in both the tumor and immune cell compartments, paradoxically promoting tumor survival and progression. Below we describe the key cellular and molecular mediators of inflammation driven immunosuppression in the TME (Fig. 1).

Immunosuppressive immune cells in the TME

Regulatory T cells (Tregs)

Regulatory T cells (Tregs) are suppressive $CD4^+$ T cells, marked by high levels of CD25 and the transcription factor FoxP3, which play an important role in the maintenance of tolerance via the suppression of effector T cell activation [10]. In cancer, Tregs are commonly enriched in the tumor and tumor draining lymph nodes, where they actively suppress anti-tumor immunity [11, 12]. Moderate infiltration of Tregs usually correlates with a

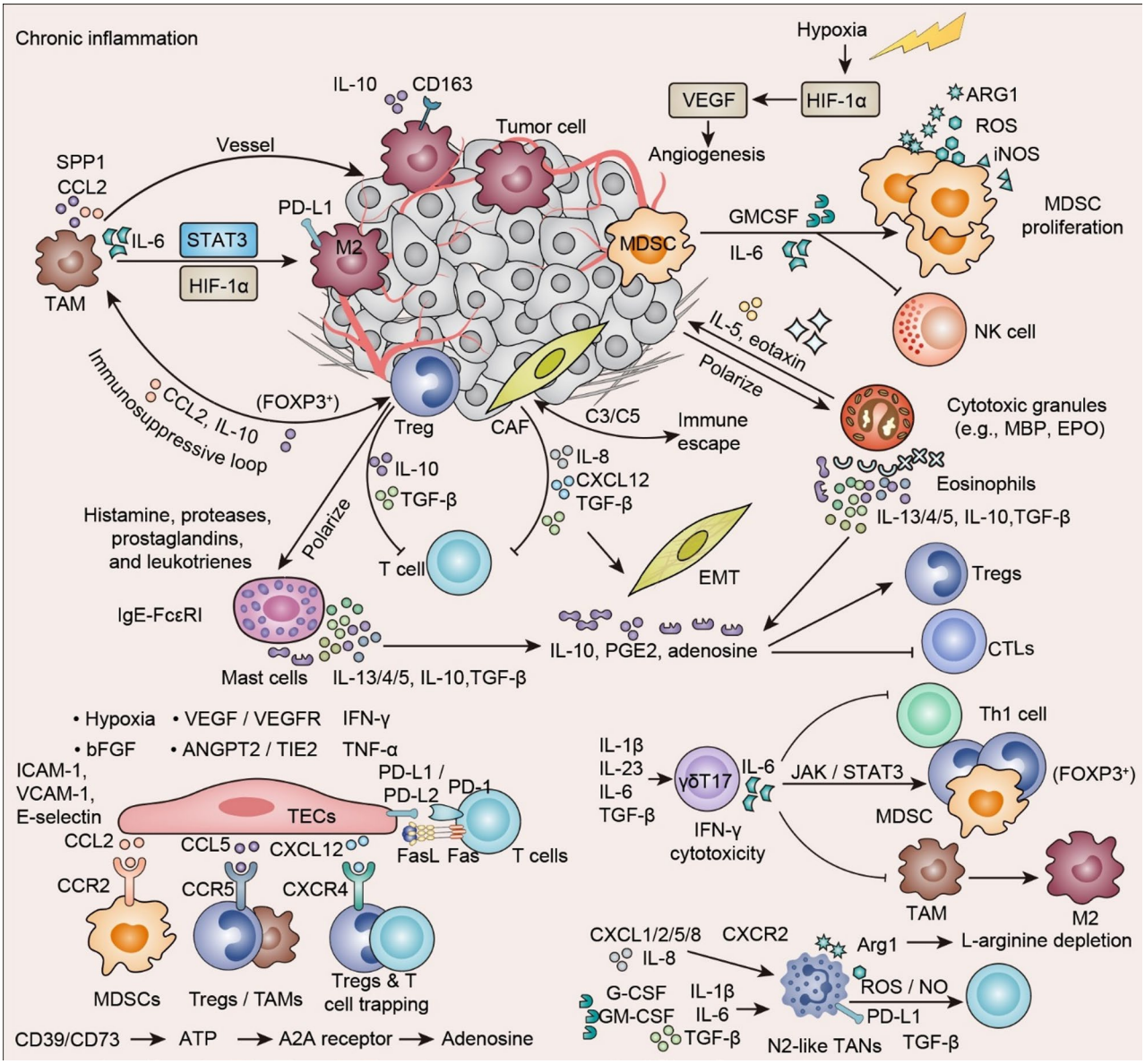

Fig. 1 The key components of the inflammatory tumor microenvironment. The chronic inflammatory state modules the TME by inducing cancer-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), Tumor-Associated Neutrophils (TANs), Tumor Endothelial Cells (TECs), Regulatory γδ T Cells and regulatory T cells (Tregs). The important cytokines which can activate downstream molecules resulting in angiogenesis, epithelial-mesenchymal transition (EMT) and immune evasion. Mast cells activated by IgE–FcεRI release histamine, proteases and lipid mediators. Eosinophils are recruited by IL-5 while eotaxins secrete granules containing cytotoxic (toxic) granules

poorer prognosis, and their presence has been associated with decreased efficacy of immunotherapy in numerous cancers [13]. For example, in gastric and esophageal cancers, tumor infiltrating FoxP3$^+$ Tregs are present in abundance and are potently suppressive, which contributes to an immune excluded TME [14, 15].

Tregs downmodulate immune responses through a variety of mechanisms. They secrete anti-inflammatory cytokines such as interleukin (IL)–10 and transforming growth factor (TGF)-β, which can directly inhibit cytotoxic T lymphocyte and dendritic cell function [16]. Indeed, Treg-derived IL-10 inhibits the production of proinflammatory cytokines (e.g., TNF-α, IL-6, IL-12) by macrophages through STAT3 signaling [17, 18]. Tregs also produce IL-35, which can inhibit CD4$^+$ and CD8$^+$ T cell expansion and, in fact, induce a subset of regulatory T cells that are devoid of FoxP3 expression [19, 20]. Furthermore, Treg-derived IL-35 can stimulate the accumulation of myeloid-derived suppressor cells (MDSCs), resulting in a feed-forward loop of suppression [21, 22]. Not only do Tregs secrete inhibitory cytokines, but they also utilize IL-2 in the thereby depriving conventional T

cells of this critical growth and survival factor [23]. This "sink" effect of IL-2 contributes to impaired cytotoxic T cell expansion and function in tumors [24]. In addition, Tregs strongly overexpress the ectonucleotidases CD39 (ENTPD1) and CD73, which catalyze the conversion of extracellular ATP into immunosuppressive adenosine [25]. The release of adenosine by Tregs through CD39/CD73 activates A2A and A2B receptors that inhibit T effector and NK cell sounds so it would promote the stability of Treg and therefore, it is this CD39/CD73-adenosine pathway that represents an important metabolic pathway for Treg immunosuppression.

Another important mechanism is through the expression of inhibitory checkpoint molecules. Tregs express cytotoxic T-lymphocyte antigen (CTLA)–4, which is constitutively expressed and outcompetes CD28 for binding to its ligands, CD80/CD86, on antigen-presenting cells, thereby limiting the costimulation of effector T lymphocytes [26, 27]. Through their engagement of CD80/CD86, Treg-expressed CTLA-4 not only delivers inhibitory signals but also induces downregulation of the expression of these ligands on dendritic cells which additionally limits T cell priming. Tregs may also express other checkpoint molecules such as PD-1, TIM-3, TIGIT, and LAG-3 [28]. Not surprisingly, Treg-derived signals can also increase the expression of inhibitory receptors on effector T cells; for instance, Tregs in the tumor microenvironment secrete factors which induce high levels of PD-1, TIM-3, TIGIT, and LAG-3 on CD8 T lymphocytes, resulting in their exhaustion [29]. In fact, data suggests that the antibody blockade of PD-1, while relieving inhibition of effector T cells, may paradoxically enhance Treg inhibitory function if Tregs themselves express PD-1 — exemplifying the fetid effects of checkpoint therapy in the presence of Tregs.

Chemokines actively recruit Tregs to tumors. Tumors produce CCL22 and CCL17, which recruit Tregs that express CCR4 [30, 31]. This CCR4/CCL22 axis has been shown in ovarian cancer, where Tregs expressing CCR4 are attracted to tumor cell and tumor-associated macrophage (TAM) produced CCL22 [32]. Additionally, Tregs can be recruited by the CCL5/CCR5 axis and chemokines that bind to CXCR3 [33]. When present, Tregs can proliferate in the TME in response to local antigen and cytokine signals. Interestingly, TAMs may be a source of signals for Treg proliferation; for example in hepatocellular carcinoma (HCC) associated with cirrhosis, $OX40L^+$ TAMs produce signals via OX40 that promote proliferation of $OX40^+$ Tregs inhibiting anti-HCC inflammation and providing an immunosuppressive milieu that favors HCC growth [34].

In addition to the mechanisms that have been outlined previously, Tregs play an important role in the development of indoleamine 2,3-dioxygenase (IDO), an enzyme that regulates the immune response by depleting tryptophan and producing kynurenines [35]. Tregs also produce IDO, which suppresses the growth of effector T cells, induces T cell anergy and stabilizes the regulatory phenotype of Tregs, thus associating Treg function with the metabolic pathways that facilitate immune escape, as described in the next section of this review. By combining their effects of suppressing immune responses (cytokines), inhibiting T cell function through metabolic factors (hepatocytes), inhibiting cell cycle progression (checkpoint blockade), and promoting the migration of Tregs through chemokines, Tregs create microenvironments that allow tumor cells to escape immune recognition and destruction. Therefore, the presence of Tregs represent a significant obstacle to the success of immunotherapy, such as immune checkpoint blockade, which depends on the reinvigoration of exhausted T cells.

Regulatory γδ T cells

γδ T cells exhibit a unique lineage within T lymphocytes, bridging the gap between innate and adaptive immunity through expression of the γδ T-cell receptor (TCR). In contrast to conventional αβ T cells which recognize antigens through major histocompatibility complex (MHC) molecules, γδ T cells detect antigens in an MHC-independent fashion and therefore can respond quickly to stressors such as microbial metabolites and inflammatory signals. Historically, γδ T cells have been viewed largely as anti-tumor effector T cells; however, more recent studies suggest that subsets of γδ T-cells develop significant immunoregulatory and immunosuppressive capabilities within the TME [36].

Varying amounts of local cytokines increased metabolic stress and proximity to the surrounding stroma appear to enable tumor-associated γδ T cells to exhibit high levels of functional plasticity. It has been shown that tumor-associated γδ T cells from breast, colorectal, hepatocellular, pancreatic and ovarian solid malignancies preferentially differentiate along an IL-17 and IL-6 producing pathway often referred to as "γδT17-like" cells in the hypoxic and cytokine-rich microenvironment of solid tumors [37–41]. IL-1β, IL-23, TGF-β and IL-6 are major cytokines that stimulate the accumulation and differentiation of tumor-associated γδ T cells [42]. Collectively, these cytokines create an inflammatory feed-forward loop. The regulatory γδ T cell phenotype correlates with a decrease in cytotoxicity and IFN-γ production but with an increase in the expression of immune-regulatory markers such as PD-1, TIGIT, and CD39. The accumulation of γδ T cells in the tumor microenvironment correlates with progressive disease and poor prognosis for several types of cancers [43]. IL-6 is the major effector of tumor associated inflammation and has previously been done little to address its source. Regulatory γδ T-cells

are now identified as a significant source of IL-6 in the tumor microenvironment, and thus, a contributor to immune suppression in several ways, including autocrine as well as paracrine pathways [44]. Therefore, regulatory γδ T-cell derived IL-6 may maintain a negative feedback loop that enhances regulatory γδ T-cell survival and proliferation through activation of the JAK/STAT3 pathway, thereby limiting active effector immune responses. In the tumor microenvironment, IL-6 produced by γδ T-cells inhibits the proliferation of cytotoxic CD8 + T-cells and decreases granzyme and perforin expression and promotes the exhaustion of T-cells [45]. Furthermore, IL-6 directs CD4 + T-cell differentiation away from Th1-type responses and promotes the amplification and stabilization of FoxP3 + T-regulatory cells. Similarly, IL-6 will increase the recruitment and suppressive capacity of myeloid-derived suppressor cells (MDSCs) and promote the M2-like polarization of tumor infiltrating macrophages, thereby further contributing to immune evasion.

Myeloid-derived suppressor cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells with potent immunosuppressive properties that are usually expanded in cancer or chronic inflammation [46]. MDSCs are further classified into monocytic MDSCs (MM-MDSCs), resembling monocytes, and granulocytic or polymorphonuclear MDSCs (PMN-MDSCs) resembling neutrophils [47]. Both subsets are characterized in humans by their expression of markers such as $CD11b^+$ and $CD33^+$ with low HLA-DR expression and are found in the blood, spleen, and tumors of cancer patients [47]. MDSC levels in patients tend to correlate well with cancer stage and prognosis, signifying their importance in tumor immune evasion [48]. MDSCs arise when normal myelopoiesis is skewed by tumor- and inflammation-derived factors. The exposure to the growth factors (G-CSF, GM-CSF, M-CSF) and inflammatory cytokines (e.g., IL-1β, IL-6, IL-13, TNF-α), immature myeloid progenitors do not complete their differentiation to mature dendritic cells or macrophages but instead expand as pathologically activated suppressor cells [46]. Tumors actively promote this process with the secretion of factors such as GM-CSF and IL-6 that drive emergency myelopoiesis and expand MDSCs in bone marrow [49, 50]. The recruitment of MDSCs to tumor sites is also aided through the chemokines: CCL2, CCL5, CXCL5, CXCL12, and others are often secreted by tumors or stroma to attract MDSCs which are circulating [51]. For example, the chemokine CCL2 is the major recruiter of M-MDSCs which migrate through the expression of CCR2, and CXCL1/CXCL5 can recruit PMN-MDSCs through the expression of CXCR2, which has been shown in studies with melanoma, lung cancer and others [52, 53].

