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REVIEW

Immunologic tumor microenvironment modulators for turning cold tumors hot

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Abstract

Tumors can be classified into distinct immunophenotypes based on the presence and arrangement of cytotoxic immune cells within the tumor microenvironment (TME). Hot tumors, characterized by heightened immune activity and responsiveness to immune checkpoint inhibitors (ICIs), stand in stark contrast

List of abbreviations: ACAT, acetyl-coA acetyltransferase; ACT, adoptive cell therapy; ADT, androgen deprivation therapy; AP2, adipocyte protein 2; APC, antigen-presenting cell; APM, antigen processing machinery; AT, adipose tissues; ATP, adenosine triphosphate; B2M, beta-2-microglobulin; BATF, basic leucine zipper transcriptional factor ATF-like; CAA, cancer-associated adipocyte; CAF, cancer-associated fibroblast; CAR, chimeric antigen receptor; cDC, conventional DC; COAD, colon adenocarcinoma; COX, cyclooxygenase; CRS, cytokine release syndrome; CRT, calreticulin; CSF, colony-stimulating factor; CTA, cancer/testis antigen; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C chemokine receptor; DAMP, danger associated molecular pattern; DC, dendritic cell; DLN, draining lymph node; ECM, extracellular matrix; FABP4, fatty acid-binding protein 4; FAP, fibroblast activation protein; FDA, food and drug administration; FGF2, fibroblast growth factor 2; FLT3L, Fms-like tyrosine kinase 3 ligand; FRβ, folate receptor beta; G-CSf, granulocyte-colony stimulating factor; GLUT, glucose-transporter; GM-CSF, granulocyte-macrophage-colony stimulating factor; HCC, hepatocellular carcinoma; HIF, hypoxia-inducible factor; HMGB, high mobility group box; HPV, human papillomavirus; HSC, hematopoietic stem cell; HSP, heat shock protein; ICB, immune checkpoint blockade; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; IDO, indoleamine 2, 3-dioxygenase; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; irAE, immune-related adverse event; IRF, interferon regulatory factor; ITH, intratumoral heterogeneity; JAK, Janus Kinase; LAT, L-type amino acid transporter; LDH, lactate dehydrogenase; LNP, lipid nanoparticle; LT, lymphotoxin; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; MerTK, Mer receptor tyrosine kinase; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; MMR, mismatch repair; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; NAD^+, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; NBR1, neighbor of BRCA1 gene 1; NF-κB, nuclear factor-kappa B; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OXPHOS, oxidation phosphorylation; PAMP, pathogen-associated molecular pattern; PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; pDC, plasmacytoid DC; PDGF, platelet-derived growth factor; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PRR, pattern recognition receptor; PRS, polygenic risk score; ROS, reactive oxygen species; SIRP, signal-regulatory protein; STAT, signal transducer and activator of transcription; STC, stanniocalcin; TAA, tumor-associated antigen; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; TAP, transporters associated with antigen processing; TCR, T cell receptor; TGF-β, transforming growth factor-beta; TH, T helper; TIL, tumor infiltrating lymphocyte; TIME, tumor immune microenvironment; TMB, tumor mutational burden; TME, tumor microenvironment; TNBC, triple negative breast cancer; TNF-α, tumor necrosis factor-alpha; Treg, T-regulatory cell; TRUCK, T cells redirected for universal cytokine-mediated killing; TSA, tumor-specific antigen; Tyro3, tyrosine-protein kinase receptor 3; VEGF, vascular endothelial growth factor.

to cold tumors, which lack immune infiltration and remain resistant to therapy. To overcome immune evasion mechanisms employed by tumor cells, novel immunologic modulators have emerged, particularly ICIs targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1/programmed death-ligand 1(PD-1/PD-L1). These agents disrupt inhibitory signals and reactivate the immune system, transforming cold tumors into hot ones and promoting effective antitumor responses. However, challenges persist, including primary resistance to immunotherapy, autoimmune side effects, and tumor response heterogeneity. Addressing these challenges requires innovative strategies, deeper mechanistic insights, and a combination of immune interventions to enhance the effectiveness of immunotherapies. In the landscape of cancer medicine, where immune cold tumors represent a formidable hurdle, understanding the TME and harnessing its potential to reprogram the immune response is paramount. This review sheds light on current advancements and future directions in the quest for more effective and safer cancer treatment strategies, offering hope for patients with immune-resistant tumors.

KEYWORDS
cold tumor, hot tumor, immunologic modulator, immunotherapy, therapeutic strategy, tumor microenvironment

1 | BACKGROUND

Tumors are intricate and heterogeneous tissue with abnormal invading and growing cells exhibiting various biological and genetic abnormalities [1]. In the past, the focus of early studies revolved around tumor cells themselves, aiming to explain drug resistance and poor prognosis in certain tumor types, often attributing these characteristics to gene mutations and activated signaling pathways [2]. Instead of concentrating solely on the tumor cells, recent research has shed light on the crucial role that the microenvironment surrounding these cells play. This cellular microenvironment's equilibrium is crucial for fostering normal cell proliferation, differentiation, maturation, and overall functionality, ensuring proper cell metabolism and activities [1]. The term tumor microenvironment (TME) specifically pertains to solid tumors, comprising tumor cells, growth factors, stromal cells, immunoinflammatory cells, and electrolytes. Together, these components dynamically remodel the extracellular matrix (ECM) during tumor progression. The complicated growth of malignant tumors, from their initial appearance to the formation of metastases, is due to the complicated interactions between tumor cells and the TME's components [3]. These interactions involve both reinforcing and antagonistic mechanisms. Depending on a sequence of adhesion molecules, receptors, and signals, such as matrix metalloproteinases (MMPs), cytoskeletal proteins, and receptor tyrosine kinase pathways, the tumor cells adapt to the TME, or the TME fosters the growth of tumor cells [1]. On the basis of how the cytotoxic immune cells are arranged and present in the TME, tumors can be divided into three main immunophenotypes: immune-inflamed, immune-excluded, and immune-desert [4] (Figure 1). Immune-inflamed tumors, often referred to as hot tumors, exhibit elevated T cell infiltration, heightened interferon-γ (IFN-γ) signaling, expression of programmed death-ligand 1 (PD-L1), and a high tumor mutational burden (TMB) [5]. Tumors displaying the immune-inflamed phenotype tend to demonstrate higher responsiveness to immune checkpoint inhibitors (ICIs) [6, 7].

Tumors falling into the immune-excluded and immune-desert categories are often referred to as cold tumors. In immune-excluded tumors, $CD8^+$ T lymphocytes are localized only at the invasion margins and fail to efficiently infiltrate the main tumor mass. Conversely, immune-desert tumors lack $CD8^+$ T lymphocytes both within the tumor and its surrounding periphery [8]. A low mutational load, low expression of major histocompatibility complex (MHC) class I, and low PD-L1 expression are some of the things that make these benign growths stand out. Additionally, they harbor immunosuppressive cell populations like tumor-associated macrophages (TAMs), T-regulatory cells (Tregs), and myeloid-derived

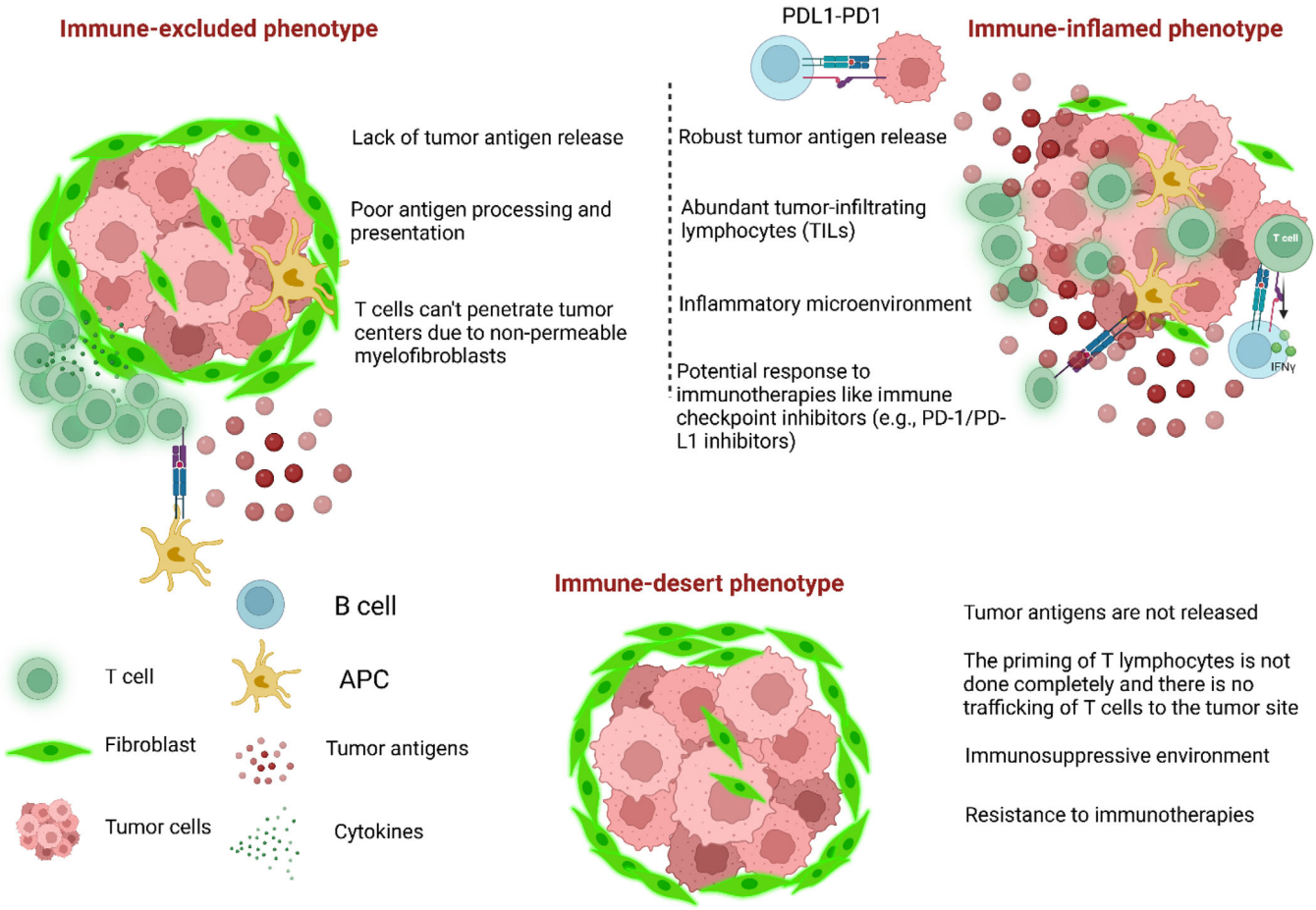

FIGURE 1 Tumor immunophenotypes. Illustration depicting the three-primary tumor immunophenotypes determined by the presence and distribution of cytotoxic immune cells within the TME. Immune-inflamed tumors, or hot tumors, characterized by abundant T cell infiltration, heightened IFN-γ signaling, PD-L1 expression, and a high TMB, often exhibit increased responsiveness to ICIs. In contrast, immune-excluded tumors display $CD8^+$ T lymphocytes mainly at the tumor invasion margins, while immune-desert tumors lack $CD8^+$ T lymphocytes both within the tumor core and its surrounding periphery. Abbreviations: APC, antigen-presenting cell; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

suppressor cells (MDSCs) [9]. These observations indicate that cold tumors may lack innate antitumor immunity, or the existing innate immune responses may be ineffective due to the exclusion of immune cells. In contrast to the immune-inflamed phenotype, cold tumors show limited responsiveness to ICIs [9]. Hot tumors exhibit various features that play a significant role in the regulation of antigen-specific responses. These features involve the expression of inhibitory signals, including the activation programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and other immune checkpoints [10]. Moreover, extracellular potassium has been implicated in the suppression of T cells within the TME [11]. These combined mechanisms contribute to the immune regulation observed in hot tumors [10]. The considerable heterogeneity in the tumor immune microenvironment (TIME) can be attributed, in part, to distinctive driver and passenger mutations present in cancer cells. These mutations contribute to the unique characteristics observed within the TIME [10]. Additionally, physical barriers, such as dense ECM [12] and tumor-associated vasculature, play a crucial role in shaping the TIME [13]. Alongside these physical factors, various cellular and humoral immunosuppressive components actively modulate the immune microenvironment of the tumor. Together, these factors act as key players influencing the complex and diverse landscape of the TME [10].