In the TME, MDSCs use many immunosuppressive mechanisms. One of the well-known is the depletion of important nutrients for T cell function: MDSCs often express high amounts of arginase-1 (Arg1) which hydrolyzes L-arginine, and inducible nitric oxide synthase (iNOS) which produces nitric oxide from L-arginine [54]. Thus, loss of L-arginine, and accumulation of NO, can stimulate T cell dysfunction: NO can cause nitration of T cell receptors and induction of T cell apoptosis, as well as suppression of IL-2 signaling and inhibition of MHC class II expression on antigen-presenting cells [54]. MDSCs also generate reactive oxygen species (ROS) through the action of various enzymes, such as NADPH oxidase (NOX2) [55]. ROS can cause oxidative stress in T cells which leads to impairment in the life span and signaling of T cells. In addition, both NO from iNOS and ROS can combine to form peroxynitrite, which nitrates chemokines and T cell receptors thereby preventing effective migration of T cells into the tumors and recognition of antigen [56]. MDSCs also secrete immunosuppressive cytokines as well. M-MDSCs produce IL-10 which serves to further mediate an anti-inflammatory environment (often in concert with TAMs and Tregs) [57]. Some MDSCs can produce TGF-β or can promote Tregs via TGF-β [58]. Indeed, one influential study showed that MDSCs in tumors produced TGF-β which promoted proliferation of Tregs, indicating a link between these suppressor populations [59]. MDSCs also express checkpoint ligands, e.g., they can express PD-L1, especially when stimulated by tumor-derived factors. COX-2 and prostaglandin E2 have been shown to up-regulate PD-L1 on MDSCs and other myeloid cells in tumors compounding their T cell inhibitory effect [60, 61].

Another mechanism is through physical interactions with various immune cell populations. MDSCs can interact with T cells or NK cells and deliver inhibitory signals (e.g., through the Galectin-9/TIM-3 pathway or via the PD-L1 found on the surface of some of these MDSCs) [62]. These cells also transdifferentiate into tumor-associated macrophages or dendritic cells that have tolerogenic properties in the TME. This is important since one of the proposed fates of tumor infiltrating MDSCs is their differentiation into M2-like macrophages due to the influence of factors such as IL-4 or IL-13, thereby blurring the line between MDSCs and TAMs in advanced lesions [63, 64]. This phenotypic plasticity is particularly evident in pancreatic cancer, where MDSC-to-TAM differentiation contributes to the establishment of a profoundly suppressive myeloid compartment [65].

Clinically, elevated levels of MDSCs in various malignancies correlate with a poor prognosis and decreased responses to immunotherapy agents. For example,

prostate cancer patients showing elevated levels of circulating MDSCs, elevated levels of TAMs, and elevations in IL-6 and IL-8 had a poor prognosis [66]. In breast cancer, circulating levels of MDSCs were found to correlate with lymph node metastasis, and the ability of MDSCs to inhibit T cell responses appeared mediated by the expression of the enzyme indoleamine-2,3-dioxygenase (IDO) [67, 68]. Similarly, in pancreatic cancer, elevated baseline MDSC frequencies and enhanced recruitment signatures are strongly associated with primary resistance to immune checkpoint inhibitors. In patients receiving checkpoint inhibitors, those that do not respond to these agents usually exhibit evidence of MDSC-mediated suppression. In some trials, non-responders exhibited higher levels of MDSC frequency at baseline or elevations in chemokines inducing MDSC recruitment [69]. These observations make MDSCs a prime target for therapeutic intervention, especially in combination treatment with standard chemotherapeutic regimens (this will be discussed later). Thus, the neutralization of MDSC recruitment or function is predicted to "take the brakes off" the immune system in the TME and allow T cells and NK cells to better attack the tumor.

Tumor-associated macrophages (TAMs)

Tumor-associated macrophages (TAMs) are one of the most abundant immune cell populations in many tumors. They can arise either from circulating monocytes that are recruited to the tumor and become macrophages or from tissue-resident macrophages such as microglia in the case of gliomas that are co-opted by tumor [70]. TAMs often have a range of activation states. In the extreme, M1 macrophages are pro-inflammatory and possibly tumoricidal, while M2 macrophages are immunosuppressive and protumorigenic [70, 71]. Tumors often direct macrophages towards a more M2-like phenotype through signals such as IL-4, IL-13 and IL-10, and colony stimulating factors (CSFs), etc [72]. Thus, high densities of TAMs, especially if skewed towards M2, generally correlate with poorer clinical outcomes such as increased invasion, increased angiogenesis, increased metastasis, increased resistance to therapy, etc [73, 74]. In glioblastoma, for instance, TAMs can comprise as much as 30–50% of tumor mass, and greater infiltration of TAMs correlates with a greater tumor grade and shorter survival [75].

M2-like TAMs serve as powerful mediators of immunosuppression and resistance to therapy. They secrete multiple cytokines and growth factors that confer tumor survival and inhibit immune function. Important TAM factors include IL-10 and TGF-β, which directly inhibit the function of T cells and dendritic cells, IL-6, which stimulates the expansion of MDSCs, TNF-α, which activates NF-κB pathways in tumor cells, VEGF, which induces aberrant angiogenesis and contributes to immunosuppressive vasculature, and chemokines such as CCL2, CCL5, and CCL22, which recruit additional monocytes and Tregs, etc [76, 77]. Indeed, TAMs in gliomas produce IL-6, IL-10, CCL5, and CCL22 that work synergistically to activate pro-survival signaling in tumor cells such as JAK/STAT and NF-κB, to attract Tregs, and to promote angiogenesis through VEGF [78]. TAM-derived CCL22 is known to be a chemoattractant for the $CCR4^+$ Tregs mentioned above, thus TAMs can create a Treg-rich environment [79]. TAM-derived IL-10 also promotes the generation of dendritic cells toward a tolerogenic phenotype and can inhibit the differentiation of T cells into Th1-type cells [77]. In addition, TAMs secrete factors that alter the environment of the local tissue: e.g., arginase-1 which is also expressed by MDSCs and depletes L-arginine, and indoleamene-2,3-dioxygenase (IDO), which affects tryptophan metabolism, as well as the enzymes that convert it to kynurenine and yield the effects produced thereby [77]. In both cases, T cells are deprived of the necessary amino acids for their function. In many cases, TAMs express PD-L1 at high levels, and thus assist in the engagement of T cell checkpoints. PGE2 signaling within the TME acts as a central upstream regulator of TAM immunosuppressive programming, inducing the coordinated upregulation of Arg1 and immune checkpoint ligands such as PD-L1, thereby amplifying metabolic and checkpoint-mediated T-cell inhibition. For example, one study demonstrated that inhibition of COX-2 or synthesis of PGE2 decreased TAM PD-L1 levels, thereby resulting in enhanced antitumor immunity [80]. In addition, TAMs can directly inhibit T cells through cell–cell contacts through expression of PD-L2, B7-H4, and even Fas ligand (FasL). Some tumor-associated macrophages have been demonstrated to express FasL, and to induce apoptosis of T cells upon contact with them [81].

As mentioned previously, TAMs contribute to therapeutic resistance by providing alternative pathways of tissue remodeling and survival in addition to their important role in immunosuppression. For example, the growth factors produced by TAMs promote proliferation and invasion of tumor cells [73]. The MMPs and cathepsins produced by TAMs degrade and remodel the components of the extracellular matrix (ECM) that influence tumor cell migration. However, such remodeling of the ECM may also act as a barrier to chemotherapy agents [82]. A dense collagenous stroma produced by TAMs and fibroblasts in breast and pancreatic cancers has been related to the poor delivery of chemotherapeutic agents to tumor cells [83, 84]. In addition, secretion of ECM components and enzymes that crosslink the ECM is done by TAMs, resulting in stiffness of tissue, which has been shown to impair diffusion of drugs in the tumor [82]. TAMs grow in a fashion that allows their participation

in metabolic intercellular communication so that survival pathways for tumor cells are promoted when under stress. When the tumors become hypoxic, TAMs express higher amounts of HIF-1α and in turn higher amounts of VEGF promoting angiogenesis, allowing tumor cell reoxygenation and survival or escape [85]. Hypoxia-induced HIF-1α signaling thus functions as a central adaptive pathway linking metabolic stress to angiogenesis and tumor cell survival. In addition, hypoxia causes TAMs to switch to anaerobic metabolism and produce adenosine that when available has strong inhibitory effects on T cell function via A2A receptors [86]. The major source of adenosine in TMEs is from TAMs in that they produce CD39 and CD73; this extra adenosine inhibits the effector T cell as well as NK cell function [86]. In addition, TAMs also transfer their mitochondria along with microRNA-containing vehicles to tumor cells so that their metabolism is influenced. TAM-derived exosomes containing miR-21 or the miR155 family of micro-RNAs have been shown to cause resistance to drug treatment in breast cancer cells by virtue of alteration of the gene expression programs in them [87].

Overall, TAMs facilitate a permissive niche for tumors by protecting them from immune destruction and promoting the repair of damage inflicted on tumors by therapy. When a fraction of tumor cells is wiped out by chemotherapy, the TAMs help to remove the debris, and they secrete cytokines such as IL-6 and TNF-α that may help remaining cells to outgrow the damages of therapy. During the application of radiation therapy, the irradiated tissues often experience an influx of macrophages as part of the wound-healing response, and macrophages in that state may secrete TGF-β and other factors that promote the radio resistance of surviving tumor cells [88]. TGF-β from TAMs and other cells is postulated to play a role in the DNA damage response that follows radiation therapy as well as in the process of EMT that leads to recurrence and metastasis [89]. The blockade of TAM-associated TGF-β has been found to increase radiation responses in preclinical models [90].

Neutrophils

Neutrophils have become more widely accepted as a main means of promoting the growth of cancer tumors, creating conditions for an immunosuppressive environment surrounding the tumor and helping to create therapeutic resistance to treatment. Tumor-associated neutrophils (TANs) are formed in response to cumulative chronic inflammation signals located within the TME and become differentiated into a form that is very different from their previous role as anti-infection cells. Increasingly, studies are finding that TANs exist centrally as regulators of chronic inflammatory immunosuppression and thus can allow both inherent as well as adaptive immunity to promote and support tumors [91].

Through the release of chemokines such as CXCL1, CXCL2, CXCL5, and CXCL8 (IL-8), tumors actively pull in neutrophils via their ability to bind to CXCR2. Additional tumor-secreted factors such as G-CSF, GM-CSF, IL-1β, IL-6, and TGF-β in both instances lead to recruitment of neutrophils at sites of infections/responses and stimulate the production of emergency granulocytes in the bone marrow, resulting in increased levels of circulating neutrophils. Neutrophils inside the TME experience a functional shift towards either a pro-inflammatory N1 phenotype or an immunosuppressive N2 phenotype due to several factors that include hypoxia, metabolic stress, and cytokine gradients [92]. The N1 phenotype is associated with various anti-tumor properties, including the ability to generate reactive oxygen species to kill tumor cells and support T-cell activation. However, the TME strongly favors the N2-like immunosuppressive phenotype; in fact, it appears that TGF-β plays a major role in generating the N2-like phenotype and is responsible for producing neutrophils that inhibit adaptive immunity, promote angiogenesis, and promote tumor invasion.

Several pathways have been identified through which TANs inhibit the development of T-cell immune responses to tumors. Most importantly is the role played by TANs in depleting the necessary nutrients for T-cell activation. TANs are abundant in Arg1, which removes the extracellular L-arginine that is required for T-cell proliferation [93]. This depletion of L-arginine results in less expression of the T-cell activation marker CD3 and ultimately a decreased ability of T-cells to mount an anti-tumor response. In addition to this negative effect on T-cell activation, TANs secrete reactive oxygen species (ROS) and nitric oxide (NO) as products of many neutrophil activation processes, which exacerbate the effects of T-cell receptor signaling leading to oxidative stress and T-cell apoptosis as well as disruption of chemokine-receptor interactions needed for T-cell trafficking to tumors [94]. TANs also secrete immunosuppressive mediators such as IL-10, TGF-β, and PGE2 that inhibit CTL and NK activity and promote the expansion of Tregs. TANs are also capable of expressing PD-L1, a ligand for PD-1 expressed on T-cells, and by doing so they can inhibit the activity of PD-1–expressing T-cells at the tumor site and may contribute to the resistance of many tumors to PD-1 blockade.

Mast cells and eosinophils

Mast cells and eosinophils are major effector cells in allergic diseases, including asthma, atopic dermatitis, and food allergies. Mast cells are tissue resident cells activated by cross-linking of IgE bound to the high-affinity FcεRI receptor, resulting in rapid degranulation and the release

of histamine, proteases (e.g., tryptase, chymase), and lipid mediators such as prostaglandins and leukotrienes [95]. These mediators produce acute allergic symptoms which include vasodilation, bronchoconstriction, and mucus hypersecretion. Mast cells also secrete type 2 cytokines such as IL-4, IL-5 and IL-13 that promote Th2 polarization and eosinophil recruitment [96]. In asthma, mast cell activation is a major contributor to bronchial hyperresponsiveness and remodeling, whereas eosinophils accumulate in airway tissue in response to IL-5 and eotaxin, releasing cytotoxic granules (e.g., major basic protein, eosinophil peroxidase), which damage epithelial cells and maintain chronic inflammation [95]. In atopic dermatitis, mast cell-derived histamine and proteases cause pruritus and dysfunction of the skin barrier, while IL-13 and IL-4 drive further Th2 skewing and increased IgE production [95]. Eosinophils contribute to amplifying this axis through the release of TGF-β and the promotion of tissue fibrosis. Together, mast cells and eosinophils provide a self-reinforcing loop of inflammation. The prominence of these cells in allergic pathology has inspired the development of targeted therapies such as monoclonal antibodies directed towards IL-5 (e.g. mepolizumab) or IL-4Rα antagonists (e.g., dupilumab) that modulate their activity to clinically effective benefits in severe allergic diseases.

Beyond their role in allergy, mast cells and eosinophils have emerged as important modulators of the TME, where they display context-dependent roles but often contribute to immunosuppression and tumor progression. In many tumor types, including breast, colorectal, and pancreatic cancers, mast cells infiltrate TME and are reprogrammed by tumor-derived IL-33, IL-4, and TSLP to adopt a regulatory phenotype [97]. These cells release IL-10, histamine, PGE2, and adenosine—factors known to suppress CTL and NK cell activity and promote Treg expansion [98]. Recent findings revealed that BTG2-deficient mast cells secrete IL-2 in tumor-draining lymph nodes, selectively expanding immunosuppressive Tregs and enabling immune escape [99]. Similarly, eosinophils in the TME may express PD-L1, release galectin-10, and produce TGF-β1, fostering fibroblast activation, desmoplasia, and suppression of $CD8^+$ T cell effector functions. In Hodgkin lymphoma and gastrointestinal cancers, eosinophil infiltration has been associated with poor prognosis and an exhausted immune phenotype [100, 101]. Notably, many of the pathways that govern eosinophil and mast cell activation in allergic diseases, including IL-5, eotaxin, and IL-33—are also active in tumors, indicating mechanistic overlap. This shared biology has prompted exploration of allergy-targeted therapeutics in oncology: for example, anti-IL-5 or anti-IL-13 antibodies, histamine blockers, or CXCR2 antagonists are being tested for their potential to modulate the TME and improve immunotherapy efficacy.

Endothelial cells

TECs (tumor endothelial cells) represent a feature of the TME which is central for evasion of immune responses from both the body's defenses and chronic inflammation, as well as causing resistance of tumors to treatment. Tumor-derived growth factors (TGF), inflammatory cytokines, hypoxic conditions (low oxygen), and metabolic stress lead TECs to undergo significant phenotypic and functional changes compared to normal endothelial cells (NECs). TECs change the properties of the vasculature at the tumor site, making it an immunosuppressive and resistance barrier.

TECs are the most well-known immunosuppressive mechanism due to their ability to promote immune exclusion [102]. Tumor-associated vasculature is abnormal in structure [102]; for example, tumor-associated blood vessels have irregular branching patterns and reduced pericytic coverage, which results in increased permeability to oxygen and nutrients and leads to tissue acidosis (due to greater concentrations of CO2 from necrotic tissue). Functionally, TECs reduce the expression of adhesion molecules necessary for the migration of leukocytes to the site of the tumor (e.g., ICAM-1, VCAM-1, E-selectin). TECs are thought to be in an endothelial-anergy state as they continuously respond to signals from persistent exposure to vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and angiopoietin-2 (ANGPT2). Because of this, even though $CD8^+$ CTLs may exist within circulation, they do not successfully adhere to or transmigrate across tumor-associated endothelium. At the same time, by producing and expressing specific molecules that promote the accumulation of immunosuppressive cell populations, TECs are actively recruiting immunosuppressive populations. Endothelial-derived chemokines such as CCL2, CCL5, and CXCL12 favor the infiltration of Tregs, MDSCs, and TAMs. Through these chemokines, the immune-suppressive environment becomes more established, and CXCL12 has been identified as a key factor in developing perivascular niches for T cells, thereby keeping them physically separated from the tumor microenvironment.

TECs not only act as a barrier to physical intrusion, but they also provide direct immunologic modulation through the actions of infiltrating immune cells. TECs have been observed to enhance the expression of immune checkpoint ligands e.g. PD-L1 and PD-L2 in response to inflammatory cytokines e.g. IFN-gamma and TNF-alpha [103]. The binding PD-1 on effector T-cells with PD-L1 from endothelial cells impairs the proliferation of T-cells, reduces cytokine production, and results in functional exhaustion of T-cells before they encounter tumor cells. Fas ligand (FasL/CD95L) is also expressed by TECs which can selectively induce apoptosis in Fas expressing effector CD8 + T-cells whilst sparing Tregs that have higher

expressions of anti-apoptotic molecules [104]. This selective deletion of lytic lymphocytes occurs at the vascular interface and represents a strong immune checkpoint not dependent upon classical PD-1/PD-L1 signaling. TECs can also mediate metabolic immunological suppression [105]. By expressing ectonucleotidases such as CD39 and CD73, TECs are involved in the conversion of extracellular ATP to adenosine. The elevated level of adenosine in the perivascular area suppresses both T-cells and NK-cells via A2A receptor signaling, inhibits DC maturation, and promotes Treg stability.

Cancer-associated fibroblasts (CAFs) and stromal components

Although immune cells are the primary mediators of suppression, the tumor stromal compartment is another important player in inducing a therapy-resistant niche. Cancer-associated fibroblasts (CAFs) are usually the major stromal cell population in the TME of carcinomas (pancreatic, breast, and colon cancers). CAFs are activated fibroblasts that secrete extracellular matrix proteins, growth factors, and cytokines, which can significantly impact tumor ecology [106]. A defining feature of tumors rich in CAFs is a desmoplastic stroma, a dense fibrotic matrix found around tumor nests that can physically block immune cell infiltration and drug delivery and biochemically modulate immune responses.

CAFs contribute to immunosuppression by several mechanisms. They produce chemokines and cytokines that recruit immunosuppressive cells and exclude effector T cells. For example, the CAF-derived chemokine CXCL12 can act as a "T cell trap", binding and trapping T cells from effectively getting to tumor cells as shown in experiments with pancreatic ductal adenocarcinoma (PDAC) models [107]. In PDAC, the depletion of CXCL12 or the blockade of its receptor, CXCR4, leads to increased penetration of T cells into tumors and synergy with checkpoint blockade [107]. CAFs secrete CCL2, which attracts monocytes that become TAMs, and LIF (leukemia inhibitory factor), which has immunosuppressive properties and promotes stem–like properties in cancer cells [108]. With those secret factors, CAFs maintain the immunosuppressive populations (TAMs, MDSCs, Tregs). CAFs can also directly suppress T cells. They are known to express FasL on their surface which can induce apoptosis of Fas-expressing effector T cells upon contact [109]. This occurs in models of ovarian and lung cancer where T cells undergo activation-induced cell death by FasL provided by the stroma. CAFs are known to express immune checkpoint ligands; CAFs have been shown to express PD-L1 and PD-L2, which at lower levels than immune cells, contribute to T cell inhibition in the stroma [110, 111]. Interestingly, these CAFs are also able to indirectly increase PD-L1 expression on tumor cells as well, e.g. CAF-secreted CXCL5 has been shown to be able to upregulate PD-L1 on colorectal cancer cells thus promoting immune evasion [111].

The ECM produced by CAFs and other stromal cells, forms a physical barrier which can prevent T cell infiltration as well as limit the distribution of therapeutically relevant agents into that tumor tissue [1]. This "stromal barrier" is even more pronounced in pancreatic cancer, which is characterized by deposition of hyaluronan which gives rise to elevated interstitial fluid pressure, collapses blood vessels and inhibits drug delivery [112, 113]. It is a physical barrier but, as seen with pancreatic cancer specifically, has distinct immunological consequences; a hallmark of pancreatic tumors is low levels of T cell infiltration (a classic "cold" tumor) which is, in part, due to exclusion from stroma. Furthermore, an aspect of the ECM is the storage and presentation of growth factors. For instance, TGF-β is often sequestered within the ECM where it can be activated by proteases released from CAFs or TAMs [114]. TGF-β now becomes activated, leading to signals to both tumor and immune cells. In immune cells, TGF-β is a potent inhibitor of cytotoxic T cells and NK cells and promotes Treg differentiation and M2 polarization in macrophages; it signals to fibroblasts to further activate their functions leading to a positive feedback loop [114]. Thus, regions of high TGF-β (often stroma-rich regions) are generally associated with areas of immune suppression within a tumor [115]. Clinically, a TGF-β gene signature present within tumors is correlated with poor responses patients to PD-L1 blockage. This has been noticed in certain trials whereby patients who do not respond have high levels of TGF-β activity in fibroblasts [116, 117]. Thus, the idea of TGF-β as a master regulator of immune exclusion has arisen, particularly in stroma-rich tumors.

It is becoming evident that the mechanical and metabolic characteristics of the stroma contribute to the development of an immuno-suppressive. The rigid fibrous tissue is a factor in aberrant production of vessels and areas of hypoxia. Hypoxia, in turn, causes the stabilization of the HIF-1 alpha, not only in malignant cells, but also in the immune cells and stroma leading to more adenosine production and less effector function (discussed below in more detail on HIF-1 alpha). Also, it is possible for crosstalk to occur on a metabolic basis. The tumor cells and stroma can enter "symbiosis" in a metabolic sense, as for example, in the case of aerobic glycolysis, Warburg type metabolism, performed by CAFs which produce lactate utilized by the tumor cells [118]. The lactate and acidity within the TME resulting from this metabolism can inhibit the function of T cells.

Key inflammatory mediators and signaling pathways

The above-mentioned cellular players act primarily via secreted factors and activation of specific signaling pathways. Tumoral inflammation is characterized by a network of cytokines, chemokines and eicosanoids that, together, promote immunosuppression as well as resistance to therapy. We will focus on the most important of these mediators, such as IL-6, TNF-α, TGF-β, IL-1β, IL-8, prostaglandin E2, and others, as well as the important intracellular pathways which lead to which are associated with inflammation, cancer cell survival and immune evasion (Fig. 2).

IL-6/STAT3 axis

Interleukin-6 (IL-6) is an archetypical proinflammatory cytokine that has emerged as a critical link between chronic inflammation and cancer progression. Many cancers and their associated stromal or immune cells produce IL-6. IL-6 acts on cells through the JAK/STAT3 signaling pathway whereby it binds to the IL-6 receptor (IL-6Rα) and gp130 co-receptor, leading to activation of JAK kinases and phosphorylation of STAT3, which then dimerizes and translocate to the nucleus [119]. In cancer, constitutive activation of STAT3 is very common and is frequently driven by persistent IL-6 signaling in the TME [119]. This pathway upregulates several genes that promote tumor survival (Bcl-2, Bcl-xL), proliferation (Myc, Cyclin D), angiogenesis (VEGF), and invasion (MMPs). In addition, immunosuppressive mediators such as IL-10, PD-L1, and others can be induced. With respect to therapy resistance, IL-6/STAT3 has several important effects. STAT3 activity in tumor cells can induce drug resistance genes and anti-apoptotic signaling pathways, rendering tumor cells less sensitive to chemotherapy and targeted agents [120]. In lung cancer and pancreatic cancer models, for example, high levels of IL-6 (frequently in response to therapy as a component of a stress response) have been shown to activate STAT3, which then upregulates genes driving EMT and stemness, leading to resistance to EGFR inhibitors and gemcitabine, respectively. IL-6 can also induce DNA repair enzymes via STAT3, helping tumor cells survive radiation-induced DNA damage [121].

Importantly, the activation of IL-6/STAT3 signaling severely inhibits antitumor immunity. In immune cells, the activation of STAT3 signaling depends on the context and type of cytokines. Although persistently activated STAT3 by pro-inflammatory cytokines (IL-6) usually fosters the development of an immune suppressor phenotype in the tumor microenvironment, at times and in some immune populations, activated STAT3 will induce an immune stimulatory phenotype: in macrophages it promotes M2 polarization and PD-L1 expression [122]; in dendritic cells it inhibits maturation and antigen presentation [123, 124]; in neutrophils it may induce suppressive activity [125]; and in T cells, chronic activation of STAT3 favors Th17 versus Th1 differentiation, or induces phases of intrinsic exhaustion programs [126]. In fact, STAT3 has been referred to as a "master regulator" of the immunosuppressive TME. It directly upregulates immune checkpoint molecules — it binds directly to the promoters of the PD-1, PD-L1, and CTLA-4 genes, resulting in their transcriptional upregulation [127]. In head and neck cancer, blocking STAT3 led to decreased

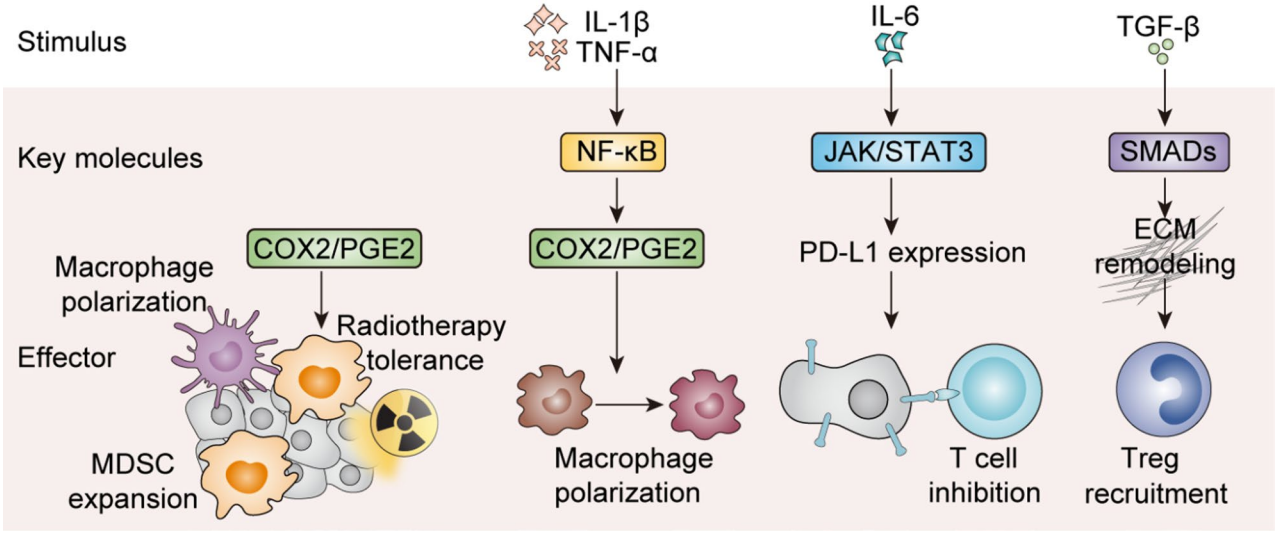

Fig. 2 Key inflammatory signaling pathways underlying immunosuppression. NF-κB pathway activated by TNF-α and IL-1β promotes transcription of pro inflammatory genes and survival signals. IL-6 activates the JAK/STAT3 signal transduction pathway stimulating the production of PD-L1 production, inhibiting cytotoxic T cells and promoting cancer stemness. TGF-β signaling modulates extracellular matrix remodeling and Treg recruitment. The COX2/PGE2 axis pathways regulate macrophage polarization and MDSC expansion

levels of PD-1 on T cells as well as decreased levels of PD-L1 on tumor cells, thus promoting antitumor immune responses [128].

Clinically, higher levels of IL-6 have been correlated with worse outcomes and more aggressive disease in many different cancers. For example, breast cancer patients with high IL-6 in serum had a higher risk of recurrence and metastasis [129]. In colorectal cancer, IL-6 promotes the cancer stem cell phenotype and resistance to therapy [130]. IL-6 is also a major contributor to cachexia and paraneoplastic syndromes in cancer patients, indicating its systemic effects [131]. Because of these facts, IL-6 and STAT3 represent major nodes to overcome resistance. The success of tocilizumab (a monoclonal antibody to IL-6R) in the treatment of cytokine release syndrome seen with CAR T cell delivers the dominant immunomodulatory effect of IL-6 [132]. In the conduct of trials in cancer, blockades of IL-6 and combination with checkpoint blockades are actively being investigated to both enhance efficiency and diminish the inflammatory toxicity. The preclinical studies in this regard are most impressive. Either IL-6 or STAT3 blockade can revert the sensitivity to immunotherapy. In mice, either IL-6 or IL-6R antibodies combined with anti-PD-L1 significantly inhibited the growth of tumors in models of pancreatic cancer and HCC where either IL-6 or IL-6R antibodies alone were much less efficient [133, 134]. In similar studies the use of JAK/STAT3 inhibitors has been shown to significantly reverse the resistance to PD-1 blockade in models of lung cancer and melanoma [135, 136]. A phase III protocol (IMbrave150) in advanced HCC where the anti/PD-L1 monoclonal antibody atezolizumab has been combined with dexamethasone (an anti-VEGF antibody which diminishes IL-6/STAT3 activity by normalizing vasculature and diminishing IL-6 secretion by macrophages) has shown a significant improvement in survival of patients with respect to the increase in survival afforded by sorafenib [137]. This highlights the importance of considering other non-tumor immunosuppressive (VEGF-vascular) approaches that can be used in combination with immunologic therapy. Although not the direct IL-6 blockade, the effects of bevacizumab decreased intra-tumoral IL-6 levels, due to the decreased hypoxic state and increased macrophage infiltration.