The purpose of this article is to provide a comprehensive exploration of the immunologic TME modulators, with a specific focus on transforming cold tumors into hot tumors. We want to shed light on the important role that TME plays in determining how well immunotherapy works and how certain immunologic interventions might be able to turn cold tumors that don't respond to treatment into hot tumors that do respond to treatment. By delving into the components and dynamics of the TME,

we will uncover the intricate interplay between tumor cells, immune cells, and various immunosuppressive factors that create an immunologically cold environment. Understanding the characteristics and challenges associated with cold tumors will provide valuable insights into the limitations of current immunotherapeutic approaches. Furthermore, this article will comprehensively discuss various immunologic modulators that have shown promise in altering the TME, including ICIs, adoptive T cell therapies, cancer vaccines, cytokines, and strategies targeting TAMs and MDSCs. In addition to looking at how these immunologic modulators work, we will also talk about the problems and restrictions that come with using immunotherapy to its fullest potential for cold tumors. These include tumors that are resistant to treatment, side effects, and differences in how the tumor responds to treatment. By taking a close look at how immunologic modulation is done now, we will show how important combination therapies and personalized approaches are as possible ways to deal with problems and make treatment work better. Moreover, we will explore promising novel immunologic modulators that are being developed, offering a glimpse into the future of immunotherapy for cold tumors.

By providing a comprehensive understanding of immunologic TME modulators and their potential for transforming cold tumors into hot ones, this article seeks to contribute to the ongoing efforts in advancing cancer immunotherapy and ultimately improving the clinical outcomes and quality of life for patients with previously refractory tumors.

2 | TME AND IMMUNE RESPONSE

Tumor advancement is heavily influenced by the interactions of non-tumor cells and secreted non-cellular elements surrounding the TME [14]. This intricate TME encompasses various cellular components, including cancer-associated fibroblasts (CAFs), pericytes, lymphocytes, adipocytes, neutrophils, Treg cells, mesenchymal stem cells (MSCs), mast cells, and other immune components, all of which play a pivotal role in mediating immunosuppression [14]. The architectural arrangement of these cells is fundamental in generating microenvironmental diversity, while the secreted non-cellular components significantly contribute to shaping tumor characteristics and responses to therapeutic drugs [14] (Figure 2).

The interaction between tumor cells and non-tumor cell components in the surrounding environment have a significant impact on the tumor phenotype rather than just the intrinsic characteristics of tumor cells. These components comprise a diverse array of factors, such as cytokines, growth factors, ligands, small RNAs, DNA, soluble factors, metabolites, and the solid-state ECM. Together, these elements create a supportive and favorable TME, facilitating the progression of the tumor [14].

ECM serves as a crucial context for cancer cells, offering both biochemical and biomechanical cues [14]. The ability of cancer cells to navigate through the ECM barrier, access the bloodstream, and form distant metastases is integral to cancer progression [15]. Substantial advancements have been made in understanding the molecular mechanisms that allow cancer cells to manipulate the immune components of the microenvironment, promoting tumor growth and metastasis [16]. In the following, we will focus on several crucial components of the TME, including CAFs, TAMs, tumor-associated neutrophils (TANs), cancer-associated adipocytes (CAAs), and the role of hypoxia, all of which play intricate roles in creating and sustaining a cold tumor. By dissecting the functions of these elements, we can gain valuable insights into the mechanisms behind cold tumor formation and, ultimately, work towards strategies to turn the tide against these resilient cancer environments.

2.1 | CAFs

Fibroblasts are the main type of cell in normal tissue stroma. They have a spindle-like shape and come from the mesenchymal lineage. Within the stroma, some fibroblasts remain quiescent or resting, not actively involved in ECM production or turnover [16]. However, these resting fibroblasts have the potential to become activated under certain conditions [17]. Activated fibroblasts, distinct from their resting counterparts, undergo changes in morphology and metabolism triggered by inflammatory responses like wound healing. Transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), platelet-derived growth factor (PDGF), hypoxia, communication between cancer cells and the surrounding microenvironment plays a vital role in this process, influencing tumor advancement and reactive oxygen species (ROS) can activate quiescent fibroblasts [16]. Once activated, fibroblasts contribute to tissue remodeling by synthesizing ECM components, releasing chemokines and cytokines, and generating tissue-level forces. Their roles include promoting epithelial cell differentiation, regulating immune responses, and maintaining tissue homeostasis [17, 18].

In the TME, activated fibroblasts become CAFs. CAFs play a crucial role in altering the ECM architecture, possibly arising from normal fibroblasts. Growth factors such as TGF-β, PDGF, and fibroblast growth factor 2 (FGF2) are released by tumor cells and immune cells, which makes

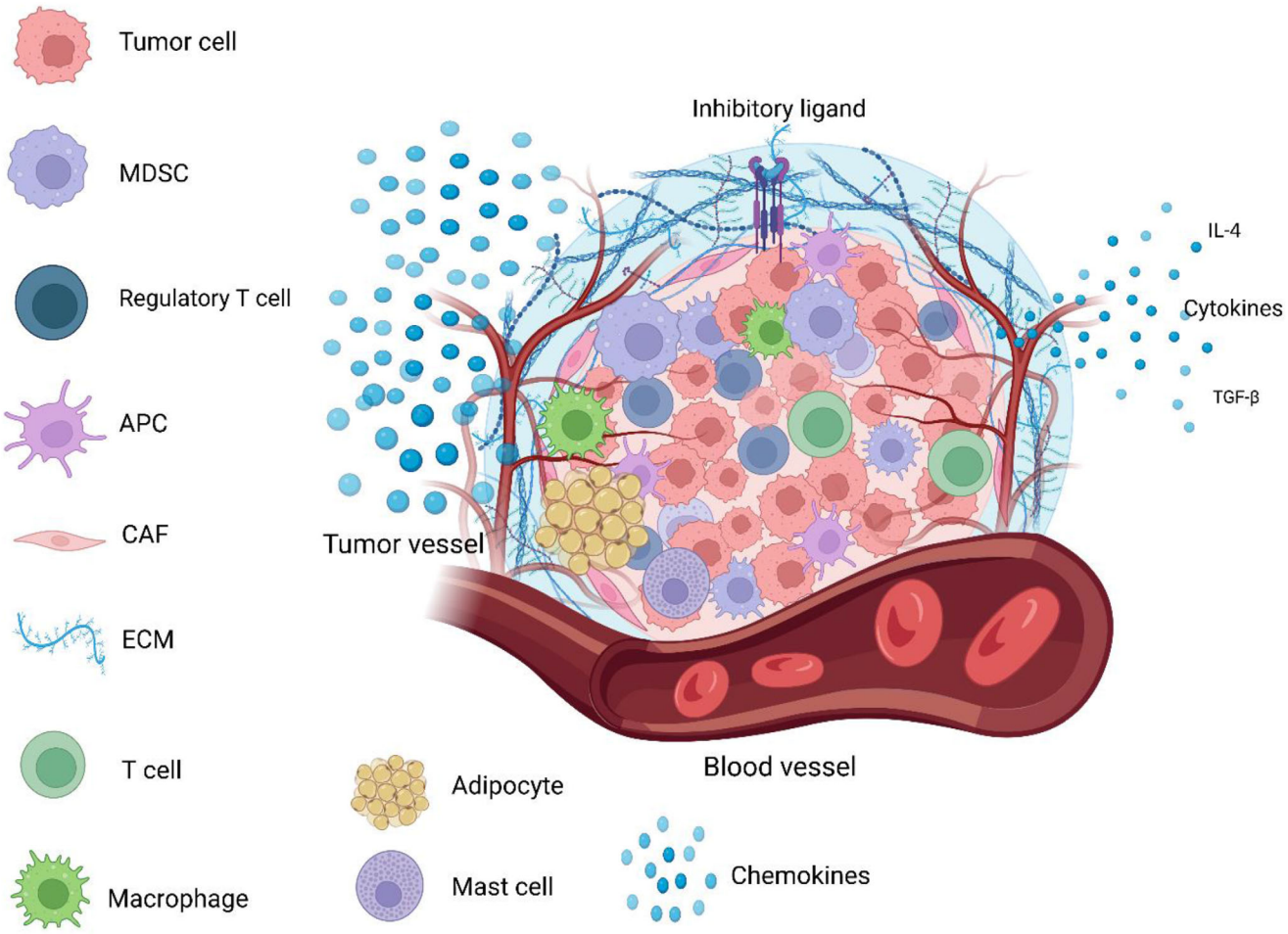

FIGURE 2 The complex TME and its impact on tumor behavior. Visual representation of the multifaceted TME composed of various cellular and non-cellular components. Within the TME, CAFs, pericytes, lymphocytes, adipocytes, neutrophils, Treg cells, mesenchymal stem cells, mast cells, and other immune elements interact and collectively influence tumor progression through mechanisms of immunosuppression. The ECM serves as a critical context for cancer cells, affecting their mobility, invasion, and metastatic potential. Abbreviations: CAF, cancer-associated fibroblast; ECM, extracellular matrix; IL-4, interleukin-4; MDSC, myeloid-derived suppressor cell; TGF-β, transforming growth factor-beta.

it easier for them to join the scene [18]. Once recruited, these CAFs can undergo proliferation and expansion, regulated by paracrine and autocrine mechanisms involving other CAF populations [16].

At tumor sites, the TME can produce an immunosuppressive milieu that is characterized by dense stroma and the presence of immunosuppressive cells and factors. This immunosuppressive environment often results in limited T cell priming and infiltration in cold tumors [19]. Among the potent immunosuppressive cytokines, TGF-β plays a crucial role in promoting immune escape and inhibiting the acquisition of the T helper 1 (TH1)-effector phenotype [19].

CAFs, abundant in the TME, are primary producers of TGF-β. Elevated TGF-β from CAFs is linked to T cell exclusion from tumors and poor response to atezolizumab, an ICIs [20]. TGF-β suppresses $CD4^+$ T lymphocyte proliferation by inhibiting interleukin-2 (IL-2) production and promotes the conversion of naïve $CD4^+$ T lymphocytes into Tregs [9, 21]. Also, TGF-β makes it harder for dendritic cells (DCs) to differentiate and present antigens, which stops T cells from being properly primed [9]. Overall, TGF-β significantly hinders antitumor immunity by influencing T cell differentiation and function, ultimately impeding T cell infiltration into tumors [22]. Understanding the role of TGF-β in the immunosuppressive TME is essential for developing strategies to overcome the challenges posed by cold tumors and improve the effectiveness of immunotherapies.

CAFs, crucial components of the tumor stroma, significantly promote tumor growth [23]. Predominantly located at tumor edges, CAFs regulate metastasis and angiogenesis by modulating the ECM and releasing cytokines [24, 25]. This leads to the transformation of tumor margins into

immune cold zones, where immune responses are suppressed and T cells are excluded [24, 26]. CAFs contribute to T cell exclusion and immunosuppression through ECM remodeling, acting as a physical barrier [9]. Additionally, CAF-secreted C-X-C motif chemokine ligand 12 (CXCL12) inhibits T-lymphocyte infiltration, as demonstrated in a pancreatic cancer model [25, 27]. Furthermore, CAFs produce immunosuppressive molecules like TGF-β and IL-6, dampening T cell responses [24].