TNF-α and NF-κB signaling

TNF-α is another important inflammatory cytokine in the TME classically produced by macrophages and T cells, but also by tumor cells in particular contexts. This inflammatory cytokine has the ability to induce apoptosis in tumor cells in acute situations, but with chronic exposure, TNF-α induces activation of the NF-κB pathway, which promotes survival of cells and inflammatory signals [138]. NF-κB is a transcription factor, which upon activation (or more commonly a result of TNF receptor signaling and IKK activation), translocate to the nucleus to induce the genes involved in inducing the pro-survival and proliferative signals and production of further inflammatory. This induces a positive loop of inflammatory signaling. NF-κB is aberrantly active in cancers either as the result of mutations or, more commonly, due to signals emanating from the inflammatory milieu [139]. NF-κB upregulates the anti-apoptotic genes Bcl-xL, IAPs (inhibitor of apoptosis proteins) and A20 which may lead to development by the tumor cells to the chemotherapeutic and radiation-induced cell death [140]. NF-κB itself regulates the pro-angiogenic factors and the metalloproteinases, which enhance the invasive nature of tumors and the potential for metastasis [141]. NF-κB in tumor cells also leads to enhanced expression of immunosuppressive molecules such as PD-L1 and COX-2, linking this signal with evasion of immune recognition. It has been shown in tumor models that blocking COX-2/PGE2 activity leads to decreased expression of PD-L1 in these tumors [60].

The activity of NF-κB signaling in immune cells may also promote an otherwise tolerogenic phenotype. For example, in dendritic cells, chronic activation of NF-κB will paradoxically lead to the production of IL-10 and poor T cell stimulatory capacity (a phenomenon referred to as DC paralysis in some contexts) [142]. In T cells, certain NF-κB-dependent genes lead to exhaustion or regulatory programs if their expression is constantly up-regulated [143]. TNF-α itself is a double-edged sword in the tumor microenvironment since it can kill tumor vascularity or cells at high acute doses which effect can be exploited in isolated limb perfusion in melanomas. However, in most tumors TNF-α is present at lower chronic levels, where its effect is as a tumor promoter. TNF-α leads to "inflamed" stroma which paradoxically promotes growth of tumors, because TNF-α activates NF-κB in cancer and in the stromal cells, and this increased NF-κB activity leads to recruitment of suppressive immune cells and increased angiogenesis [141]. In fact, high levels of TNF-α have been correlated with cachexia and resistance to therapy, e.g., in breast cancer, TNF-related activation of NF-κB has been found to lead to resistance to endocrine or chemotherapy, due in part to induction of EMT and an invasive phenotype [144]. There is cross-talk between TNF/NF-κB and other signal transduction pathways. For example, NF-κB and STAT3 exhibit cross-talk, since they can regulate gene expression together and interact in relation to gene promoters. Indeed, numerous genes require activation by both NF-κB and STAT3 in terms of complete induction, e.g., IL-6 itself can be induced by NF-κB, which leads to activation of STAT3, leading to amplification of a cytokine loop [145]. Furthermore, NF-κB also indirectly up-regulates immune

checkpoint ligands via inflammatory cytokine signaling, e.g., IL-6 is driven by NF-κB to induce PD-L1 expression through STAT3, as discussed. Hypoxia may also activate NF-κB, thus further linking it to the HIF-1α pathway in tumors [146].

Targeting TNF-α or NF-κB to improve therapeutic responses is complicated because their major roles are in normal immunity. Studies have indicated that TNF-α blockade can improve outcomes in some settings. In mouse models of checkpoint blockade, transient TNF-α inhibition (such as using etanercept, a TNF receptor-Fc fusion protein) has been shown to improve T cell response and decrease Treg activity, which can enhance anti-PD-1 effectiveness [147]. The rationale is that TNF-α is one of the players causing T cell exhaustion through NF-κB-mediated expression of TIM-3 and other T cell checkpoints; blockade of TNF might reverse this induction and maintain T cell effector function. Indeed, high serum TNF in patients has been found to correlate with inadequate checkpoint inhibitor responses [148]. Direct blockade of NF-κB (such as IKK inhibitors) has been tested preclinically to overcome chemoresistance [149]. These might act in resensitizing tumors to apoptosis by lowering the threshold of the cell death signal. For example, bortezomib (a proteasome inhibitor) prevents degradation of IκB (thus blocking NF-κB) and thus was thought to chemosensitize tumors per se; while bortezomib is used in myeloma primarily for its direct cytotoxic effects, part of its action is through NF-κB blockade which can decrease IL-6 and other growth factors in the microenvironment [9, 150].

TGF-β and immune exclusion

TGF-β a cytokine with strong immunoregulatory and pro-fibrotic effects, is usually found elevated in advanced tumors. TGF-β is secreted by many different cell types found in the TME, including tumor cells, TAMs, Tregs, and CAFs. TGF-β signals through threonine kinase receptors (TGF-β RI/II), activating SMAD transcription factors which thereafter regulate gene transcription [151]. TGF-β has a context-dependent role in cancer, and it can be suppressive for early tumorigenesis through inhibition of proliferation, but in established tumors it promotes invasion, metastasis and immune evasion. One of the important actions of TGF-β is to promote EMT in cancer cells, which increases their motility and drug resistance [152]. This is very well established: TGF-β signaling drives transcription factors such as Snail, Slug and Zeb1 which repress E-cadherin expression, leading to the acquisition of a mesenchymal invasive phenotype [153]. EMT leads to increased metastasis as well as resistance to therapy. For instance, EMT-ed tumor cells may also be less proliferative and differing antigenic profiles may be produced or increased expression of PD-L1 may be seen [154].

TGF-β is profoundly inhibitory to immunity. It inhibits CTL and NK cell capacity and function for proliferation in part by downregulating cytolytic gene expression (perforin, granzymes) and receptors like NKG2D found on NK cells [155]. Similarly, TGF-β promotes direct expansion of Tregs and enhances their suppression. Also, TGF-β skews macrophage populations to the M2 phenotype and promotes the differentiation of monocytes to MDSCs or TAMs rather than immunostimulatory DCs [156]. In the case of checkpoint blockade therapy, high values of TGF-β activity in the tumor stroma have been associated with lack of success of the therapy. The proposed mechanism is a TGF-β created "walled off" tumor site which is a combination of physical walled off (via fibrosis) and an immunoinhibitory (via T cell inactivity) site [157, 158]. In the radiation context, TGF-β has been proposed to be a major pathophysiologic mechanism involved in the reactions of tissues which result in radioresistance [159]. The active TGF-β in normal cells and immune cells can be released because of radiation therapy. The TGF-β then is active on tumor cells which survive the initial radiation exposure facilitating their negative entry into a state of cell cycle arrest and DNA repair, which protects them from a state of mitotic catastrophe, and is able to induce EMT in these irradiated cells [160]. At the same time, the TGF-β suppresses any immune function which might be provoked by the radiation. The radiation can lead to the immunogenic death of tumor cells but the TGF-β can quench the adaptive immune priming to occur with this event. Studies in mice have shown that blockade of TGF-β can enhance the outcome of radiotherapeutic approaches [88].

Many inhibitors of TGF-β have been tested clinically. Fresolimumab is a neutralising antibody to TGF-β. In a phase I trial in breast cancer fresolimumab combined with focal radiotherapy induced one increase in effector phenotype T-cells as well as some evidence of prolonged survival [161]. Another approach involves small molecule inhibition of the TGF-β receptor I kinase (e.g. galunisertib also known as LY2157299). Trials in glioblastoma which have shown advantage of combined therapy with chemotherapy or others have had limited results [162]. A particularly interesting approach was with bintrafusp alfa (M7824) a bifunctional fusion of a TGF-β trap and an anti-PD-L1 antibody [163]. The hypothesis being that blockade of TGF-β signaling in the stroma and PD-L1 in the interphase of the tumor and immune components could be accomplished. Early trials in PD-L1–naïve patients showed some complete and durable responses in difficult to treat tumors such as biliary tract cancer while a further phase trial in lung cancer had limited success exhibited, exemplifying the delicate

balance between efficacy and toxicity [154]. There are, however, distinct examples where targeting of TGF-β has improved therapy. In metastatic urothelial carcinoma, patients with high TGF-β signatures in fibroblasts showed poor response to PD-L1 inhibitor when given alone, but the combination of PD-L1 inhibitor and bevacizumab (anti-VEGF which can indirectly reduce TGF-β) showed improved responses [164]. This may imply that by conquering TGF-β mediated exclusion conversion of non-responders to responders can be accomplished in immunotherapy.

PGE2 and COX-2

Prostaglandin E2 (PGE2) is an eicosanoid inflammatory mediator produced from arachidonic acid by cyclooxygenase-2 (COX-2) and PGE synthases. PGE2 is typically produced in high concentrations at the sites of a tumor, released by both tumor cells and infiltrating myeloid cells [165]. It binds to EP receptors (EP1-EP4) on a variety of cells and produces signaling cascades that generally lead to suppression of host immunity and pro-tumor effects [165]. The COX-2/PGE2 pathway is a well-established avenue for carcinogenesis and immune evasion [166]. In the TME, PGE2 has various effects: it can be an effective attractor and inducer of MDSCs and TAMs [167]. PGE2 together with others can induce skepticism. It is necessary, in some models, for MDSC accumulation from tumor-derived PGE2. It polarizes macrophages to M2; rather than restating individual targets, PGE2 is discussed here as a pleiotropic mediator that reinforces TAM immunosuppressive functions through coordinated metabolic (Arg1), cytokine (IL-10, IL-6), and checkpoint-related pathways, as described above. PGE2 can act directly as an inhibitory agent of T cell function. It effects an increase in intracellular cAMP through its action on the EP2 or EP4 receptors found on T cells, resulting in inhibition of stimulation of T cell proliferation and IL-2 secretion after stimulation [168]. PGE2 has the effect of inhibiting NK cytotoxicity and dendritic cell maturation. PGE2 has a synergistic effect in stabilizing Tregs and inducing Treg expansion. PGE2 has been found in some studies to have the ability to increase FoxP3 expression and/or that of Tregs in their suppressor function. It is instrument in the upregulation of checkpoint molecules on immune cells. PGE2 in chronic amounts in the TME may increase PD-1 expression on CD8 + T cells, while it may increase PD-L1 expression on myeloid cells [169]. Inhibition of either COX-2 or PGE2 synthesis, it is found, will be associated with a decrease in PD-L1 levels on the tumor. PGE2 promotes milieu favorable to metastasis via promoting angiogenesis and promoting tumor cell invasiveness.

In tumors, high relative levels of COX-2 are frequently a marker of inferior prognosis. For example, in colorectal cancer, COX-2 overexpression has been shown to correlate with immune evasion and rapid change to a lethal phenotype [170]. PGE2 has been shown to cause inhibition of the antigen presenting cell (APC) function of dendritic cells thereby inhibiting T helper (Th) cell 1 immune responsive results while skewing the T cell phenotype to Th2 or inducing tolerance. In breast cancer, PGE2 has been shown to increase the production of immunosuppressive factors and myeloid cells which inhibit the cytotoxic lymphocytes [171]. The relationship of PGE2 to chemoresistance is perhaps most clearly illustrated in studies of colorectal cancer prevention. Long term aspirin (a COX-1/2 inhibitor) use has been shown in epidemiologic studies to decrease the incidence and mortality of colorectal cancer by as much as ~ 30–40% [172]. While the effect of aspirin is in part due to the actions of the COX-2 pathways in the tumor cells, a great deal of it would appear to be immune mediated, i.e., aspirin appears to enhance the immune surveillance function in tumors by inhibiting the negative immune effects of PGE2. In cancer therapy, selective COX-2 inhibitors (i.e., Celecoxib) have been tried as adjuncts. In some studies, the addition of celecoxib to chemotherapy in lung cancer has shown slight improvement in responses, however mixed results have been obtained and the issues of side effects in terms of COX-2 inhibitors due to cardiovascular toxicity and decreased formation of prostacyclin has limited other studies [173]. Importantly, new concepts are being pursued to examine specifically the PGE2-EP receptors. EP4 is felt to be an important receptor in mediating the tumor immune suppression effects of PGE2 in the TME [174]. There are initial clinical investigations of using small molecule antagonists to the EP4 receptors for cancer treatment which have as the goal the restoration of immune function through stimulation of T cell function and decreased MDSC influx into tumors. One such agent, TPST-1495, an EP2/EP4 dual agent, is presently undergoing phase I trials [175].

There is also a clear link between PGE2 and the response of tumors to radiotherapy and chemotherapy. For example, dying tumor cells may release factors mediating COX-2 expression in the tumor stroma. This may in turn stimulate the production of PGE2 which may, in accordance with its actions in the normal wound healing process, protect the surviving tumor cells from attack by T cells as it may be able to recruit suppressive cells to its support at once [176]. Experimental studies have indicated that the use of anti-inflammatory agents such as NSAIDs at the time of administration of radiation or chemotherapy may improve tumor control in being able to block this increase in PGE2 and so maintain the immune environment in that of an activated state [177]. In this way the COX-2/PGE2 axis acts as an important mediator of inflammation related to immune suppression

in tumors. By blunting this pathway using systemic anti-inflammatory medication (NSAIDs) or using specific EP receptor antagonists, it may be possible to break this cycle of immune suppression. This is a rationale for the use of inhibitors of checkpoint mechanisms in combination with celecoxib for instance, or with other PGE2 pathway blocking agents, to increase the number of patients who mount effective immune responses against their tumors.