2.2 | TAMs

Macrophages exhibit remarkable plasticity, influenced by their surroundings [28]. In response to infection or injury, macrophages release pro-inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and nitric oxide, initiating host defense and tissue remodeling [29]. Tissue remodeling involves a crucial switch between pro-inflammatory and anti-inflammatory macrophage sub-populations. Failure to regulate pro-inflammatory responses can lead to chronic inflammation or autoimmune diseases [29]. Besides their essential roles in innate immunity, macrophages contribute significantly to various developmental processes, including bone morphogenesis, neuronal patterning, angiogenesis, branching morphogenesis, and adipogenesis [16]. Remarkably, tumor cells exploit these functions in many cancers, co-opting macrophages to support their growth and progression. The versatility of macrophages and their diverse functions make them significant contributors to both immune responses and the development of various tissues, but their involvement in cancer highlights the intricate relationship between the immune system and tumor cells.

Macrophage polarization is a fundamental concept involving categorization based on distinct surface markers induced by specific environmental stimuli [30]. Traditionally, macrophages have been classified into two categories known as M1 and M2. However, recent understanding recognizes that macrophages exist on a continuum within various disease and tissue-specific contexts, where the M1 and M2 states represent the two extremes [16]. M1 macrophages, which are thought to be classically activated, make substances that cause inflammation which are important for protecting the host and also kill tumors [16]. In contrast, M2 macrophages, termed alternatively activated, secrete anti-inflammatory cytokines that predominantly suppress inflammatory responses [31]. This M2 population is associated with immune suppression within the TME, promoting tumor angiogenesis, facilitating ECM remodeling, and contributing to wound healing processes [31]. TAMs are sometimes referred to as M2-polarized macrophages, although it is important to note that even within this context, heterogeneous populations of TAMs can exist along the M1-M2 continuum [32]. The specific localization of TAMs within a tumor has been established as a significant indicator of their pro-tumor activity, with TAMs mainly found in perivascular regions or at the invasive front of the tumor [16]. Monocytes are recruited to the invasive front and undergo differentiation into macrophages in response to signals from tumor and stromal cells. Various cytokines (such as interleukin-4 [IL-4], interleukin-10 [IL-10], interleukin-13 [IL-13]), chemokines (including C-C motif chemokine ligand 2 [CCL2], CXCL12), and growth factors (like colony-stimulating factor-1 [CSF-1], TGF-β, vascular endothelial growth factor A [VEGF-A], PDGF, and angiopoietin-2) produced at the invasive margin play a crucial role in stimulating monocyte recruitment, differentiation, and survival [16, 33].

TAMs express various receptors, including members of the TAM receptor tyrosine kinase family, such as Tyrosine-protein kinase receptor 3 (Tyro3), Axl receptor tyrosine kinase, and Mer receptor tyrosine kinase (MerTK). These receptors play a crucial role in mediating the immunosuppressive effects of TAMs within the TME. Recent studies have highlighted the significance of the TAM receptor tyrosine kinase family in contributing to the pro-tumor activity of TAMs [34–36]. In addition, the interaction between the cytokine CSF-1 and its receptor (CSF-1R) helps myeloid cells change into an immune-suppressing M2 macrophage phenotype. Targeting TAMs with CSF-1R inhibitors has been shown to be an effective strategy for reducing the number of TAMs and, in turn, increasing the infiltration of effector lymphocytes, such as $CD8^+$ T cells [37]. By modulating the TAM population and their immunosuppressive activities, therapies that target TAMs hold promise as potential approaches to enhance the antitumor immune response and improve the effectiveness of immunotherapies in cancer treatment [9].

2.3 | TANs

The development and maturation of neutrophils represent a multifaceted process [38] primarily under the control of granulocyte-colony stimulating factor (G-CSF). Besides G-CSF, other factors like granulocyte-macrophage-colony stimulating factor (GM-CSF), IL-6, and KIT ligand (KITL) also play significant roles in facilitating neutrophil production [16]. In the context of cancer, tumor cells can release G-CSF, leading to an excessive generation of neutrophils, which, in turn, contributes to immunosuppressive responses during the early stages of tumorigenesis [16]. Maturing neutrophils form cytoplasmic granules containing antimicrobial proteins, including MMPs and

neutrophil elastase, implicated in ECM remodeling and facilitating tumor progression [39–41]. Neutrophils, similar to fibroblasts and macrophages, undergo polarization, leading to the designation of anti-tumor neutrophils as N1 and pro-tumor neutrophils as N2 [42]. When TGF-β levels are high, neutrophils become N2 polarized. This causes more C-X-C chemokine receptor type 4 (CXCR4), Vascular endothelial growth factor (VEGF), and Matrix metalloproteinase-9 (MMP9) to be expressed, which helps the tumor grow. Conversely, blocking TGF-β prompts N1 neutrophils to upregulate TNF-α and IFN-γ, inducing C-X-C motif chemokine ligand 2 (CXCL2), C-X-C motif chemokine ligand 5 (CXCL5), and Chemokine (C-C motif) ligand 3 (CCL3) production, further recruiting neutrophils to the tumor site [42]. Tumor-secreted factors, such as CXCL5, mediate neutrophil recruitment, as demonstrated in hepatocellular carcinoma models. This correlation between CXCL5 levels and neutrophil infiltration was confirmed in three independent clinical hepatocellular carcinoma (HCC) patient cohorts [43].

In conclusion, neutrophils play a crucial role in the formation of cold tumors, characterized by low immune cell infiltration and limited anti-tumor immune response. When factors like TGF-β cause neutrophils to change into the pro-tumor N2 phenotype, molecules like CXCR4, VEGF, and MMP9 are made. These molecules help the tumor grow by changing the TME. Inhibiting TGF-β and promoting the recruitment of anti-tumor N1 neutrophils, through factors like TNF-α and IFN-γ, may hold potential therapeutic strategies to reverse the immunosuppressive state of cold tumors and enhance anti-tumor immunity.

2.4 | CAAs

Adipocytes in adipose tissues (AT) store lipids and regulate energy storage and metabolism. They secrete adipokines, hormones, and molecules crucial for paracrine and endocrine functions in physiological processes, including obesity, AT fibrosis, inflammation, tumorigenesis, and cancer metabolism [16]. Adipocytes mainly derive from MSCs or undifferentiated adipocyte precursors, in the AT stroma [44]. A smaller fraction of adipocytes can also originate from hematopoietic stem cells (HSCs) [45, 46]. In cancers like breast, ovarian, prostate, renal, gastric, and colon cancers, adipocytes serve as crucial components of the TME [47]. Tumor cells can activate adipocytes, altering their programs to support tumor growth. These activated CAAs have distinct features compared to normal adipocytes [48]. In co-culture with cancer cells, adipocytes experience changes, including the downregulation of markers like adipocyte protein 2 (Ap2) and fatty acid-binding protein 4 (FABP4), upregulation of MMP11, and increased release of inflammation-promoting cytokines like IL-6 and IL-1β. The presence of IL-6-expressing CAAs has been confirmed in primary breast cancer samples [48]. There's a current discussion on how obesity-induced changes in the TME impact cancer progression [49]. Obesity promotes inflammation and fibrosis by activating hypoxia-induced transcriptional programs in adipocytes, leading to immune cell recruitment. Studies in mouse models of pancreatic ductal adenocarcinoma (PDAC) revealed that adipocyte-mediated inflammation contributes to a desmoplastic response, attracting TANs and enhancing tumor formation in obese animals [50]. Additionally, mammary AT in obese mice has larger myofibroblast populations than their lean counterparts [51]. These myofibroblasts contribute to ECM stiffness by synthesizing components, promoting collagen alignment, and unfolding fibronectin, fostering enhanced invasive behaviors in both malignant and pre-malignant human breast cancer cells [51].

CAAs drive myofibroblast activation, causing ECM remodeling and stiffness. This supports cold tumor progression, marked by low immune cell infiltration and a weakened anti-tumor response. Understanding this interplay offers insights for therapeutic strategies targeting ECM changes in tumor development.

2.5 | Tumor cells

Tumor cells are commonly characterized by their elevated glucose uptake and active glycolysis, even when oxygen is present, known as the Warburg effect [52]. This process leads to rapid glucose consumption and an increase in lactate abundance within the TME. The TME, which is low in glucose and high in lactate, puts metabolic stress on T cells that are infiltrating it. This makes the immune system weaker in the area and makes it resistant to ICIs [52]. Glucose deprivation in the TME contributes to T cell hyporeactivity by inhibiting mammalian target of rapamycin (mTOR) activation and reducing glycolytic capacity and IFN-γ production [53]. Furthermore, a negative correlation exists between glycolytic activity and T cell infiltration in various tumors [9, 54]. Notably, high expression of glucose-transporter 1 (GLUT-1) in renal cell carcinoma is associated with reduced infiltration of $CD8^+$ T cells [55]. These findings point to a correlation between glycolytic (Warburg) tumors and a noninflamed T cell phenotype. Interestingly, besides tumor cells, stromal cells like CAF and TAM can also contribute to lactate accumulation in the TME through the Reverse Warburg effect [54]. Inhibiting glucose metabolism and lactate production in both tumor and stromal cells, such as by targeting lactate dehydrogenase-A (LDH-A), may offer a promising strategy to promote T

cell infiltration [56]. Lactate accumulation and subsequent acidification of the TME play a suppressive role in antitumor immunity [57]. The lactate-induced acidosis hampers the differentiation of monocytes into DCs and inhibits the antigen-presenting function of DCs, leading to a subsequent inhibition of T cell activation [9]. Elevated lactate in the TME hinders lactate release from T cells, suppressing their proliferation and inhibiting the chemotaxis and antitumor activity of cytotoxic T lymphocytes (CTLs) [58]. Metabolic competition between tumors and immune cells also involves amino acids and fatty acids, impacting T cell receptor (TCR) aggregation and immune synapse formation through increased cholesterol esterification in tumors [52]. Targeting the cholesterol esterification key enzyme acetyl-CoA acetyltransferase1 (ACAT1) with the inhibitor avasimibe has been shown to promote the proliferation of $CD8^+$ T cells and exhibit potent antitumor effects [59]. Finally, it can be said that tumor cells help the cold-tumor phenotype develop by changing metabolism, building up lactate, and making the TME more acidic. These factors lead to immunosuppression, hindering T cell infiltration and antitumor immune responses, making cold tumors resistant to immunotherapy. To make immunotherapeutic approaches more effective in cold tumors, it might be helpful to target the tumor's metabolism and make the TME less hostile.

3 | HYPOXIA

In the process of tumor development and progression, cancer and stromal cells often face limited access to nutrients and oxygen. This scarcity arises due to aberrant vascularization and inadequate blood supply, leading to the presence of hypoxic regions within most solid tumors [60]. The response to hypoxia is primarily attributed to hypoxia-inducible factors (HIFs). It is important to note that HIF-dependent signaling helps both cancer cells and stromal cells adapt and choose based on their environment, which supports changes that help cancer grow [61]. The HIF family of transcription factors comprises HIF1, HIF2, and HIF3, each containing an oxygen-sensitive HIF-α subunit (HIF1-α, HIF2-α, or HIF3-α, respectively), which dimerizes with the constitutively expressed HIF1-β subunit. Furthermore, HIF activity triggers a shift in cell metabolism towards a glycolytic mode, leading to increased glucose consumption and the production of pyruvate, lactate, and H^+ ions [61] (Figure 3).