Other cytokines and mediators

An extensive variety of inflammatory mediators, including cytokines, chemokines, metabolic byproducts and components of the inflammasome participate in generating a protective immunosuppressive TME for cancer progression and drug resistance. One of these mediators is IL-1β, a major proinflammatory cytokine produced chiefly by inflammasome activated myeloid-derived cells. This mediates the expansion of MDSCs and the Th17 lymphocyte population and chronic exposure desensitizes the effector cells to the immune response and, through genes that promote survival, induces drug resistance to chemotherapeutic agents. A significant decrease in incidence and mortality of lung cancer was observed in patients treated with the IL1β neutralizing antibody, canakinumab, in the CANTOS cardiovascular study, implying that inhibitory strategies to IL-1β-induced inflammatory responses may boost immune responses to cancer [178]. The overexpression of IL-1β has been associated with aggressive phenotypic designs and inhibition of IL-1β or of the NLRP3 inflammasome produces a decreased accumulation of MDSCs and increases the efficacy of therapeutic checkpoint blockade in preclinical models [179]. The same is true of IL-8, a chemokine that is increased not only under conditions of hypoxia but also through activation of RAS which aids the recruitment of neutrophils and granulocytic MDSCs through CXCR1/2 signaling [180]. Increased levels of IL-8 are associated with poor responses to PD-1 or PD-L1 blockades and reduced survival [181]. Therapeutic neutralization of IL-8 is being examined with the IL-8 neutralizing antibody BMS-986,253 and antagonists of CXCR2 such as SX-682 which in clinical trials have shown promise in their ability to reduce neutrophil and MDSC infiltration into the tumor mass [182].

IL-10 is secreted by TAMs, Tregs, and tumor cells exert its classical anti-inflammatory and immunosuppressive effects through the suppression of antigen presentation and altered production of various cytokines. Historically viewed as an anti-inflammatory cytokine, IL-10 has more recently been noted to have immunomodulatory abilities based on the conditions under which it is administered. Administration of IL-10 via pegilodecakin is an example of this as it was demonstrated that IL-10 could increase both the quantity and quality of cytotoxic CD8 + T cells, thereby modifying the tumor environment [183]. However, this will require additional research to achieve consistent clinical efficacy from high dosage levels of IL-10. Also, signaling through the IL-10 receptor will generate increased effector activity for many immune cell types including both T and NK cells; hence again demonstrating that IL-10 has a dual role in regulating antitumor immune activity. Not by a direct inhibition of the action of IL-10 but by decreasing the upstream inducers such as PGE2 or STAT3 perhaps may be useful in minimizing the suppressive effects of IL-10. Metabolic immunosuppression involves the increased levels of adenosine which is formed in significant quantities by means of the sequential action of CD39/CD73 expressed on Tregs, TAMs, and tumor cells during conditions of hypoxia. Adenosine may then in turn suppress T and NK cells by means of A2A receptors found on these cells. Inhibitors of adenosine formation, like oleclumab, an anti-CD73 Ab or ciforadenant an A2A antagonist are being administered in combination with inhibitors of the checkpoints to restore function in the T. cells. Meanwhile indoleamine-2,3-dioxygenase (IDO1) converts tryptophan to kynurenine which leads to an anergic state in the T cells but is also involved in the production of TGF-β. The Phase III study in malignant melanoma was negative but renewed efforts are being put forth to utilize dual IDO/TDO inhibitors or in combination with other therapeutics, including radiotherapy or vaccines [184]. The chemokines CCL2, CCL5, CXCL12 may also play a role in the recruitment of the immunosuppressive monocyte and Treg populations into the tumor in that function blocking agents of their receptors have shown promise in preclinical and early clinical studies. Finally, the DAMPs released from the inflammasomes such as HMGB1 and S100A8/A9 play a role in maintaining chronic inflammatory milieu observed in tumors through their influence on RAGE and TLR4. Targeting the S100A8/A9 and NLRP3 inflammasome (e.g. MCC950) reduces the recruitment of the MDSCs and synergizes with PD-1 blockade.

Impact of inflammatory microenvironments on therapy resistance

In TME, immunosuppression-driven inflammation has major effects on antitumor effectiveness for all classes of therapy. This means that immunotherapy, chemotherapy, radiotherapy, and precise therapies all suffer from an immunosuppressive, inflammation-driven microenvironment. We will consider how factors mentioned above translate into resistance mechanisms for each class of therapy, using examples across various cancers (Fig. 3).

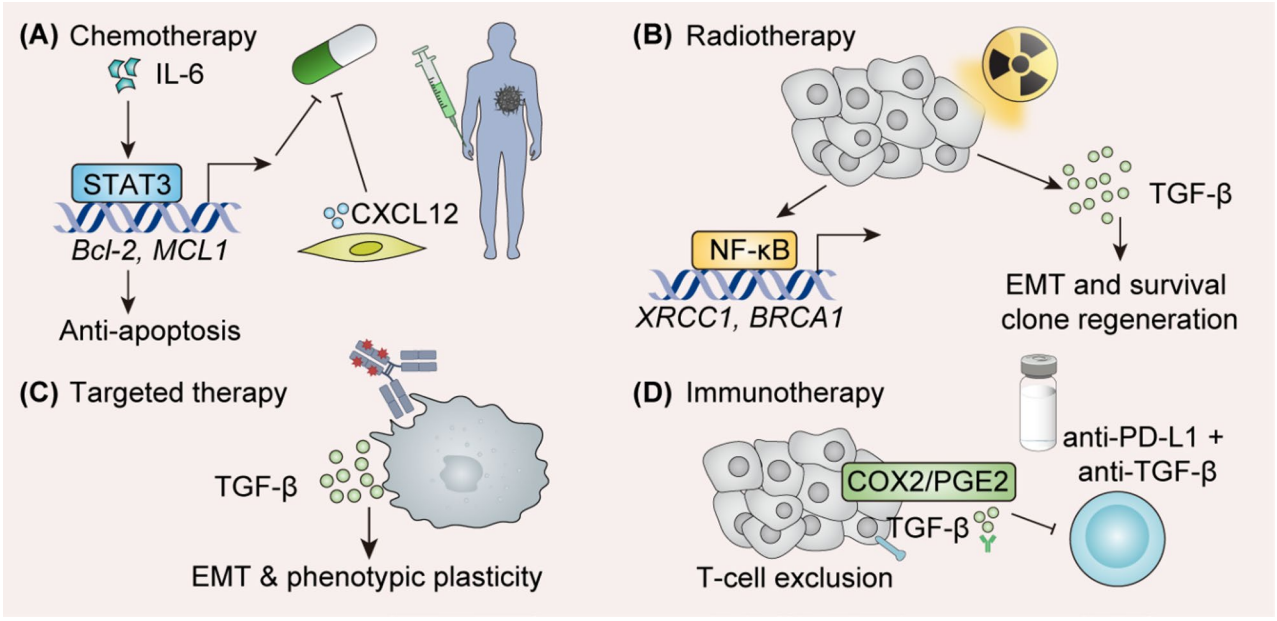

Fig. 3 Mechanistic overview of inflammation-induced resistance across therapeutic modalities. **A** Chemo- therapy: IL-6/STAT3 activation leads to anti-apoptotic signaling. **B** Radiation therapy: NF-κB activation leads to DNA repair and repopulation of resistant clones. **C** Targeted therapy: TGF-β signaling leads to phenotypic plasticity and escape pathways. **D** Immunotherapy: PGE2 and TGF-β signaling limits T-cell infiltration efficacy and checkpoint blockade

Resistance to immune checkpoint inhibitors

Therapy with immune checkpoint inhibitors (ICIs), such as antibodies against PD-1, PD-L1, or CTLA-4, has revolutionized the treatment of several cancers. However, most patients do not achieve durable responses, for example, the average objective response rates to anti-PD-1 monotherapy are only about 20% for all solid tumors, with many "primary resistant" cases [185]. A major reason for the limited effectiveness of these drugs is the immunosuppressive TME that fails to allow for adequate T cell infiltration or function, despite checkpoint blockade. In the so-called "cold" tumors, ICIs often fail to engage new immune responses [186]. The exclusion of T cells is frequently a consequence of the stroma, which is often inflammatory: as discussed, although various factors (CXCL12 from CAFs and endothelia with aberrant vasculature driven by VEGF, etc.) can literally wall off T cells from the nascent tumor nests, even though some T cells may be present at the margins, they may not inhabit deep tumor spaces. For instance, in pancreatic cancer, there are abundant CAFs and a lot of CXCL12, which creates a T cell belt around the tumor, but few T cells inside the tumor: this is the circumstance in which anti-PD-1 drugs are almost without activity [187]. Only when drugs or procedures eliminate these barriers (i.e., CXCR4 inhibitor to inhibit CXCL12, or PEGPH20 to degrade hyaluronan) will T cells penetrate and ICIs yield activity in experimental models [188].

In tumors with T cells but T cells that are functionally deficient, the high presence of Tregs, MDSCs and TAMs is correlated with an absence of ICI response. Clinical correlative studies have revealed repeatedly that those who do not respond to PD-1/PD-L1 blockades have higher baseline levels of these suppressing factors. For example, in a study of melanoma patients given Nivolumab it is shown that the nonresponses had greater frequency of circulating monocytic MDSCs and more TAMs at baseline in tumor biopsies than responders [189]. In a quin like manner, high intratumor content of Tregs correlated with nonresponse to anti-PD-1 in renal cell carcinoma [190]. Mechanistically, even if the checkpoint receptors such as PD-1 are blocked, there can still be inhibition of T cells from means in the inflamed TME. High expression of suppressive ligands such as galectin-9 (binding TIM-3), adenosine (binding A2A), Arg1/IDO (metabolic suppression), and TGF-β all can still blunt T cell activity. Thus a tumor can be unresponsive to blockade of PD-1 if for example invigorate penetration or activation of T cells is inhibited at the same time by TGF-β, as was clearly shown in the case of the metastatic urothelial cancers in which a high TGF-β gene signature was found to be associated with poor response to Atezolizumab until TGF-β was countered [191]. In addition, some of the elements of inflammatory TME additionally actively induce adaptive resistance to immunotherapy. When checkpoint therapy is applied to a certain number of T cells then those T cells produce IFN-γ. However, IFN-γ also upregulates PD-L1 on tumor and myeloid cells which is a known feedback loop [192]. In addition, IFN-γ may increase the IDO and upregulate other checkpoints

such as LAG-3 on T cells [193]. The MDSCs in the TME will respond to the IFN-γ derived from T cells by increasing production of iNOS and the production of nitrosylated chemokines [192]. Thus, unless the suppressing cell populations are eliminated or reprogrammed, the initial wave of T cell activity produced by ICI may be nullified by a resultant reactive suppression.

The best example of inflammatory feedback in the development of ICI resistance is the IL-8. It has been showed that high IL-8 levels lead to poor clinical outcomes with ICIs in melanoma, lung and bladder cancer patients [194]. The explanation given was that IL-8 recruited neutrophils and G-MDSC which then excluded T cells and possibly directly led to resistance due to the expression of various other inhibitory ligands [195]. Furthermore, patients who developed high IL-8 levels after commencing immunotherapy showed a poor clinical outcome indicating that immunotherapy in some patients itself could cause an inflammatory compensatory response, possibly due to necrosis and acute inflammation caused by tumor cell death which is naturally suppressive [196]. This has led to an interest in combining IL-8/CXCR2 inhibitors with the ICIs to negate such myeloid cell-mediated resistance. Related to this is the issue of antigens and priming. Chronic inflammation can lead, paradoxically, to a poor functioning of dendritic cells [197]. If dendritic cells are unable to present tumor antigens effectively to the T cells, then there is nothing for the checkpoint inhibitors to act on. This is why treatments such as radiotherapy or oncolytic viruses which cause immunogenic cell death and dendritic cell activation are being put together with checkpoint inhibitors to create an initial T cell response which the checkpoint inhibitors can sustain [198]. However, if the TME is high in suppressive cytokines then these approaches can fail. Thus, in a lung cancer model the radiation plus anti-PD-1 approach failed unless TGF-β blockade took place, since TGF-β was precluding the post radiation immune priming from taking place [199].

The conclusion is that the inflammatory immunosuppressive TME is the major block to the success of immunotherapy in many tumors. To overcome ICI resistance will probably require neutralizing the important TME factors: Treg depletion, blocking of MDSC recruitment, re-education of TAMs, and inhibition of troublesome cytokines (IL-8, IL-6, TGF-β). Clinically this is under investigation e.g. Pembrolizumab trials (anti-PD-1) + itacitinib (a JAK1 inhibitor which lowers IL-6/IL-8 signaling) in PD-1-refractory NSCLC or tremelimumab (CTLA-4) + CSF-1R inhibitor in pancreatic cancer to tackle TAMs [200, 201]. Early data of these combinations appear to produce responses in tumors which have historically not responded to ICIs and thus validate the theory that modulation of the inflammatory microenvironment can convert an ICI non-responder into a responder.

Chemotherapy resistance

Cytotoxic chemotherapy is still a cornerstone of treatment in many malignancies, but its effectiveness can be severely limited by the tumor microenvironment. Traditionally, it has been due to intrinsic factors of the tumor cells, such as drug efflux pumps, mutations in drug targets, enhanced DNA repair, etc.,that lead to the observed chemo resistance. However, it has become apparent that the tumor microenvironment provides sanctuary to tumor cells from chemotoxic assaults, provided by the inflammatory and suppressive elements that exist. One way this occurs, as previously explained in the macrophage section, is by way of "drug pumps" and metabolic processing provided by peripheral macrophages. For example, in gliomas, peripheral macrophages express high levels of CYP450 enzymes and ATP-binding cassette transporters such as P-glycoprotein, which can metabolize or export chemotherapeutic drugs (i.e., temozolomide or doxorubicin), thus tending to deplete the intra-tumoral concentration of these treatments [78]. Therefore, the more peripheral macrophage rich a tumor, the more rapidly it can deactivate chemotherapeutic drugs within its vicinity and thus protect the tumor cells that are nearby. Additionally, peripheral macrophages may sequester drug types such as antibody-based drugs, i.e., in chronic lymphocytic leukemia, similar nurse-type cells can sequester monoclonal antibodies from their target T- or B-cells, thus decreasing their availability to interact with the target cells [202]. Inflammatory processes can also lead to tumor cell quiescence or slow cycling, so that these are not as susceptible to chemotherapeutic modalities aimed at those that are cycling, such as conventional chemotherapy. In fact, inflammatory agents such as TNF-α and TGF-β can lead to a slow-cycling state which may even include cellular senescence in certain tumor fractions, rendering them capable of surviving chemotherapy and subsequently being able to regrow. Conversely, agents such as IL-6 will lead to STAT3 activation and the upregulation of pro-survival autophagic processes in the presence of chemotoxic stress [203]. In multiple myeloma, for example, IL-6 is known to protect myeloma from the effects of melphalan and steroids by way of activating STAT3 and the subsequent upregulation of anti-apoptotic proteins [204].

MDSCs and TAMs inhibit chemotherapy-induced immunity. One poorly understood feature of chemotherapy is that it can induce a host immune response against the tumor. However, when present in high amounts, MDSCs can take up the cellular debris and antigens, but they also can secrete IL-10, thereby inhibiting the ability for dendritic cells to cross-prime the T cells. The MDSCs

express PD-L1 which may interact with any activated T cells post-chemotherapy. Certain chemotherapeutic agents, for instance, 5-fluorouracil (5-FU), can kill selectively MDSCs at certain dosages, and correlate with a decrease in MDSCs and more events in T cell stimulation in murine tumors [205]. This demonstrates that MDSCs were a hindrance to the immune-mediated part of chemotherapy effectiveness. In patients, low spiking of MDSCs during chemotherapy treatment was correlated with improved results [206]. Inflammatory-related fibrosis and poor perfusion in tumors can directly inhibit chemotherapy [207]. The stroma driven by CAFs and TAMs may be sufficiently dense to physically compress the blood vessels, leading to a hypoperfused area. Areas of the tumor poorly perfused receive sub-lethal doses of drug, leading to survival and recovery of such cells. Furthermore, the hypoxic and acidic surroundings which may be due to lactic acid from tumor and stroma, may be so that several drugs have decreased effects [208]. HIF-1, the hypoxia-inducible factor, may stimulate expression of genes that boost survival in cancer cells when subjected to chemotherapy. For instance, it provides the glycolytic enzymes that make possible production of ATP, even for damaged mitochondria via chemotherapeutic means. Inflammatory cytokines may turn pathways on to acquire drug resistance in tumor [209]. IL-1β and IL-6 may cause activation of NF-κB and STAT3 which may lead to up-regulation of MDR1, and Bcl-2 family of genes related to anti-apoptosis. IL-8 may drive AKT and ERK in cancer cells, which would help these cells resist apoptosis mediated by chemotherapy drugs. TNF-α activates NRF2 which is an event that up-regulates the capability of cells to detoxify and increases antioxidant capabilities. Some chemoresistant tumors have high NF-κB and NRF2 signaling due to the TNF environment, and when TNF is blocked these tumors are more chemosensitive but only if TNF levels are low.

From a clinical point of view, markers of inflammation traditionally correlate with chemotherapy outcomes. For instance, in diffuse large B-cell lymphoma, elevated monocyte counts and elevated C-reactive protein predict diminished response to R-CHOP chemotherapy [210]. Similarly, in breast cancer, extensive infiltration of tumors by TAMs associates with residual tumor after neoadjuvant chemotherapy, especially in the triple-negative subtype [211]. In contrast, the depletion and re-polarization of TAMs may lead to restoration of chemosensitivity: Clodronate-mediated macrophage depletion improved the efficacy of the chemotherapeutic agent doxorubicin in breast cancer models [212]. A dramatic example of the pharmaceutical phenomenon of microenvironmentally mediated chemoprotection is pancreatic cancer. Pancreatic cancer cells almost uniformly resist the chemotherapeutic agent gemcitabine. Studies showed that pancreatic stellate cells (a type of CAF) absorb gemcitabine into the CFS and express an enzyme (cytidine-deaminase) which neutralizes its action, thus rendering a lower effective dose of the drug [213]. Moreover, TAMs in the pancreas express insulin-like growth factors (IGF) that activate survival pathways in pancreatic neoplastic cells in the presence of gemcitabine administration. When gemcitabine is used with an anti-fibrotic agent (a potential CCR-2-antagonist, which prevents macrophage recruitment) increased tumor regression was recognized in murine model studies, suggesting that removal of TAM support rendered tumor cells more susceptible to the drug.

Radiotherapy resistance

Radiation therapy (RT) destroys tumor cells primarily by inducing DNA damage, which indirectly leads to the generation of free radicals such as ROS. The effectiveness of RT is significantly modified by the TME, particularly hypoxia and immune context. An inflammatory, immune-suppressive TME allows tumor cells to be more highly resistant to radiation and to more readily survive radiation exposure. A major cause of radio resistance is hypoxia, which is very intimately associated with inflammation [214]. Under conditions of low oxygen tension X-rays create DNA damaging free radicals less effectively. Various solid tumors have hypoxic zones where radiosensitivity is significantly decreased. Chronic inflammation leads to disorganized vascularity and to anemia of chronic disease that contributes to hypoxia in tumors. Furthermore, hypoxia induces HIF-1α in tumor cells, leading to the expression of genes responsible for survival and repair of intracellular damage such as VEGF, glycolytic enzymes, and DNA repair enzymes. HIF-1 also upregulates PDK1 which shifts the metabolism of the cells to glycolysis making them less susceptible to mitochondrial ROS induced by radiation [215]. TGF-β released after radiation can protect the remaining cells of the tumor and makes the tumor bed more favorable for regrowth. TGF-β as indicated above increases the DNA damage response and can stimulate cell cycle arrest, allowing tumor cells to repair DNA breakage and continue to survive as well as not dying [216]. TGF-β also increases the late effects of radiation, which in ironic fashion may protect tumor clonogens from attack by the immune system. Preclinical studies in which the effect of blocking TGF-β during RT is carried out reveal a greater incidence of immune-mediated abscopal effects, supporting the notion that TGF-β restrains this occurrence [217].

Radiation can cause a local influx of myeloid cells as part of a wound-healing response to tissue damage. These cells arrive to clean up dead material and secrete factors including Arginase-1, TGF-β, IL-10, etc.

in response to the destroyed irradiated tumor, which in turn leads to suppression of any radiation-induced T-cell response [218]. In fact, in cancer patients after radiation there occurs a percentage increase in circulating MDSCs, that correlated with poor outcome in some studies. In a mouse tumor model, there was shown an increased spike in CCL2 production, which recruited monocytes, which differentiated into TAMs, which aided in the continued growth of the tumor [219]. Blocking of CCL2/CCR2 led to improved local control. Inflammation and DNA repair NF-κB, which has been induced by radiation causes the tumor cells to switch to a cell-survival mode [220]. If NF-κB is active in a chronic fashion, the tumor cells repair the radiation damage, and in some cases, apoptosis is more rapid. Thus, studies show that high levels of NF-κB at baseline, which in fact are present in much of the HPV-negative group of head and neck cancers, cause radioresistance, but the HPV-induced tumors, which show significantly less NF-κB activation, are radiosensitive [221].

An immunosuppressive TME blunts the ability to capitalize on the immunogenicity of RT. Radiation can create a tumor in a manner akin to that of an in-situ vaccine by the induction of tumor antigen and DAMP release. This will be quenched by the suppressive mechanisms so that the response that could be mounted toward making an anti-tumor immune response is lost. Trials in which radiation is given in combination with GM-CSF or with check-point blockade are efforts to cause a rebalancing of this situation. One interesting example: In a trial in metastatic breast cancer patients received radiotherapy with either a TGF-β blocking drug or not. Those who had TGF-β blockade had an abscopal tumor shrinkage out with the field of radiation and those who did not do this [222]. This suggests that the TGF-β from the irradiated tissue was inhibiting a systemic immune response and blockade caused the abscopal effects to happen. Further also, the STING induction by radiation can be tapped into if inhibited not by that TME. A number are seeking to associate STING agonists with radiation to upregulate this immune signaling pathway beyond that figured that TMEs can suppress it [223].

Resistance to targeted therapies and others

The emergence of resistance to conventional therapies means that alternative targeted therapies, such as tyrosine kinase inhibitors or hormones, represent the next major therapeutic approach. However, certain targeted therapies also have their problems with resistance. The right inflammatory milieu may be involved. Tyrosine Kinase Inhibitors are drugs designed for targeting oncogenic proteins. Tumors frequently develop mutations in the cells to avoid TKIs, but now we have learned that TME mediated resistance to TKIs is a new facet. For example, in EGFR mutant lung cancer, it was found that the HGF (hepatocyte growth factor) excreted by TAM could activate the parallel MET signaling in the tumor cells, whereby the desirable effect of the EGFR inhibitors was diminished [224]. The inflammatory cytokines may activate bypass pathways, e.g. IL-6 secreted by the fibroblasts in the stroma activates the JAK/STAT3 in the melanoma cells and makes them resistant to the BRAF inhibitors [225]. In fact, if the melanoma cells are treated with the BRAF-inhibitor but not killed, they start secreting large amounts of cytokines which in turn recruit the TAM, subsequently secrete growth factors that reactivate ERK signaling pathway, which is the pathway that BRAF inhibitors are trying to block. The combination of BRAF inhibitors plus anti-IL-1β or anti-CSF-1R inhibitors increase tumor control [226].

Resistance to targeted therapies, hormonal therapies, and immune therapies often arises from inflammation in the TME. Each of these therapies can lead to inflammatory responses. For example, VEGF inhibitors such as bevacizumab that are directed against the blood vessels of the tumor to normalize them and deprive the tumor cells of oxygen can paradoxically lead to compensatory inflammation [227]. This inflammation leads to recruitment of TAMs that release alternative angiogenic stimuli such as basic fibroblast growth factor (bFGF) or granulocytic-colony stimulating factor (G-CSF) leading to restoration of neovascularization and maintenance of an immunosuppressed state. Clinical trials are presently evaluating the potential for combinations of anti-VEGF agents with CXCR4 inhibitors to decrease TAM infiltration and enhance efficacy of therapy in ovarian cancer [228]. Hormonal resistance in hormone driven cancers is greatly influenced by inflammatory cytokine loops. In estrogen receptor breast cancers, cytokines such as TNF-α and IL-1β cause activation of NF-κB and AP-1 which increased aromatase in adipose tissue, thus increasing local estrogen production and decreasing the efficacy of tamoxifen or aromatase inhibitors [229]. Prostaglandin-rich TME can also cause changes in estrogen receptor co- regulators that can further lead to aromatic resistance of control over estrogen receptor signaling. In prostate cancer chronic inflammation caused by infection or metabolic stresses lead to increase in activation of STAT3 and NF-κB causing an increase in castration-resistant prostate cancer (CRPC) through IL-6 induced androgen receptor splice variant production and anti-apoptotic gene expression [230]. Even immune therapies such as CAR T cell therapies and bispecific T cell engager (BiTE) therapies have problems with efficacy in solid tumors due to Tregs, MDSCs, and former cytokines such as TGF-β that impair CAR T-cell destructive capacity. Newer designs of CARs have been developed that incorporate dominant-negative receptors for TGF-β

or secretion signals for IL-12 to reverse some of these problems. Similarly, oncolytic viruses and vaccines also depend on a permissive immune environment [231].

In every instance, a pattern emerges: when a therapy exerts pressure upon the tumor, then the inflammatory microenvironment allows for a protective response employed by the tumor that circumvents that pressure. This is a classical form of "adaptive resistance" engineering by the ecosystem of the tumor. This is why combination therapies are borne in increasing abundance in the next generation of treatment strategies, targeting both the cancer itself and the protective niche within which it resided. Table 1 below summarizes key components of the inflammatory microenvironment, their roles in immunosuppression and therapy resistance, and examples of therapeutic strategies targeting them:

Therapeutic strategies to reprogram the inflammatory microenvironment

In consideration of the pivotal role of inflammatory, immunosuppressive TME in mediating resistance to therapy, many different strategies are being devised to target these non-malignant components in conjunction with direct tumor-targeted therapies. The aim is to re-establish immune surveillance and improve efficacy of current treatments by converting a permissive microenvironment into a hostile one for the tumor. Below we highlight key approaches, many of which are already in clinical trials, categorized by the primary TME target being (Fig. 4).

Targeting immunosuppressive immune cells

The reduction of Tregs either in number or by function in tumors can lead to the unlocking of latent anti-tumor T-cell responses. One such method has been low-dose cyclophosphamide, a chemotherapeutic agent which depletes proliferating Tregs selectively, and which has been used in trials to enhance cancer vaccines and has shown enhanced immune responses in breast cancers [232]. Other specific methods include monoclonal antibodies. Anti-CD25 (IL-2Rα) antibodies such as daclizumab or engineered IgG1 (RG6292) can deplete Tregs via ADCC [233]. However, conventional anti-CD25 also inhibits IL-2 and thus places effector T-cells at risk. The new generation (such as RG6292) is engineered not to inhibit IL-2 signaling and thus allows IL-2 to be used for activation of effector cells while handling Tregs [234]. Another promising area is in antibody-cytokine fusion proteins which can selectively hit Tregs. For example, ATOR-1015 is a CTLA-4×OX40 bispecific, which aims to bind and stimulate OX40 on Tregs, simultaneously delivering a block of CTLA-4 which has led to preclinical depletion of intratumoral Tregs and activation of T-cells [235]. A linked bispecific, PD-L1 × 4-1BB (ATOR-1017) or PD-1×IL-2 which stimulate effector cells in tumor more than Tregs are also being studied [236]. There is also being developed a CD25-targeted toxin conjugate (ADCT-301, camidanlumab), which delivers a cytotoxin specifically to $CD25^+$ cells. This is under trial in solid tumors, and has shown some Treg elimination, and increase in CD8 T-cells [237].

As stated above, strategies to block MDSCs are being attempted with agents such as ATRA which has already shown benefit. In melanoma patients for example, the addition of ATRA to ipilimumab significantly reduced the presence of MDSCs and enhanced immune function [238]. The combination ATRA + pembrolizumab was evaluated in melanoma resulting in better response rates. Another strategy is that of blocking chemokine receptors. A CCR2 antagonist (PF-04136309) in addition to FOLFIRINOX chemo in pancreatic cancer led to improved tumor resection rates in an early phase clinical trial due to blocking the recruitment of monocyte/MDSCs and thus making the tumor more sensitive to chemo [239]. Similarly, drugs such as CXCR1/2 inhibitors (e.g., SX682, AZD5069) are in trials with anti-PD-1 again in melanoma and lung cancer to diminish neutrophil/MDSC infiltration [240]. Other drug approaches to MDSC suppression include phosphodiesterase-5 enzyme inhibitors (e.g., tadalafil) which reduce Arg1 and iNOS in MDSCs [241]. In a trial in head and neck cancer tadalafil was shown to reduce circulating MDSCs and improve T cell responses [242]. When combined with a cancer vaccine, better immune activation occurred. NLRP3 inflammasome inhibitors such as canakinumab indirectly or small molecule inhibitors directed against NLRP3 directly could decrease IL-1β levels and thereby reduce MDSC generation [243]. Combinations of ICIs with some of these are planned with the interest of the CANTOS results, such as canakinumab improved lung cancer outcome across the board [244]. Other MDSC checkpoints are also targets, such as the fact that MDSCs express PD-L1, and were found to have S100A9 and IL-4R. The "blocking of MDSC checkpoints" tries to use strategies directed at blocking signals used by MDSCs such as S100A8/A9-TLR4 or IL-4Rα-STAT6. In preclinical studies blocking these signals made MDSCs much less immunosuppressive.