Hypoxia has been linked to the potentiation of immunosuppression through the activation of an immune-suppressive network. It induces chemokine CCL28 expression, promoting Treg recruitment, angiogenesis, and tumor tolerance, contributing to tumor immune evasion [62]. Further research is needed to clarify the direct role of hypoxia in regulating Treg functions. Hypoxia-induced Nanog, a stemness-associated transcription factor, plays a role in immune suppression [63]. Targeting Nanog reduced immunosuppressive cells and increased $CD8^+$ T effector cells in tumors, partially dependent on TGF-β1 production, suggesting a link between Nanog and TGF-β1 regulation [63]. Tumor-infiltrating myeloid cells like MDSCs and TAMs contribute to tumor-mediated immune escape under hypoxic conditions. HIF-1α influences their function and differentiation, with PD-L1 expression upregulated in hypoxic MDSCs and cancer cells, promoting T cell tolerance [62]. So, under hypoxic conditions, the activation of an immune suppressive network hinders T cell function and differentiation while promoting the recruitment of Tregs and MDSCs. Hypoxia-induced factors, such as Nanog and HIF-1α, also make immunosuppression worse by controlling the expression of immune checkpoint molecules, such as PD-L1. These processes work together to make an immune-hostile TME that stops T-cells from entering and weakens immune responses against tumors, which is typical of cold tumors.

4 | CHARACTERISTICS OF COLD TUMORS

Non-inflamed or cold tumors are characterized by low immune cell infiltration and a lack of sufficient immune response [64]. TME has innate anti-tumor features, which stem from genetic mutations that activate signaling pathways (Wnt-β-catenin, MAPK, JAK, STAT3, and NF-κB), involving the expression and secretion of cytokines and chemokines to inhibit T cell recruitment and activation [64]. What distinguishes cold tumors from hot tumors is the number and distribution pattern of $CD8^+$ T cells in TME (Figure 4). However, based on the literature, tumor infiltrating lymphocyte (TIL) levels and expression of B7-H1/PD-L1 can be combined to characterize tumors into: (A) high anti-tumor immune response, known as hot tumors with more infiltrating T cells and high levels of B7-H1/PD-L1 and (B) low anti-tumor immune response, known as cold tumors with almost no infiltrating T cells and low levels of B7-H1/PD-L1 [65].

Lack of immunostimulatory signals and tumor neoantigens are other phenotypes of cold tumors. Neoantigens are abnormal polypeptides, providing a more immunogenic response compared with tumor antigens. However, a lack of neoantigens may result in insufficient antigen-presenting cell (APC) activation and poor immunogenicity [66]. Activation of neoantigen-specific T cell responses requires cleaved peptide, which is presented by MHC class

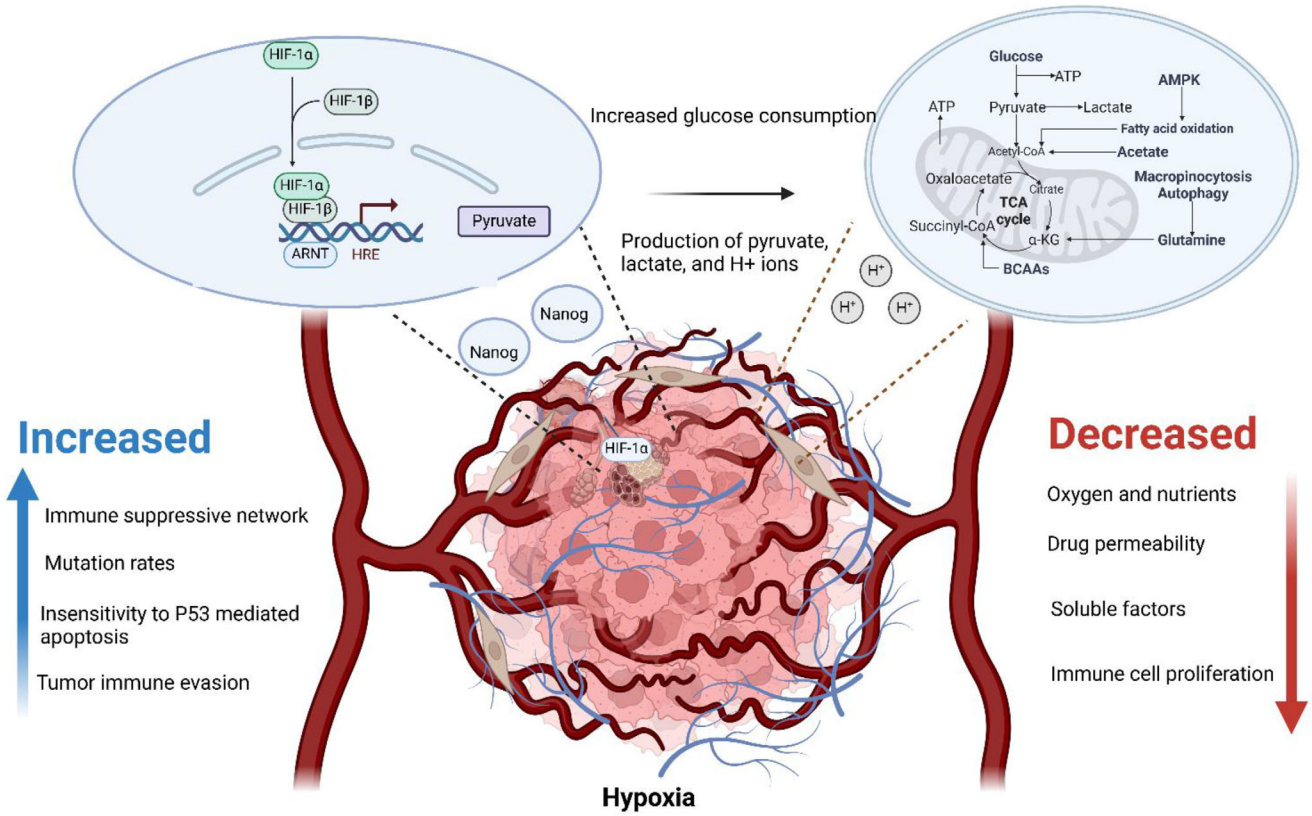

FIGURE 3 Hypoxia-induced immunosuppression in the TME. Visual representation of the impact of hypoxia on the TME. Hypoxia, caused by limited access to nutrients and oxygen, triggers the activation of HIFs, leading to metabolic shifts, increased glycolysis, and the production of lactate and H^+ ions. Hypoxia in the TME promotes immunosuppression through various mechanisms, including the recruitment of Tregs, the induction of stemness-associated factor Nanog, and the influence of HIF-1α on MDSCs and TAMs. Abbreviations: Acetyl-CoA, acetyl coenzyme A; AMPK, adenosine monophosphate-activated protein kinase; ARNT, aryl hydrocarbon receptor nuclear translocator; ATP, adenosine triphosphate; BCAAs, branched chain amino acids; HIF-1α, hypoxia inducible factor-1 alpha subunit; HIF-1β, hypoxia inducible factor-1 beta subunit; HRE, hypoxia responsive element; TCA cycle, tricarboxylic acid cycle; α-KG, alpha-ketoglutarate.

I on the surface of tumors or by MHC class II on the surface of APCs [67]. However, many tumors express low levels of MHC class I and may therefore not be capable of activating CTLs [9]. Cold tumors are also characterized by impaired recruitment of APCs and, consequently, the absence of T cell priming and activation [67]. Moreover, tumor cells hinder the presentation of antigens by APCs. One way to treat cancer might be to get APCs to enter tumor cells, pick up tumor antigens, and shoe them to T cells. This would trigger a strong immune response against the tumor [68]. Absence of DCs and/or impaired DC maturation and activation, as the main APC in the tumor site, is strongly correlated with non-T cell-inflamed TME. Immature DCs do not express co-stimulatory molecules, and a lack of T cell co-stimulation and activation after antigen presentation results in T cells being anergic [9].

The binding of Pathogen-Associated Molecular Patterns and Danger-Associated Molecular Patterns (PAMPs and DAMPs) with toll-like receptors on APCs surface has been previously indicated as a crucial factor in the differentiation of immature APCs into professionals which can directly activate $CD8^+$ T cells [69]. DAMP is the exposure of molecules such as calreticulin (CRT), heat shock protein 70 (HSP70), heat shock protein 90 (HSP90), adenosine triphosphate (ATP), high mobility group box 1 (HMGB1), type I IFN (IFN-I) family, and ultimately members of the IL-1 family to the cell surface [70]. However, studies demonstrated that tumor cells express low PAMP/DAMP to inhibit APCs and T cell priming [71, 72]. Priming and activation of $CD8^+$ T cells also require the interaction of CD40 on APCs with CD40L, expressing on $CD4^+$ T cells, and secretion of IL-12 and IFN-I by activated APCs [70]. Therefore, a reduction in $CD8^+$ T cell responses in cold tumors is mostly caused by inactivated APCs.

Impaired immune cell infiltration in cold tumors stems from modified cytokine and chemokine patterns, which affect cell trafficking and activation. In particular, CCL2, CCL7, CCL8, as well as CCL3/macrophage inflammatory protein-1(MIP-1alpha), CCL5/RANTES, and CCL4/MIP-1β are the main chemokines that act on DC recruitment

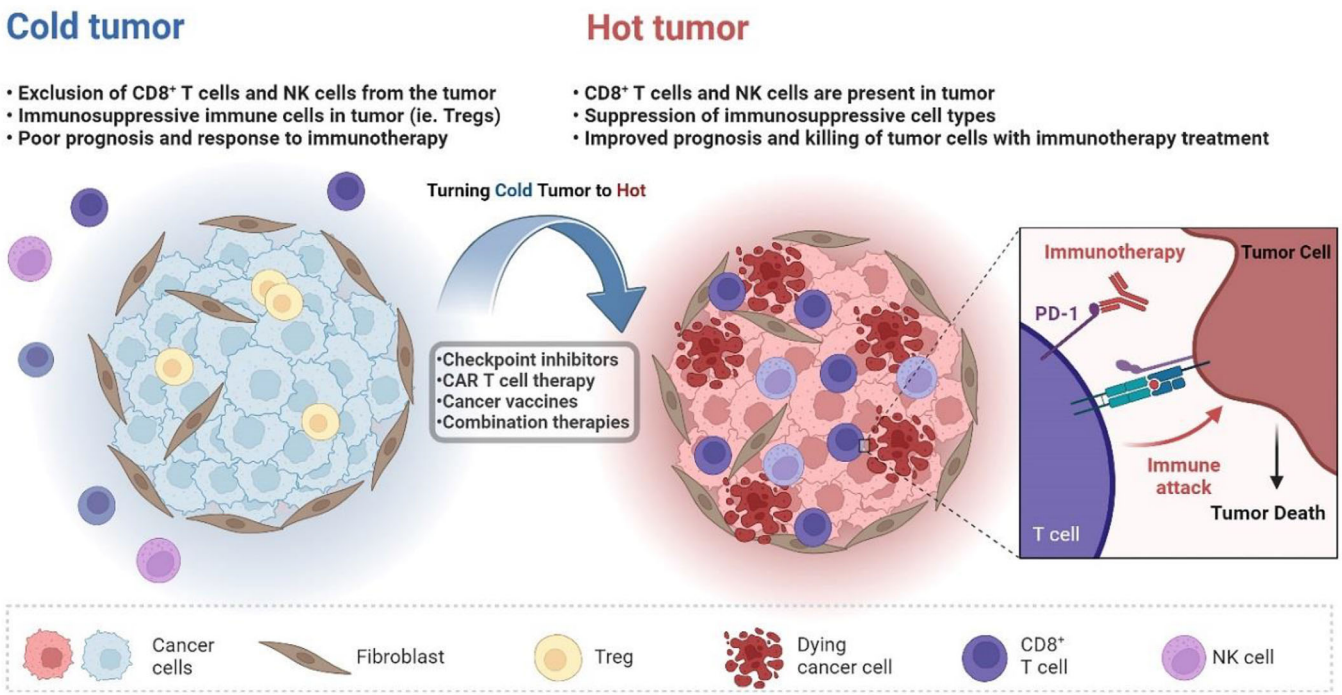

FIGURE 4 The characteristics of cold and hot tumors. One of the main features of cold tumors is low immune cell infiltration and the existence of immunosuppressive cells, such as regulatory T cells. In contrast, tumor-infiltrating lymphocytes are remarkable in hot tumors and anti-tumor immune response inhibits tumor growth and ultimately, these tumors have better prognoses and outcomes. In this regard, immunotherapies by enhancing the efficacy of tumor-infiltrating lymphocytes function, provide promising approaches in turning cold tumors into hot ones. Abbreviations: CAR, chimeric antigen receptor; PDL-1, programmed death-ligand 1; Treg, T regulatory.

and activation [73]. Matured DCs secreting CXCL16, the ligand of CXCR6, could prime $CD8^+$ and $CD4^+$ T lymphocytes in colorectal cancer [73]. However, tumors significantly deregulate cytokine and chemokine secretion, as chemokines participating in T lymphocyte recruitment are dramatically decreased in non-$CD8^+$ T cell-inflamed tumors [74]. In this context, it has been proven [75] that TAMs, by recruiting $CCR6^+$ regulatory T cells, developed colorectal cancer via increasing CCL20, the ligand of CCR6.

In colorectal cancer, it has been demonstrated that proficient mismatch repair system (MMR) and stability of microsatellites are two main reasons for the cold colorectal tumor, leading to a low mutational burden and an immune-undetectable tumor [76]. Hence, immunotherapy for such tumors is accompanied by poor efficacy and therapy failure [76]. Moreover, RNA sequencing data on human breast cancer have revealed that genes involved in antigen presentation and promotion of effector T cell were significantly low; however, genes associated with pro-tumorigenic M2 macrophages and ECM stiffness were high, which demonstrated an immune-deserted cold tumor [77]. According to Wang *et al.* [78] the implementation of magnetic nanoparticles can rewire the immunoecology of breast cancer from cold to hot by promoting the maturity of DCs and the polarization of macrophages from M2 to M1, leading to effective infiltration of $CD8^+$ T cells. Triple-negative breast cancer (TNBC) and colon adenocarcinoma (COAD) are typically considered cold tumors due to overexpression of PD-L1 and CD47, respectively [79].

PD-L1 is a co-inhibitory factor of the immune response, which, after combining with PD-1 on T cells, induces anti-proliferative signals, resulting in inhibiting cytokine secretion and finally apoptosis. Many tumors utilize PD-L1 to escape the anti-tumor immune response [80]. For instance, prostate cancer is considered immunologically a cold tumor with high expression of PD-1 and low infiltrated T lymphocytes [81]. Immunotherapy-based ICIs rely on T cell infiltration to some extent, and a lack of enough T cells in tumor sites makes cold tumors nonresponsive to immune checkpoint inhibitors compared with hot tumors [82]. Therefore, improving the immunotherapy response of a cold tumor is considered a challenging and research hotspot.

Generally, cold tumors are challenging and difficult to treat, with poor clinical outcomes. Acidic TME, which is mainly due to lactic acid play a critical role in suppressing immune response [54]. Studies demonstrated that the Warburg effect by increasing lactate generation turns tumors into cold ones, while in oxidation phosphorylation (OXPHOS) dependent tumors the density of T cells is higher [54, 83-85]. In addition, the Warburg effect of

stromal cells may be immunosuppressive to some extent, turning tumors into non-T cell-inflamed [54]. In fact, glycolytic stromal cells not only increase in lactic acidosis but also, by increasing GLUT1 and rapid glucose consumption, cause metabolic stress for immune cells, leading to T cell apoptosis and dysfunction [86]. Hence, toxic TME is a crucial barrier for immunotherapy of cold tumors. Recently, immunogenic cell death (ICD) of cancer cells has been deeply taken into consideration, which consists of releasing DAMPs from dying tumor cells due to any interventions [87]. Boosting specific anti-cancer immune responses and, thereby, ICD improves both antigenicity and adjuvanticity to reprogram the TME, amplifying innate and adaptive anti-tumor immune responses [88]. Various strategies have been developed to overcome cold tumors. In this context, tumor vaccines, adoptive cell therapy (ACT), ICIs, and the removal of MDSCs could be promising approaches.

5 | ROLE OF IMMUNE CELLS IN TUMOR

TILs encompass various cell types, such as $CD8^+$ lymphocytes, $CD4^+$ lymphocytes, Treg, $\gamma\delta$T cells, and B cells. While T helper and cytotoxic T cells have well-studied tumor-suppressing roles, TILs can also promote tumor growth through interactions with stromal components like macrophages and neutrophils, influenced by the cytokines they secrete [16]. In certain conditions, $\gamma\delta$T cells release IL-17, triggering angiogenesis and G-CSF-mediated activation of neutrophils, promoting cancer-cell metastasis [89]. IL-4-secreting $CD4^+$ T lymphocytes indirectly enhance tumor invasiveness and pulmonary metastasis by influencing the pro-tumor properties of TAMs [90]. Tregs are believed to exert an immunosuppressive impact within the TME. They can induce apoptosis of natural killer (NK) cells through direct cell-to-cell contact and TGF-β secretion [91]. However, in certain situations, Tregs may also contribute to tumor angiogenesis by producing VEGFA, as evidenced in an ovarian cancer murine xenograft model [92]. Activated B cells contribute to pre-malignant inflammatory responses and support tumor growth in the human papillomavirus 16 (HPV-16)-driven multistage epidermal carcinogenesis model [93]. In castration-resistant prostate cancer, tumor-infiltrating B cells secrete lymphotoxin (LT) -α/-β, engaging with LTβR on cancer cells to activate the STAT3 pathway, promoting androgen-independent cancer cell growth [94]. Interestingly, STAT3 activation in B cells leads to increased angiogenesis in B16 melanoma and Lewis lung cancer models; however, the direct role of B cells in angiogenesis remains unclear [16].

$CD8^+$ T cells play a critical role as lymphocyte cells, actively suppressing tumor growth and impeding metastasis by directly recognizing and eliminating tumor cells through intracellular antigens. Past research has revealed the positive correlation between $CD8^+$ T cells and improved cancer prognosis, as they also contribute to controlling infections and cancer development [2, 95]. However, the precise mechanisms governing the activation of tumor-infiltrating T cells and their ability to eliminate tumors remain incompletely understood. The quantity of $CD8^+$ T lymphocytes, acting as antigen-specific effectors, is considered a marker of cancer regression [2, 95]. Nevertheless, tumor cells exhibit limited $CD8^+$ immunogenic markers due to their inherent heterogeneity [96]. The unfavorable combination of immunosuppressive elements in the TME, including stromal components, immune cells, and various factors, leads to insufficient activation of $CD8^+$ T cells [97]. Furthermore, evidence indicates that TME-stromal components can hinder $CD8^+$ T lymphocyte activity [98]. While the majority of $CD8^+$ T cells develop into fully functional CTLs, a dysfunctional $CD8^+$ T cell pool may arise, compromising their responsiveness to tumor cells and inadvertently promoting cell proliferation [1].

The decline in T cell function during cancer progression encounters three main obstacles [99]. First, a lot of tumor-specific T cells are killed during thymic maturation because many tumor cells have self-antigens, which means that self-tolerance mechanisms don't like them. Nonetheless, due to a partially effective immune tolerance mechanism, some self- or tumor-specific T cells persist but with lower affinity for antigen recognition compared to virus-specific T cells [99, 100]. Also, APCs aren't activated very well in tumors that aren't inflamed because there aren't enough innate stimulators. This makes tumor-specific T cells less activated than they could be [101]. The next challenge arises from the TME, which induces and sustains T cell hyporesponsiveness. Cancer immunoediting illustrates the dual roles of immunity in both protecting the host against tumor cells through immune surveillance and promoting tumor growth [102]. As the immune system seeks to eliminate tumor cells, the tumor cells, in turn, recruit immunosuppressive cells and release inhibitory factors to establish an immunosuppressive TME. This environment persists during tumor development, continuously suppressing T cell immune function [103].

Indeed, $CD8^+$ cytotoxic T cells have a crucial function in eradicating tumor cells [104]. However, they frequently undergo differentiation into an exhausted state and lose their ability to effectively control tumor progression during the advanced stages [105]. There are some similarities between tumor-specific exhausted T cells and immune cells that are worn out by long-term viral infections,

but these cells are different because they are immune tolerance and immunosuppression mechanisms. Consequently, devising effective strategies to reinvigorate these exhausted T cells holds significant potential to profoundly influence the course of tumor development and progression [106].

6 | MECHANISMS OF IMMUNE EVASION BY TUMOR CELLS

Tumor cells utilize various mechanisms to evade the immune system, impeding effective cancer treatment. One of the well-known strategies involves impairing antigen presentation through mutations or downregulation of MHC class I molecules, which hampers T cell recognition and response. However, some tumors, such as PDAC, predominantly downregulate MHC class I expression rather than experiencing MHC class I loss due to mutations [107]. Another important immune evasion mechanism involves enhanced autophagy or lysosome function, selectively targeting MHC class I molecules for degradation. Inhibition of autophagy has shown promise in reversing this effect, leading to improved antigen presentation and a more robust anti-tumor immune response [107]. Moreover, combining autophagy inhibition with dual immune checkpoint blockade (ICB) presents a potentially effective therapeutic strategy against immune-resistant tumors like PDAC, opening new avenues for improving cancer treatment outcomes [107].

Two prominent mechanisms at the forefront of cancer immunotherapy research are related to immune checkpoint molecules, CTLA-4 and PD-1. CTLA-4 acts as a co-inhibitory molecule on T cells, dampening T cell activation and hampering antitumor responses [108]. Similarly, PD-1 expressed on T cells acts as a negative regulator, and its interaction with the ligand PD-L1, expressed by tumor cells, induces immune tolerance and allows tumors to escape recognition and elimination [108].

Another mechanism of tumor escape is the upregulation of CD47, a potent macrophage immune checkpoint, on tumor cells [109]. CD47 binds to its ligand, signal-regulatory protein alpha (SIRPα), on macrophages, inhibiting phagocytosis and immune recognition [109]. Additionally, enhanced amino acid uptake through upregulated amino acid transporters, such as L-type amino acid transporter 2 (LAT2), supports cancer cell metabolism and protein synthesis [110]. Chemotherapy makes macrophages release IL-8, which increases the expression of LAT2 in tumor cells. This causes more glutamine and leucine to be taken in. This, in turn, activates mTOR-dependent CD47 expression, promoting tumor immune evasion [110].

MYC activation in cancer cells plays a crucial role in promoting tumor immune evasion. MYC is known to mediate various hallmarks of cancer, including immune evasion, by influencing both the intrinsic biology of cancer cells and their interactions with the TME [111]. One of the critical effects of MYC is its impact on the expression of immune checkpoint molecules, which are essential regulators of the immune response. By upregulating immune checkpoint molecules, such as PD-L1, cancer cells can inhibit the function of cytotoxic T cells, preventing them from recognizing and attacking the tumor [111]. Additionally, MYC activation in cancer cells may lead to changes in the TME, creating an immunosuppressive environment that hinders the immune system's ability to mount an effective anti-tumor response [111].

Nicotinamide adenine dinucleotide (NAD^+) plays a vital role as a mediator of energy metabolism and signal transduction pathways. Recent studies have demonstrated that nicotinamide phosphoribosyltransferase (NAMPT), a key enzyme in NAD^+ metabolism, promotes an immune-suppressive microenvironment [112]. It facilitates the mobilization and immune suppressive functions of immature MDSCs and stimulates the differentiation of monocytes into tumor-supporting M2-macrophages [112].

In order for a tumor to get away, things like poor antigen presentation, increased immune checkpoints like PD-L1, better autophagy breaks down MHC class I, and NAD^+ metabolism-driven PD-L1 expression all work together to make the TME immune-cold. These mechanisms dampen the immune response and hinder T cell recognition and infiltration, promoting tumor immune evasion and making the TME less susceptible to immune-based therapies.