The depletion or repolarization of TAMs via various methods is the focus of several approaches. CSF-1R inhibitors have been demonstrated to facilitate reduction of numbers of these cells while polarizing ones left to an M1 type. Pexidartinib was quite efficacious in cases of pigmented villonodular synovitis where it was approved [245]. However, CSF-1R inhibitors alone have not shown adequate reduction of tumors, however in combination with other therapies have shown better promise. For instance, cabiralizumab + nivolumab in cancer showed a low but significant response rate had at least a partial

Table 1 Key immunosuppressive components of the TME and targeted therapeutic strategies

Component	Role in Immunosuppression	Resistance	Targeting Strategies	Reference
Regulatory T cells (Tregs)	Suppress T cell and NK cell function via IL-10, TGF-β, IL-35. consume IL-2. Express CTLA-4 to disable APCs. Recruit via CCR4/CCR5 chemokines;	High Treg signature Correlate with poor ICI response.	*Anti-CTLA-4* (depletes some Tregs via ADCC). *Anti-CD25* (IL-2Rα) to deplete Tregs (e.g., RG6292). *CCR4 antagonists* (e.g., mogamulizumab) to block Treg recruitment. *OX40 or GITR agonists* to inhibit Treg suppression and enhance Teffs.	[16–20, 23–32, 34]
Regulatory γδ T Cells	IL-17/IL-6–producing regulatory phenotype driven by inflammatory cytokines; reduced cytotoxicity; promotion of Tregs, MDSCs, and M2-like macrophages	Chronic inflammation-mediated T-cell exhaustion and impaired Th1 responses; association with poor prognosis	*IL-6/IL-6R blockade; JAK/STAT3 inhibition; modulation of γδT17 differentiation; immune checkpoint targeting*	[36–45]
Myeloid-Derived Suppressor Cells (MDSCs)	Inhibit T cells via Arg1, iNOS. Secrete IL-10, TGF-β. Express PD-L1 and Gal-9. Recruit via CCL2, CXCL5, etc. promote tumor angiogenesis and metastasis.	High MDSCs correlate with poor immunotherapy outcomes.	*ATRA* differentiates MDSCs into mature cells. *CXCR2 inhibitors* (block PMN-MDSC recruitment by IL-8/CXCL1). *CCR2 inhibitors* (block M-MDSC recruitment). *Phosphodiesterase-5 inhibitors* (sildenafil) reduce MDSC suppressive function. *IDO inhibitors* prevent tryptophan depletion. *NLRP3 inflammasome inhibitors* reduce IL-1β-driven MDSC expansion.	[54–56, 58, 62–64, 66–68]
Tumor-Associated Macrophages (TAMs) (M2-polarized)	Produce IL-10, TGF-β. Express PD-L1, B7-H4. Release IL-6, TNF-α, VEGF activating STAT3/NF-κB in tumor cells for survival and angiogenesis. Scavenge drugs (CYP450, P-gp). Promote EMT and metastasis via MMPs and TGF-β;	Mediate resistance to chemo and to anti-angiogenics.	*CSF-1R inhibitors* (e.g., pexidartinib, cabiralizumab) deplete TAMs or reprogram to M1. *CCR2 or CXCR4 inhibitors* stop monocyte recruitment. *TLR agonists* re-educate TAMs toward immunostimulatory phenotype. *CD40 agonist antibodies* activate macrophages to kill tumor cells. *STAT3/STAT6 inhibitors* push macrophages away from M2 state. *Trabectedin*, a chemotherapeutic that selectively kills TAMs. *Adenosine A2A receptor blockers*, prevent TAM-generated adenosine from suppressing T/NK cells.	[73, 74, 76–79, 83–86, 88]
Tumor-Associated Neutrophils (TANs)	CXCR2-dependent recruitment and TGF-β–driven N2 polarization; suppression of T cells via Arg1-mediated arginine depletion, ROS/NO, IL-10, TGF-β, and PD-L1	Metabolic and oxidative T-cell dysfunction; promotion of angiogenesis; resistance to PD-1 blockade	*CXCR2 antagonists; TGF-β inhibition; Arg1 or ROS/NO targeting; combination with immune checkpoint inhibitors*	[91–94]
Mast Cells and Eosinophils	Release histamine, proteases, prostaglandins, and type-2 cytokines. Polarized by IL-33/IL-4/TSLP to regulatory phenotypes that suppress CTL/NK activity and expand Tregs.	Create Th2-skewed, fibrotic, immunosuppressive niches leading to immune evasion and checkpoint resistance.	Anti-IL-5 (mepolizumab), IL-4Rα blockade (dupilumab), anti-IL-13, histamine or COX-2/EP4 inhibitors, CXCR2 antagonists.	[95–99]
Tumor Endothelial Cells (TECs)	Induce immune exclusion via abnormal vasculature and endothelial anergy; reduced adhesion molecules; recruitment of Tregs, MDSCs, and TAMs; endothelial checkpoints (PD-L1/PD-L2, FasL) and adenosine production (CD39/CD73)	Impaired $CD8^+$ T-cell infiltration and function; resistance to immunotherapy due to vascular and metabolic barriers	*Anti-angiogenic and vascular normalization strategies; CXCL12–CXCR4 blockade; endothelial checkpoint targeting; adenosine pathway inhibition*	[102–105]

Table 1 (continued)

Component	Role in Immunosuppression	Resistance	Targeting Strategies	Reference
Cancer-Associated Fibroblasts (CAFs)	Secrete CXCL12, CCL2, etc., creating chemokine gradients that exclude CTLs. Express FasL to induce T cell apoptosis;	Produce TGF-β, promoting immune exclusion and Radioresistance; Build dense ECM causing high pressure and poor drug delivery.	*TGF-β pathway inhibitors* (e.g., fresolimumab antibody, galunisertib TGF-βRI inhibitor) reduce CAF activation and immune exclusion. *CXCL12/CXCR4 inhibitors* (plerixafor, NOX-A12) allow T cell infiltration in stroma-rich tumors. *Enzymatic ECM modifiers* (PEGPH20 hyaluronidase) decompress stroma to enhance chemo and T-cell entry. *FAK inhibitors* can disrupt fibrosis and reduce CAF-mediated immunosuppression. *Vitamin D analogs* shown to induce a more quiescent state in CAFs.	[107–114, 116–118]
IL-6/STAT3 signaling	IL-6 from TAMs/CAFs/tumor activates STAT3 in tumor and immune cells upregulate survival genes, EMT regulators, VEGF. Induces immunosuppressive factors;	High IL-6 linked to chemo and endocrine therapy resistance and poor ICI response.	*Anti-IL-6 antibodies* (siltuximab) or *IL-6R blockers* (tocilizumab) being combined with ICIs to enhance T cell activity. *JAK inhibitors* (e.g., ruxolitinib, itacitinib) reduce STAT3 activation in tumor and myeloid cells (trials in combo with checkpoint inhibitors). *Direct STAT3 inhibitors* (napabucasin, AZD9150) in trials to overcome immunotherapy and chemo resistance. *STAT3 decoy oligonucleotides* experimental approach to block STAT3 DNA binding.	[120, 121, 125–127, 129, 131–137]
TNF-α/NF-κB pathway	Chronic TNF in TME activates NF-κB in tumor cells and macrophages: Induces anti-apoptotic proteins, drives inflammation and upregulates checkpoints indirectly;	NF-κB in immune cells can cause tolerance. High TNF is associated with cachexia and ICI resistance.	*Anti-TNF-α therapy* (infliximab, etanercept) is being tested to prevent ICI-induced or tumor-induced immune suppression. *IKK/NF-κB inhibitors* can sensitize tumors to chemo/apoptosis. *Thalidomide/lenalidomide* reduces TNF-α and IL-6. XIAP inhibitors in trials to boost chemo.	[60, 139–149]
TGF-β (immunosuppressive cytokine)	Prevents T cell and NK cell cytotoxicity, promotes Tregs and M2 TAMs. Induces fibrosis via CAF activation. causes EMT and DNA repair in tumor.	High TGF-β signature correlated with T cell exclusion and ICI failure;	*TGF-β neutralizing mAb* (fresolimumab) showed improved survival with radiotherapy. *Small molecule TGF-βRI kinase inhibitors* (galunisertib, vactosertib) in trials with chemo and ICIs. *Bifunctional inhibitors* aimed to tackle immune exclusion. *Integrin avβ3/β5 inhibitors* indirectly reduce TGF-β activation. *SHIP1 activators* macrophage response away from TGF-β production.	[88, 152–159, 161–163]
Prostaglandin E2 (PGE2)/COX-2	PGE2 from tumors and myeloid cells skew TAMs to M2 and expands MDSCs. Suppresses T cells and NK via EP2/EP4 receptors. Increases tumor PD-L1 expression. Promotes angiogenesis and metastasis.	COX-2/PGE2 pathway is upregulated by NF-κB and is key in inflammation-driven cancer progression.	*NSAIDs (aspirin, celecoxib)* inhibit COX-2/PGE2. epidemiologically reduce cancer incidence and being repurposed as adjuncts. *Selective EP4 antagonists* (e.g., EP4 inhibitor grapiprant) block PGE2 signaling on immune cells. *Dual EP2/EP4 inhibitors*; *mPGES-1 inhibitors* prevent PGE2 synthesis downstream of COX-2. Combined with ICIs to relieve PGE2-mediated immunosuppression.	[60, 165, 171–177]
Adenosine (ADO) pathway	CD39/CD73 on Tregs, TAMs convert ATP to adenosine. ADO binds A2A receptors on T cells/NK, raising cAMP and broadly inhibiting their function. ADO stimulates TAMs to produce more IL-10.	High adenosine signature correlated with poor immunotherapy response.	*CD73 inhibitors* (oleclumab, CPI-006) prevent adenosine generation. *A2A receptor antagonists* (ciforadenant, etrumadenant) lift adenosine-mediated T/NK cell suppression. *CD39 inhibitors* in preclinical development. Targeting hypoxia can reduce extracellular ATP breakdown to ADO.	[178, 179, 182, 184, 271]

response in a phase I trial [246]. This is relatively good in a genetically PD-1 resistant type of cancer where typically PD-1 alone, indicating some modicum of immune modulation in this cold tumor type. TLR agonists are also able to polarize or induce TAMs to become more M1. Hence a TLR9 agonist would activate TAM's and resident DCs to an M1 inflammatory state, thus modifying the characteristics of the TME to favor support of T cells. Trials with TLR9 agonist + anti-PD-1 have shown melanoma improved response rates versus historical controls [247]. CD40 agonists have also been used systemically in cancer purposely to stimulate macrophages and dendritic cells. One CD40 agonist, APX005M plus chemotherapy in pancreatic cancer has exhibited marked major

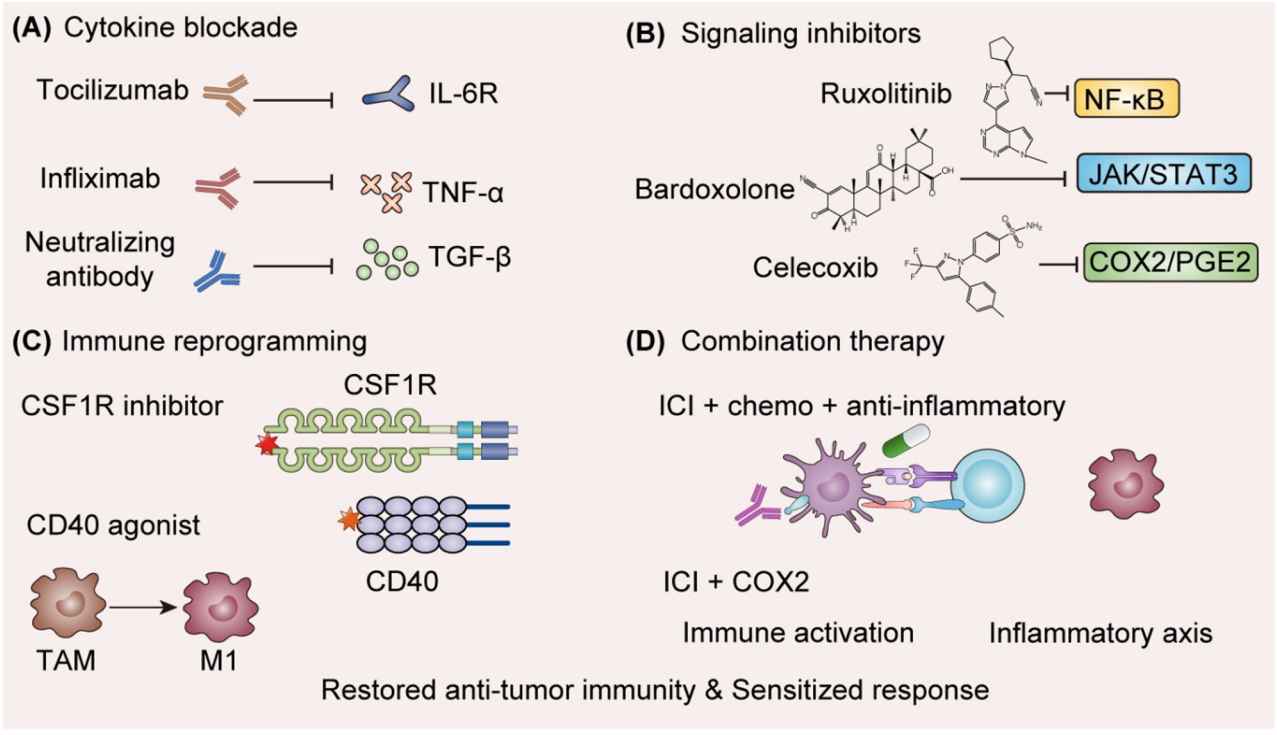

Fig. 4 Overview of therapeutic strategies targeting inflammation-driven immunosuppression. **A** Cytokine blockade: IL-6R, TNF-α inhibitors, and TGF-β neutralization. **B** Signaling inhibitors: JAK/STAT3, NF-κB, and COX2/PGE2 axis blockade. **C** Reprogramming immune cells: CSF1R inhibitors and CD40 agonists to convert TAMs into pro-inflammatory phenotypes. **D** Combinatorial approaches: Integration of anti-inflammatory therapy with immune checkpoint inhibitors, chemotherapy, or CAR-T to overcome resistance and restore anti-tumor immunity

pathologic response in a Phase I trial, presumably due to priming of macrophages and DCs, bringing upon a more favorable antigen presentation of T cell response [248].