7 | MECHANISMS OF ACTION OF IMMUNOLOGIC MODULATORS

Response rates to ICIs are minimal when dealing with cold tumors, which are distinguished by their lack of T cell infiltration [9]. When attempting to induce T cell presence within tumors, numerous variables come into play, impacting T cell activation and their migration to the tumor site. This complex interplay can result in a non-inflamed T cell profile, ultimately leading to ineffective antitumor immune responses [9].

7.1 | Tumor antigen presentation

Insufficient T cell priming disorders primarily stem from a lack of proper T cell recognition, often attributed to inadequate tumor antigens. Broadly speaking, these targeted tumor antigens fall into two main categories: nonmutated

self-antigens and neoantigens generated through nonsynonymous somatic mutations [113]. Among self-antigens are nonmutated proteins that exhibit abnormal expression or heightened levels in tumor cells, such as tumor-associated antigens (TAAs) and cancer testis antigens (CTAs). While self-antigens do trigger an immune response against tumors, the principal focus of the immune system is on neoantigens, also referred to as tumor-specific antigens (TSAs). Neoantigens are exclusive to tumor cells and emerge from somatic mutations within cancerous genomes [113]. Recognizing these tumor-specific neoantigens can stimulate T cell priming and infiltration, potentially resulting in sustained clinical responses over the long term [104, 113]. The TMB is a comprehensive measure encompassing the total count of nonsynonymous single-nucleotide mutations found within a tumor [114]. Generally, tumors exhibiting elevated TMB levels are thought to harbor an increased load of neoantigens, which T cells can recognize. This propensity enhances their likelihood of initiating an immune response [114]. Several studies have highlighted significant connections between higher TMB and enhanced responses to ICIs across various tumor varieties [115, 116]. As a novel biomarker, TMB has been employed to predict the effectiveness of inhibitors targeting PD-1 [114, 116]. Notably, a strong correlation exists between heightened TMB and heightened infiltration of immune cells, underscoring the significance of ICI efficacy [117].

7.2 | Key mechanisms impeding optimal antigen presentation

Upon recognizing tumor antigens, APCs undergo antigen processing, leading to the display of the corresponding antigen peptide-MHC class I complex on their surface [118]. However, alterations in the antigen processing machinery (APM), such as the downregulation of MHC class I molecule expression or the absence of beta-2-microglobulin (B2M), constrain the presentation of antigen peptide-MHC class I complexes when tumor antigens are present [118]. Antigen processing and presentation is done by transporters associated with antigen processing (TAP), which move cleaved antigens from the cytosol to the endoplasmic reticulum and bind to MHC molecules there. Deletions within the TAP system lead to deficiencies in antigen presentation, consequently impacting the priming of T lymphocytes [118]. B2M, a vital component of MHC, plays a crucial role in the proper folding and transportation of MHC class I to the cell surface [119]. Experiments involving the knockdown of the B2M gene in human melanoma cell lines M202 and M233 resulted in the absence of MHC class I molecules on their surfaces, leading to the failure of tumor-specific T cell recognition and cytotoxicity [120]. Comparable outcomes were observed in a mouse model of lung cancer with a B2M knockout, which exhibited resistance to PD-1 blockade [121]. Furthermore, the lysosomal pathway has been implicated in diminishing the infiltration of $CD8^+$ T lymphocytes. In PDAC, the autophagy-associated receptor Neighbor of BRCA1 gene 1 (NBR1) triggers the degradation of MHC class I on the cell surface of tumor cells, consequently influencing T cell responses [107].

7.3 | DCs activation and immune evasion

DCs function as specialized APCs, playing a unique role in acquiring antigens, migrating to secondary lymphoid organs like lymph nodes and spleen, and initiating immune responses [122]. The activation of DCs hinges on the recognition of danger signals through pattern recognition receptors (PRRs) located on their surface. These signals encompass PAMPs as well as DAMPs [122]. Through this recognition process, DCs become capable of presenting the tumor antigen peptide-MHC class I complex to T cells upon direct contact. Additionally, DCs express costimulatory molecules such as B7 (including CD80 and CD86), which furnish secondary signals vital for the activation of T cells [123]. In the context of tumor immunity, certain tumor cells can impede the phagocytosis of DCs by sequestering these critical danger signals [124]. One illustrative instance involves stanniocalcin 1 (STC1), an intracellular checkpoint that can ensnare DAMPs like CRT [124]. STC1, initially recognized for its diverse biological functions, has emerged as a noteworthy factor in the context of tumor immunity and immunotherapy resistance [124]. Recent research has shed light on the role of STC1 in modulating the interactions between APCs and T cells within the TME. Studies have shown that STC1 interferes with APC antigen presentation by interacting with CRT, a key phagocytic signal [124]. This makes it harder for T cells to become activated. This newly identified mechanism highlights STC1 as a potential intrinsic immune resistance factor, offering insights into novel strategies aimed at overcoming immunotherapy resistance by targeting STC1 and its interplay with CRT.

Normally, DCs are split into two main groups: plasmacytoid DCs (pDCs), which are known for making IFN-α, and conventional DCs (cDCs), which are experts at helping T cells multiply. Within cDCs, a further distinction is made between two subsets: Basic leucine zipper transcriptional factor ATF-like 3 (BATF3)-dependent DCs and Interferon regulatory factor 4 (IRF4)-dependent DCs [125]. BATF3 DCs possess the ability to cross-present antigens derived from tumors via the MHC class I pathway, thereby

initiating T cell responses [126]. Also, BATF3 DCs are the main source of CXCL9 and CXCL10, which are two important chemokines needed to bring $CD8^+$ T cells expressing CXCR3 to tumor sites[127]. Notably, a notable correlation exists between markers of BATF3 DCs (such as BATF3 and IRF8), the expression of CXCL9, CXCL10, CXCL11, and the $CD8^+$ effector T cell phenotype within melanoma [127, 128]. Devoid of BATF3 DCs, the migration of $CD8^+$ effector T cells to tumor locales is impeded, resulting in defective antitumor immune responses [127].

Maintaining balance in the regulation of Fms-like tyrosine kinase 3 ligand (FLT3L) and GM-CSF plays a pivotal role in orchestrating the differentiation and recruitment of DCs [129]. FLT3L serves as a growth factor that facilitates the differentiation of hematopoietic progenitor cells from the bone marrow into the DC lineage [129]. Notably, tumor-derived FLT3L has been demonstrated to heighten the infiltration of BATF3 DCs and $CD8^+$ T lymphocytes within murine tumors [130]. This effect extends to enhancing both migratory and resident DC subsets within draining lymph nodes (DLNs), suggesting that FLT3L exerts a mobilizing influence on DC populations [130]. It is crucial to note that the deficiency of FLT3L or GM-CSF has been linked to a diminished presence of DCs within secondary lymphoid organs, resulting in weakened T cell immune responses [131]. Thus, antigen presentation bridges cold tumors to hot ones by activating immune responses. It exposes tumor antigens to T cells, driving inflammation and immune cell infiltration, which is crucial for effective immunotherapy and tumor control. This transformation hinges on DCs recognizing antigens and priming T cells.

7.4 | Overcoming immune checkpoint inhibition

In spite of the remarkable advancements in ACT therapies, a novel category of monoclonal antibodies (mAbs), known as ICIs, have now made their way into the realm of medical practice and emerged as a pivotal form of immunotherapy [108]. Immune checkpoints constitute molecules within coinhibitory signaling pathways that play a role in upholding immune tolerance [108]. However, these checkpoints are frequently exploited by cancer cells to evade detection by the immune system. ICIs are meant to boost the immune system's ability to fight tumors by blocking these signaling pathways that stop them from working properly. This makes it easier for the immune system to get rid of cancerous cells. The primary targets of ICIs are CTLA-4, PD-1, and PD-L1, and they have gained widespread utilization [108]. A detailed overview of these immune checkpoints and their corresponding therapies is provided in Table 1.

CTLA-4, a coinhibitory molecule present on T cells, operates to negatively modulate T cell activation [132, 133]. A groundbreaking study illustrated that the blockade of CTLA-4 through antibody intervention could trigger potent immune responses, leading to the regression of tumors [134]. This marked the onset of a new phase in which antibodies were employed to dismantle the restrictions on immune cells, thus bolstering antitumor immune reactions. Following comprehensive clinical trials and assessments of effectiveness, ipilimumab, an antibody targeting CTLA-4, emerged as the inaugural ICI sanctioned for cancer therapy. Its approval was attributed to its capacity to amplify T cell activation and elicit sustained reactions [135–137].

PD-L1 regulates immune tolerance by curbing TCR-mediated lymphocyte proliferation and cytokine secretion upon binding to PD-1 [138, 139]. Intriguingly, tumor cells also exhibit abnormal PD-L1 expression, enabling them to evade immune surveillance [140, 141]. Scientific inquiry revealed that inhibiting PD-1 or PD-L1 could rejuvenate the cytotoxic capabilities of T cells, triggering tumor regression [142, 143]. Consequently, PD-1 and PD-L1 emerged as potential therapeutic targets. The clinical benefits of PD-1 pathway blockade have been extraordinary, leading to the approval of antibodies targeting PD-1 or PD-L1 for the treatment of various cancers [135, 144]. Overcoming immune checkpoint inhibition switches cold tumors, which lack immune activity, into hot ones by disrupting inhibitory signals that suppress immune responses. This reactivation empowers immune cells to target and eliminate cancer cells effectively, leading to heightened antitumor activity.

7.5 | Augmenting T cell infiltration and activation

The triumph in cancer immunotherapy, exemplified by strategies like ACT and ICI therapies, has eloquently showcased the potential of immune cells, particularly T cells, as formidable agents for eradicating tumor cells [145]. Despite the sustained clinical efficacy of these approaches, their benefits remain confined to a fraction of cancer patients [145]. This accentuates the pressing need to delve deeper into the intricate interplay of immune infiltrates, a pivotal component of the TME, which has been unequivocally demonstrated to wield a dual impact on both tumor progression and the outcomes of immunotherapy [146]. Because of this, it becomes very important to understand better how innate and adaptive immune cells work together in the TME. This profound insight is poised to unveil the enigmatic mechanisms governing immunotherapies, unravel elusive predictive biomarkers, and

TABLE 1 Checkpoint inhibitors in cancer immunomodulation.

Name of drug	Target	Approved for subsets of cancers	Reference
Atezolizumab (Tecentriq®)	PD-1/PD-L1	Breast cancer, liver cancer, lung cancer, and sarcoma	[237–240]
Avelumab	PD-1/PD-L1	Kidney cancer and Merkel cell carcinoma	[241, 242]
Cemiplimab (Libtayo®)	PD-1/PD-L1	Cutaneous squamous cell carcinoma, basal cell carcinoma, and lung cancer	[243–245]
Dostarlimab (Jemperli)	PD-1/PD-L1	Uterine (endometrial) cancer	[246]
Durvalumab (Imfinzi™)	PD-1	Bladder cancer, liver cancer, and lung cancer	[247–249]
Ipilimumab (Yervoy®)	CTLA-4	Melanoma, mesothelioma, liver cancer, and lung cancer	[250–253]
Nivolumab (Opdivo®)	PD-1/PD-L1	Bladder cancer, colorectal cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, lymphoma, melanoma, and mesothelioma	[254, 255]
Pembrolizumab (Keytruda®)	PD-1/PD-L1	Bladder cancer, breast cancer, cervical cancer, colorectal cancer, cutaneous squamous cell carcinoma, esophageal cancer, etc.	[256–261]
Relatlimab	LAG-3	Melanoma (in combination with nivolumab [together known as Opdualag™])	[262]
Tremelimumab (Imjudo®)	CTLA-4	Liver cancer and lung cancer (in combination with durvalumab and chemotherapy)	[263]

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

illuminate novel and promising avenues for therapeutic targeting in the ever-evolving war against cancer [108].

T cells have emerged as the focal point in the realm of tumor immunology, revered for their formidable prowess in eliminating tumors [147, 148]. The process of T cells working starts with the complex interaction between TCRs and short peptide fragments of tumor antigens, which are skillfully presented by MHC molecules or human leukocyte antigen. TCRs, masterpieces crafted through genetic rearrangements involving an intricate dance of diverse TCR gene segments, bestow T cells with an unparalleled tapestry of diversity and specificity [149]. At the heart of effective antitumor immunity reside TILs, a cadre of T cells of varying lineages. CTLs, TH cells, and Tregs synergistically contribute to the T cell-mediated immune responses within the tapestry of the TME [108]. Of these, CTLs hold the mantle of prominence, functioning as the primary effector cells armed with a formidable arsenal of cytotoxic molecules, including granzymes and perforin, to engage and dismantle tumor targets [108]. So, increasing the number and activity of T cells in a planned way causes a major change that turns dormant cold tumors into highly responsive hot tumors. Through a combination of immune checkpoint inhibition, enhanced T cell priming, and microenvironmental modulation, this approach dismantles barriers to T cell entry, diminishes immunosuppressive elements, and revitalizes T cell function. The resulting synergistic impact revitalizes the TME, fostering a vibrant landscape primed for potent antitumor responses.

7.6 | Reprogramming the TIME

The complex immune evasion mechanisms driving cold tumor formation stem from the intricate interplay of multiple factors within the TME [150]. Immunosuppressive cells, TGF-β, STAT3 signaling, adenosine, physical barriers, and intricate vascular networks all work together to make the TME immunosuppressive. The presence of these factors shapes the development of an environment hostile to immune responses [150]. Thus, reprogramming the TIME stands as a pivotal strategy to revolutionize the battle against cancer [57]. By strategically altering the immunosuppressive factors within the TME, this approach creates fertile ground for robust antitumor responses. It enhances T cell infiltration, neutralizes immunosuppressive cells, and reshapes cytokine profiles, leading to heightened immune activity [57]. This reprogramming reinvigorates the immune response, driving potent recognition and elimination of cancer cells. Ultimately, it holds immense promise for transforming the oncological landscape by unleashing the full potential of the immune system against malignancies. Table 2 lists the different types of immunotherapy, the corresponding drugs, targets, and cancer subtypes for which they are approved.

TABLE 2 Diverse immunomodulation therapies in cancer treatment and cancer vaccines.

Type of immunotherapy	Name	Target	Approved for subsets of cancers	Reference
Cytokine	Aldesleukin (Proleukin)	IL-2/IL-2R pathway	Kidney cancer and melanoma	[264]
	GM-CSF	GM-CSFR	Neuroblastoma	[265]
	Interferon alfa-2a	IFNAR1/2 pathway	Leukemia and sarcoma	[266]
	Interferon alfa-2b	IFNAR1/2 pathway	Leukemia, lymphoma, melanoma, and sarcoma	[267]
	Peginterferon alfa-2b	IFNAR1 pathway	Melanoma	[266]
Adjuvant	Imiquimod	TLR7	Basal cell carcinoma	[268]
Small molecule	Pexidartinib	Inhibitor of the KIT, CSF1R, and FLT3 pathways	Tenosynovial giant cell tumor	[269]
Cancer vaccine	Cervarix	Two strains of HPV- and 18	Cervical cancer (preventing)	[270]
	Gardasil	HPV-16, 18, 6, and 11	Anal, cervical, head and neck, penile, vulvar, and vaginal cancer (preventive)	[271]
	Gardasil-9	HPV-16, 18, 31, 33, 45, 52, 58, 6, and 11	Anal, cervical, head and neck, penile, throat, vulvar, and vaginal cancers (preventive). Warts caused by HPV-6 or 11	[271]
	HBV vaccine (HEPLISAV-B)	HBV	HBV-related liver cancer (preventive)	[272]
	Bacillus Calmette-Guérin (BCG)	To stimulate the immune system	Early-stage bladder cancer (therapeutic)	[273]
	Sipuleucel-T (Provenge)	Composed of patients' own stimulated DCs	Prostate cancer	[274]
Oncolytic virus	T-VEC (Imlygic)	Tumor cells	Melanoma	[275]
Adaptive cell therapy	Axicabtagene ciloleucel (Yescarta)	CD19-targeting CAR-T cell	Lymphoma	[276]
	Brexucabtagene autoleucel (Tecartus)	CD19-targeting CAR-T cell	Leukemia and Lymphoma	[277]
	Ciltacabtagene autoleucel (Carvykti)	BCMA-targeting CAR-T cell	Advanced multiple myeloma	[278]
	Idecabtagene vicleucel (Abecma)	BCMA-targeting CAR-T cell	Advanced multiple myeloma	[279]
	Lisocabtagene maraleucel (Breyanzi)	CD19-targeting CAR-T Cell	Lymphoma	[280]
	Tisagenlecleucel (Kyrmriah)	CD19-targeting CAR-T cell	Leukemia and lymphoma	[281]

Abbreviations: CAR-T cell, chimeric antigen receptor T cell; CD19, cluster of differentiation 19; CSF1R, colony-stimulating factor 1 receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBV, hepatitis B virus IL-2, interleukin-2; HPV, human papillomavirus; IFNAR1/2, interferon alpha receptor 1 and 2; IL-2R, interleukin-2 receptor; KIT, kit proto-oncogene receptor tyrosine kinase; TLR7, toll-like receptor 7; T-VEC, talimogene laherparepvec.

Reprogramming the TME holds key importance in transforming cold tumors into hot ones. Metabolic interventions offer a potent strategy by targeting tumor cell metabolism. Glutamine metabolism modulation enhances T cell antitumor activity. Suppressing immunosuppressive metabolites and optimizing immune cell metabolism show promise [57].

Combining metabolic interventions with immunotherapy yields synergistic effects. Metformin enhances ICIs. Manipulating T cell metabolism during adoptive cell transfer boosts T cell survival and function. Dietary interventions and microbiome modulation impact antitumor immune responses [57]. Understanding tumor and immune cell metabolism is crucial for effective

interventions. Reprogramming the TME through metabolic strategies can ignite robust antitumor immunity, shifting cold tumors into hot, responsive environments.

8 | IMMUNE-TARGETED THERAPIES FOR TURNING COLD TUMORS TO HOT

Vaccines for cancer are mainly composed of whole tumor cells and/or DC-based vaccines. The only U.S. Food and Drug Administration (FDA)-approved vaccine is known as sipuleucel-T for the treatment of asymptomatic or minimally symptomatic metastatic hormone-resistant prostate cancer, while other tumor vaccines failed to meet expectations. Therefore, several strategies are considered to improve the efficacy of cancer vaccines, particularly in cold tumors [151]. These strategies take measures to improve the outcome of cancer vaccination and overcome its challenges. Researchers utilize adjuvant therapies to boost first and second co-stimulatory signals to generate an optimal immune response. However, immuno-potentiators like PAMPs and some cytokines (IL-2, IL-12, IL-15, IL-18, IL-21, and IFN-γ) were shown to improve the effectiveness of cancer vaccines in the real world [151]. In addition, the combination of tumor vaccines with other therapies, such as chemotherapy, radiation therapy, and ICIs in cold tumors provokes a strong immune response [151]. Table 3 offers a comprehensive overview of ongoing clinical trials focusing on immunotherapies. These trials encompass a range of interventions, including adaptive cell therapy, immunomodulation by checkpoint inhibitors, tumor vaccines, oncolytic viruses, and more. In this context, it has been demonstrated that radiation therapy augments the cancer vaccine in immunologically cold breast cancer, melanoma, and lung cancer in vivo models [152]. In this study, it was also shown that a combination of radiation therapy and a cancer vaccine promotes OX40 expression on the TIL surface and induction of memory $CD4^+$ T cells. Moreover, such therapy might increase $CD4^+$ and $CD8^+$ T cell activation and enhance the $CD4^+$ effector T cell/regulatory ratio at the tumor site. In comparison, radiation therapy and tumor vaccines alone fail to stimulate tumor regression [152].

Generally, immunotherapy approaches rely on T cell infiltration to some extent; hence, CTLA-4-PD-1 dual therapy in cold tumors is mostly unsuccessful, which is due to the fact that the cold tumors have a limited number of infiltrated T cells and are capable of suppressing immune responses. Studies on 369 patients with recurrent glioblastoma demonstrated that anti PD-1 immunotherapy had a disappointing outcome [153]. This result was shown to stem from the secretome of glioblastoma, which mainly consists of immune suppressor cytokines (IL-10 and TGF-β) as well as CCL-2 chemokines, thereby recruiting and activating MDSCs and TAMs; hence, any infiltrated T cells may be suppressed, ultimately causing apoptosis [154]. According to the studies by Frederico *et al.* [155], due to the broad tumor heterogenicity, monotherapy may not be effective. However, a combination of PD-1/PD-L1 targeted therapy with a cancer vaccine has undergone promising clinical trials [156]. In melanoma, it has been proven that tumor-intrinsic Wnt/β-catenin signaling is correlated with the depletion of type-1 DCs and, consequently, effector $CD8^+$ T cells, resulting in resistance to anti-PD-L1 and anti-CTLA4 therapy [157].

Chimeric antigen receptor-T cells (CAR-T cells) therapy provides a promising therapeutic approach for liquid malignancies. CAR-T cells are patient-derived T lymphocytes that express genetically modified antigen receptors to recognize and eliminate cells expressing a specific target antigen. CAR-T cell therapy was approved by the U.S. FDA in 2017 for use in multiple B cell malignancies [158]. Although promising results were achieved while using CAR-T cell therapy, it is associated with many reported toxicities. In this context, cytokine release syndrome (CRS) is a life-threatening toxicity and the most frequent event after CAR-T cell therapy, which is a systemic inflammatory response to infusions and certain drugs [159].

Typically, upon fractionating the peripheral blood mononuclear cell (PBMC), these cells undergo *ex-vivo* activation with either beads or cytokines. Then, vectors containing genes for CAR expression are introduced to these autologous expanded T cells. After that, these genetically engineered cells are expanded just before infusion [160]. As CAR-T cells have several limitations, such as toxicities, T cell exhaustion, and T cell survival, the idea of CAR-T cell therapy has undergone several structural adjustments in recent years. To this end, a combination of co-stimulatory domains was generated in the third generation of CARs, which consisted of CD3z, CD28, OX40, or CD3z, 4-1BB and CD28. Soon it became clear that some tumor cells are resistant; hence, compared to second-generation CARs no significant efficacy was obtained [161].

In fourth-generation CARs, there is a genetically modified cassette possessing a transgenic protein, for instance, a cytokine gene cassette [162]. Therefore, these genetically altered T-cells are known as universal cytokine-mediated killings (TRUCKs). It has been proven that the anti-tumor performance of IL-12 producing TRUCKs is more efficient while encountering large tumor burdens and capable of changing infiltrated T cell polarization toward Th1 [163]. Gene-modified CARs produce IL-12 and IL-18, which enhance pro-inflammatory immune responses within cold tumors. Moreover, CXCR1 or CXCR2-engineered CAR-T cells significantly promote tumor regression and

TABLE 3 Clinical trials on immunotherapy of cold tumors.