Novel modalities also such as STING agonists are relevant [249]. STING agonists turn the tumor "cold" to "hot" by provoking acute inflammation - if we can keep that localized to the tumor and not produce systemic inflammation, that would be very useful. TREX1, a cytosolic DNA exonuclease, has been the focus of many new approaches in addition to direct STING agonists. As previously discussed, inhibiting TREX1 allows for more accumulation of cytosolic DNA, leading to the subsequent activation of cGAS-STING signaling, resulting in a potent induction of type I IFN responses [250]. When appropriately controlled, this transient inflammatory signaling supports dendritic cell activation and antitumor T-cell responses; however, sustained or uncontrolled activation of the same pathways may induce counter-regulatory mechanisms, including immune exhaustion or recruitment of suppressive myeloid populations. Many of the studies to date have shown that blocking TREX1 along with radiation therapy or a DNA-damaging agent can effectively enhance STING-mediated antitumor immune response through synergism [251]. Some inflammatory cell types not as commonly targeted are neutrophils, and TANs but rather indirectly through the blockade of CXCR2 or the use of recombinant IL-15/IL-21 to skew neutrophils to a more anti-tumor phenotype.

Targeting cytokines and inflammatory pathways

Cytokines were investigated as relevant therapeutic targets it is thought that their important role in the progression of tumors under inflammatory conditions as well as the development of tolerance to therapies would suggest their targeting to reverse these syndromes. Antibody or receptor neutralizing agents directed against these cytokines were approved for treatment of inflammatory diseases and are now being investigated in their anti-cancer effects. Nevertheless, due to the physiological action of these mediators in immunoregulatory processes the therapy was associated with considerable systemic toxicity. With respect to IL-6 a phase trial is ongoing in melanoma with the IL-6 receptor antibody tocilizumab and the chemotherapy drug atezolizumab, based on preclinical evidence indicating that neutralization of IL-6 may induce a decrease in the side effects of checkpoint-related therapy as well as the increase of anti-tumor efficacy of existing therapies [252]. At the same time a neutralizing antibody against IL-1 (canakinumab) is now being used in patients with lung cancer in combination with chemotherapy and pembrolizumab because of the cachexia induced by IL-1

and its immune suppressive effect [244]. The TICIMEL trial is in progress using the anti-TNF- alpha agent infliximab in conjunction with ipilimumab for melanoma with the hope to increase the efficacy of treatment by decreasing Treg-mediated resistance [253]. Interestingly anecdotal observations show that patients who were progressing on ipilimumab who subsequently received infliximab were shown to get stable disease probably because of the elevated levels of TNF produced. Targeting TGF- ß is still a difficult exercise, although fresolimumab in relationship to stereotactic radiotherapy has been shown to have reasonable safety in patients with metastatic breast cancer, but the trial of bintrafusp alfa versus pembrolizumab in patients with lung cancer was stopped prematurely because of poor effectiveness of treatment which indicated the absolute necessity of better biomarker studies and patient selection [254]. Furthermore, attempts to inhibit the IL-8/CXCR-2 axis such as the use of SX-682 in trials with pembrolizumab in melanoma (NCT03400332) and pancreatic cancer is being designed to inhibit the recruitment of MDSC cells and to assist T-cell infiltration [255]. Other possibilities included the use of an IL-8 antibody produced by BMS, which is presently being used in early phase trials together with nivolumab, where the dynamic changes in the frequency of MDSC cells and T-cell activity is being monitored.

Recently, there has been increased attention towards the use of cytokine-based approaches to help convert "cold" tumors into "hot" (immunologically activated) tumors. Several cytokines including IL-2 and IL-15 may be important for inducing cytotoxic T lymphocyte and NK cell expansion, survival and function within the TME. However, there have been limitations associated with the systemic use of IL-2 with regards to its potential for causing serious toxicities, namely, vascular leak syndrome. More recently, there has been encouraging preclinical data with IL-15 based approaches. IL-15 maintains memory $CD8^+$ T cells and NK cells without causing preferential expansion of Tregs, unlike IL-2 [256]. Renewed enthusiasm has been generated around the use of the IL-15 superagonists which demonstrate improved biological stability and potency compared to IL-15. Preclinical and early clinical studies have shown that IL-15 superagonists are able to restore antitumor immune responses and work synergistically with immune checkpoint blockade to convert previously poorly infiltrated tumors into inflamed, immune responsive lesions [257]. Emerging data from clinical trials indicate that IL-15 superagonist strategies have the potential to overcome primary resistance to immunotherapy [258]. To reduce systemic toxicity, various novel delivery methods have been developed that enable targeted delivery of IL-2 and IL-15 to the site of the tumor. This includes the use of immunocytokines, which are antibody-cytokine fusion proteins that conjugate IL-2 or IL-15 to a tumor associated antigen-specific antibody, thereby delivering increased amounts of cytokine activity at the site of the TME [259, 260]. This localized delivery of cytokine improves immune activation and limits the potential for off-target inflammatory side effects and represents a rational, and increasingly validated, approach to reprogramming the TME.

Small-molecule inhibitors, anti-angiogenic combinations, and viral immunotherapies are vital strategies to reprogram the TME and to overcome the immune resistance that tumors offer. Small-molecule inhibitors attack intracellular networks of signal transduction, such as JAK and NF-κB. JAK inhibitors (e.g., ruxolitinib and baricitinib) can affect multiple cytokine pathways, such as IL-6 and IFN-γ, and their use in conjunction with immune checkpoint inhibitors is being explored in malignant lymphomas and in selected solid tumors [261]. It has been deemed necessary for the use of JAK inhibitors to be limited and transient, as their effect on T-cells, if maintained too long, may hamper their function. A similar problem paralyzes the use of IKKβ inhibitors, which inhibit NF-κB, an intracellular signaling anomaly, whose use is paralyzed for practical purposes by situations of systemic toxicity [262]. Some suppression of NF-κB is gained using dexamethasone, a palliative drug that requires a careful adjustment of dosage, to reach a balance between not compromising the new immunotherapy by immuno-suppressive doses, obtaining adequate palliation from a palliative drug. On the field of metabolic and angiogenic targets we may see that there is now much more potential. The use of adenosine A2A receptor antagonists (ciforadenant) together with PD-1 blockade has been found to open a new area of improved responses to renal cell carcinoma [263]. The use of arginase inhibitors (INCB1158) and IDO inhibitors in trials is being pursued to restore the sort of metabolics that enable T-cell activation [264]. Combinations of anti-angiogenic and immune drugs are to be seen in the use of bevacizumab plus atezolizumab in hepatoma [265]. Here, the malignant veins are normalized, and VEGF-induced immunosuppression is restricted, allowing T-cell infiltration to be established. The use of oncolytic viruses and cancer vaccines is being tried to modify the TME sensu stricto, for inflammatory purposes. The oncolytic virus, HSV, T-VEC, induces responses that are pro-inflammatory in melanoma [266]. Enhanced, again with combination therapy with anti-CTLA-4. Novel engineered viruses are in trial armed with IL-12 or IL-15, for reinforcing local immune activation. Multi-modal immune therapy is now in evidence, e.g., triple combinations of anti-PD-1, anti-CTLA-4, with the metabolic or angiogenic modifiers. This holistic approach to TME reprogramming tries to encompass immune, the stromal and the neoplasmatic compartments together.

The growing insight into the TME has given rise to adaptive and platform-based clinical trials that customize the treatment to individual TME profiles. The targeted treatments are based not on a uniform treatment plan but directed by the principal immunologic features of the tumor. Diagnostic techniques, including multiplex gene expression panels and molecular imaging of TAMs using radiolabeled CSF-1R PET tracers, are used to find actionable signatures, and produce optimum therapeutic combinations. The early success stories of clinical trials have proved the rationale for the TME targeted strategies. In Hodgkin's lymphoma, checkpoint blockade is especially effective due to PD-L1 gene amplification and the amenability of Reed–Sternberg cells to depletion of TAMs by CSF-1R inhibitors [267]. In the case of melanoma, the combination of the LAG-3 antibody relatlimab with nivolumab was recently shown to increase progression-free survival, this shows that blocking the pathways of TME-induced exhaustion could revitalize T-cell responses [268]. Other three-way combinations (PD-1 + CTLA-4 + A2A blockade) are being tried [269]. In the case of the microsatellite-stable (MSS) colorectal cancer which has been traditionally ICI resistant, regimens are appearing, corresponding to MEK inhibitors, CD40 agonists, radiation therapy and PD-L1 blockade, which are producing an early immune boost [270].

Clinical and translational perspectives

Resistance to therapy and immune evasion in cancer is not simply a matter of tumor intrinsic characteristics. The inflammatory microenvironment of tumors also has a profound effect on these phenomena. Tumors in a state of chronic inflammation create an immunosuppressive microenvironment, characterized by Tregs, MDSCs, TAMs, IL-6, IL-10 and TGF-β that protect the cancer from the immune system and conventional therapies. As we have reviewed, these elements also engage in crosstalk leading to activation of the survival pathways in tumor cells and induction of metastasis and EMT, as well as altering cytolytic functions of T-cells and NK cells. This has the effect of reducing the efficacy of not only immunotherapy, but also chemotherapy, radiotherapy and targeted therapies.

To overcome these problems, new paradigms in combination therapy are being developed that target both the tumor and the TME. There is now a realization that control of cancer in a durable manner will frequently require reprogramming of the tumor microenvironment from a tolerogenic resistant phenotype to an immunogenic and therapeutic sensitive one. Therapeutics which can be used include depletion/inhibition of immunosuppressive cell subtypes, neutralization of immunosuppressive cytokines, blockade of metabolic immune checkpoints, normalization of abnormal stroma. Importantly, some of these approaches have progressed to clinical trials and shown proof of principle: anti-CTLA-4 and anti PD-1 combinations have successfully released T cells and improved outcomes with PD-1 plus anti-VEGF in a number of different cancers. Additionally, early results with the addition of such combinations of regimens with agents to inhibit MDSCs to CD40 agonists to stimulate TAMs/DCs, can convert non-responders to responders. Collectively these suggest that targeting the tumor microenvironment mediated mechanisms of resistance can greatly enhance therapeutic efficacy.

An important challenge in the future will be to tailor therapy according to the immunosuppressive mechanisms in each patient's tumor. Reliable biomarkers will be critically important to select the appropriate combination for the appropriate patient. In addition, the scheduling and dosing of combinations must be optimized to avoid unnecessary toxicity, since many of the TME-targeted agents possess systemic effects. The good news is that several clinical trials are currently underway, which will systematically examine these variables.

Conclusions

Increased levels of inflammatory cells in tumors create an environment that promotes tumor growth, while at the same time, reduces tumor responsiveness to treatment. Inflammatory cells create the potential for new types of therapies that will not target the tumor cells directly but rather will utilize additional targets that inflammatory signaling pathways create to destroy tumor cells. The research moving forward will be to identify how we can selectively disrupt the pro-tumor inflammatory signaling pathways while promoting or amplifying the anti-tumor immune response in that same environment. If we can neutralize the inappropriate inflammatory and immunosuppressive features of the tumor microenvironment, we can re-program the host's immune system to bring about long-term tumor control and increase the synergistic effects of cytotoxic, targeted, and immunotherapeutic drugs. This review describes that inflammatory signaling is not only a marker for tumor progression, but it is a dynamic and targetable regulator of tumor plasticity, immune exclusion, and treatment resistance; in essence, the future of cancer therapy will lie in combining immune modulators and tumor microenvironment therapies with currently utilized standard of care. Currently unresolved issues regarding the optimal timing and patient selection for inflammation-targeting therapeutic strategies and which biomarker(s) to monitor for precision therapy will be the primary focus of future research. The improvement of these factors will ultimately lead to the conversion of "cold" and resistant tumors to "hot" and treatable diseases. Therefore, the advancement of these various avenues of research will ultimately lead to

improved long-term clinical benefit for patients suffering from currently "untreatable" cancers due to impending treatment resistant biological responses.

Abbreviations

APC	Antigen–presenting cell
ATRA	All–trans retinoic acid
CAFs	Cancer–associated fibroblasts
CAR	T–Chimeric antigen receptor T cell (therapy)
CTLA	4–Cytotoxic T–lymphocyte–associated protein 4
CTL	Cytotoxic T lymphocyte ($CD8^+$ T cell)
DC	Dendritic cell
ECM	Extracellular matrix
EMT	Epithelial–mesenchymal transition
HIF	1α–Hypoxia–inducible factor–1 alpha
ICI	Immune checkpoint inhibitor
IDO	Indoleamine 2,3–dioxygenase
IFN	Interferon
IL	Interleukin
JAK	Janus kinase
LAG	3–Lymphocyte activation gene–3
MDSCs	Myeloid–derived suppressor cells
MDSC	Myeloid–derived suppressor cell (general term)
M	MDSC–Monocytic myeloid–derived suppressor cell
PMN	MDSC–Polymorphonuclear (granulocytic) myeloid–derived suppressor cell
NF	κB–Nuclear factor kappa–B
NK cell	Natural killer cell
NSAID	Nonsteroidal anti–inflammatory drug
PGE2	Prostaglandin E2
PD	1–Programmed cell death protein 1
PD	L1–Programmed death–ligand 1
RCT	Regulatory T cell (often written Treg)
STAT3	Signal transducer and activator of transcription 3
TAMs	Tumor–associated macrophages
TGF	β–Transforming growth factor beta
Th1/Th2	T helper type 1/type 2 (T cell subsets)
TILs	Tumor–infiltrating lymphocytes
TIM	3–T cell immunoglobulin and mucin–domain containing–3
TKI	Tyrosine kinase inhibitor
TME	Tumor microenvironment
TNF	α–Tumor necrosis factor alpha
Tregs	Regulatory T cells ($CD4^+CD25^+FoxP3^+$ cells)

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YZ, MB, LC, and HH contributed equally to this work. YZ and MB collected and analyzed the literature on inflammatory microenvironments and therapy resistance. LC and HH contributed to data interpretation and figure preparation. SH and XW assisted in summarizing recent advances in immunosuppressive mechanisms. PF and SH provided critical insights into therapeutic strategies targeting immune modulation. FC, JL, JW, and QW supervised the project and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability
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Declarations

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