Identifier	Intervention/treatment	Type of immunotherapy	Status	Disease setting
NCT05812326	PD-1 gene knockout anti-MUC1 CAR-T cells	Adaptive cell therapy	Phase II	Breast cancer
NCT03025035	Pembrolizumab; Olaparib	Immunomodulation by checkpoint inhibitor	Phase II	
NCT05559177	Chimeric exosomal tumor vaccine	Tumor vaccine	Early phase I	Bladder cancer
NCT05248789	OH2 injection	Oncolytic virus	Phase II	
NCT03113266	Toripalimab	Humanized anti-PD-1 monoclonal antibody	Phase II	
NCT03484962	Activated CIK and CD3-MUC1 bispecific antibody	Adaptive cell, armed with anti-CD3-MUC1 bispecific antibody	Phase II	HCC
NCT03949231	PD1/PD-L1 inhibitor	Immunomodulation by checkpoint inhibitor	Phase III	
NCT02089919	Cancer stem cell vaccine	Tumor vaccine	Phase III	
NCT02459067	Immune cell	Autologous $\gamma\delta$ T lymphocyte therapy	Phase II	Melanoma, RCC, and NSCLC
NCT04949113	Neoadjuvant Ipilimumab + Nivolumab	PD-1 inhibitor	Phase III	Melanoma
NCT00300612	MDX-010 (anti-CTLA4) monoclonal antibody; MDX-1379 (gp100) melanoma peptide vaccine	ICI/peptide vaccine	Phase II	
NCT00006434	Tumor lysate-pulsed DCs	Cancer vaccine	Phase III	Lymphoma and non-Hodgkin

Abbreviations: CAR-T, chimeric antigen receptor-T cell; CIK, cytokine-induced killer; DC, dendritic cell HCC, hepatocellular carcinoma;ICI, immune checkpoint inhibitor; MUC1, mucin 1; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma.

immunologic memory generation. However, a combination of CAR-T cells with ICIs provokes anti-tumor immune responses against cold tumors [164]. The tumor-killing ability of CARs is attenuated by suppressor cells such as MDSCs and TAMs [164]. MDSCs affect TIME via several mechanisms, such as depletion of tryptophan by indoleamine 2,3-dioxygenase (IDO), cytokine secretion (e.g., TGF-β, IL-10), activation of arginase-1 (ARG1) and inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) [165]. In prostate cancer, MDSCs have been implicated in contributing to resistance against anti-PD-1 antibody therapy. Studies shed light on the crucial role of MDSCs in modulating the responsiveness of tumors to anti-PD-1 treatment [166]. Nevertheless, combination therapies, which focus simultaneously on the inhibition of MDSC activation and expansion as well as blocking the immunosuppressive activity, may provide promising therapeutic efficacy. In this context, a clinical trial (no. 2015-002525-19) was conducted on prostate cancer patients, which consisted of a STAT3 inhibitor (AZD9150), a selective CXCR2 antagonist (AZD5069), and a PD-L1 inhibitor (MEDI4736), and its results demonstrated a significant inhibition of MDSC expansion and function [167].

Moreover, TAMs play a crucial role in inhibiting responses to chemotherapy and checkpoint inhibition in cold tumors. The distribution of TAMs in the cancer microenvironment and their immunoregulatory roles are accompanied by poor clinical outcomes [168]. Interestingly, recently engineered CAR-T cell therapies aimed to target M2 macrophages and focused on a specific receptor, folate receptor beta (FRβ), which could effectively inhibit ovarian tumor growth [169, 170]. However, other strategies targeting TAMs consist mainly of depletion, recruitment inhibition, and reprogramming toward M1 [171]. In this regard, macrophage depletion by pharmacological inhibition of the CSF-1/CSF-1R pathway demonstrated promising results in KRAS-mediated pancreatic tumors resistant to ICB [172]. In addition, inhibition of CCL-2 and anti-CCL-2 antibodies effectively prevents macrophage recruitment in pre-clinical murine models of cold tumors [173]. In addition, in cold preclinical tumor models that were not responding to ICB, the combination of anti-CD40 and anti-CSF-1R antibodies was capable

of turning cold tumors into hot tumors by decreasing immune-suppressive cells [174]. Observations demonstrated that the systemic immune function of cancer patients is approximately normal and that it is unnecessary to boost systemic immune responses, such as peripheral tumor-specific T cells. However, specific strategies to target particular immune dysfunctions may be urgently considered for reactivating anti-tumor immunity [65].

9 | CHALLENGES AND LIMITATIONS

In the field of cancer treatment, immunotherapy has recently brought about notable advancements that are best exemplified by the use of ICIs. Nevertheless, one major problem with ICIs' widespread effectiveness is that they don't work well enough or at all in many tumors. This challenge is, in part, attributed to the dearth of TILs, which substantially constrains the applicability of ICIs [175]. The transformation of these immunologically cold tumors into hot tumors, rendering them more amenable to ICI intervention, stands as an unresolved inquiry within the domain of cancer immunotherapy [175].

In the contemporary landscape of oncology, ICIs, particularly those designed to target PD-1 and PD-L1, have received regulatory approval for the management of diverse malignancies [176–178]. These ICIs have demonstrated remarkable success in certain solid tumors, such as lung cancer and melanoma [178, 179]. However, the efficacy of ICIs is hampered by the stark reality that only about one-third of patients exhibit a favorable response to these therapies [175]. A unique thing about cold tumors is that they don't have any T cells that can get inside them, which makes them resistant to ICIs. These tumors harbor a TME infiltrated by an array of immunosuppressive cells, including stromal cells, M2 macrophages, MDSCs, and Treg cells [180, 181].

Some immunotherapeutic approaches exhibit notable autoimmune side effects, exemplified by the CTLA-4-specific antibody ipilimumab, despite extensive endeavors to disentangle its toxicity from its efficacy and amplify its potential as a regulatory T cell-depleting antibody [182]. The constrained clinical advantages observed in a relatively minor proportion of patients can be attributed to various factors, chief among them being the dearth or restricted infiltration of immune cells within the microenvironment [183].

Within the realm of cancer immunotherapy, while remarkable strides have been made in recent years, several significant challenges persist. These challenges encompass resistance to immunotherapy, the often-encountered issue of toxicity and side effects, and the intricate web of tumor response heterogeneity. In this study, we will delve into each of these facets, unraveling the complexities and shedding light on the latest advancements aimed at overcoming these hurdles in the pursuit of more effective and safer cancer treatment strategies.

9.1 | Resistance to immunotherapy

A conspicuous limitation of current ICB strategies is the refractory nature of certain cancers, notably glioblastoma and pancreatic cancer, which are characterized by diminished intrinsic immunogenicity [184]. Even in malignancies where ICB has exhibited efficacy, such as melanoma, the attainment of robust and enduring responses has been confined to a subset of patients. For a considerable portion of individuals, the initial response to treatment is conspicuously absent, constituting primary resistance. Furthermore, a subset of patients who initially respond positively may eventually succumb to acquired resistance, prompting the imperative need for therapeutic adaptations [184]. We are still learning about the complex mechanisms that make cells resistant to ICB. This is because we are learning more about how the tumor, the immune system, and systemic variables all interact with each other. Notably, there is a growing recognition that environmental factors to which patients are exposed, collectively termed the exposome, can exert a profound influence on their immune responses. This review embarks on an exploration of the mechanisms underpinning resistance to checkpoint inhibitors, categorized into two overarching domains: (1) Host (patient)-intrinsic factors, encompassing tumor-specific and systemic elements, and (2) Host (patient)-extrinsic factors, which encompass the impact of environmental exposome factors [184]. Our objective is to provide an insightful understanding of the intricate web of variables contributing to the complex landscape of response and resistance to ICB.

9.1.1 | Host-intrinsic factors

When we delve into the myriad forces influencing anti-tumor immune responses, we cast a wide net, encompassing both the tumor and the patient. Within the TME, a complex tapestry unfolds, comprising not only the tumor cells themselves but also their secreted products, an array of non-tumor cells, including immune cells and stromal cells, and even the presence of microbes [184]. All of these components have the potential to exert profound influences on the dynamics of tumor immunity and, consequently, the response ICB. Moreover, as we navigate this multifaceted terrain, we must not overlook systemic

factors that hold the capacity to modulate the systemic immune milieu of patients. These systemic influences, which extend far beyond the confines of the TME, emerge as significant contributors to the ultimate outcome of ICB therapy [184].

9.1.2 | Host-extrinsic factors: the exposome

In addition to factors intrinsic to the host, encompassing both tumor-specific and systemic elements, it is imperative to consider external influences on cancer biology and therapeutic responses, including ICB [185]. These external factors, collectively referred to as the exposome, constitute a comprehensive spectrum of non-genetic determinants that wield substantial sway over health and disease outcomes [185].

In essence, the exposome comprises the totality of environmental determinants and their associated biological repercussions across the lifespan. It encompasses exposures stemming from the environment, dietary choices, behavioral patterns, and endogenous biological processes [186]. Within this intricate framework, the exposome encapsulates various facets of our lives, including our residential environments, occupational settings, dietary habits, and the utilization of medications and cosmetics. Furthermore, it extends its reach to encompass psychosocial elements such as chronic stress and the presence of depression or anxiety, all of which bear significant relevance. Going beyond these immediate factors, it becomes apparent that these exposures are inextricably linked to broader societal constructs. These encompass socioeconomic status, educational attainment, access to healthcare and nourishment, the specter of climate change, and even issues of racial injustice and sexual discrimination. In this expansive view, these societal constructs also form a vital component of the exposome [185–188]. In the context of cancer and the response to therapies like ICB, recognizing the pivotal role played by the host-intrinsic factors and exposome is paramount. Its encompassing influence underscores the need for a holistic approach to understanding the intricate interplay between external factors and the host's immune responses in the pursuit of more effective cancer treatments. Both host-intrinsic factors and host-extrinsic factors (representing the exposome) are depicted.

9.2 | Toxicity and side effects

The human immune system operates through an intricate network of regulatory mechanisms, striking a delicate balance between mounting effective responses against pathogens or tumors while maintaining tolerance towards non-tumor self-tissues and even certain beneficial microorganisms [184]. However, the introduction of ICBs can disrupt this carefully maintained equilibrium, potentially causing a breakdown in self-tolerance. This disruption may trigger misguided immune responses directed against non-tumor self-tissues, ultimately culminating in Immune-Related Adverse Events (irAEs), as illustrated in Figure 5 [184].

irAEs encompass a wide spectrum of more than 70 distinct pathological conditions that can affect nearly every organ system within the body. These adverse events impact systems such as the neurological, genitourinary, gastrointestinal, pulmonary, cardiovascular, and integumentary systems [189, 190]. The severity of these pathologies varies significantly, with some irAEs reaching severe or even life-threatening levels in certain cases [191].

irAEs are relatively common, with low-grade effects (Grade 1-2) observed in over 90% of patients, while more severe manifestations (Grades 3-5) can be encountered in 20%-60% of cases [189, 190]. In contrast to toxicities associated with other anti-cancer modalities like chemotherapy and radiation therapy, which often follow a relatively predictable time course, the onset of irAEs is highly variable. Some may manifest within days to weeks after initiating immunotherapy, while others may appear months later. It's worth noting that the scope and intensity of irAEs can diverge among different immunotherapy agents, especially between anti-CTLA-4 agents and anti-PD-1/PD-L1 agents, as well as combination therapies [189, 190]. Presently, the standard approach to managing irAEs typically involves discontinuing ICB and instituting a regimen of high-dose corticosteroids [192–194]. However, research is actively underway to develop more targeted therapeutic strategies [195]. Regardless of the treatment pathway, the successful management of irAEs hinges on early recognition of pathology and a proactive therapeutic strategy, often requiring collaboration among a multidisciplinary team of specialists [192, 194].

Anomalies in T cell activity are considered a central factor contributing to the onset of irAEs. When there are shared antigens between the tumor and healthy tissues, they can activate T cells for the first time. This can have both on-target and off-target effects on the tumor [184]. This phenomenon has been observed in conditions like myocarditis and rash, where infiltrating T cells have been detected not only in the tumor but also within cardiac muscle or skin tissues [196, 197]. The scope of this activation can further expand through a process known as epitope spread. Epitope spread occurs when tumor cell death releases additional antigens into an immune microenvironment. In this setting, T cells can become activated against normal tissue [198, 199].

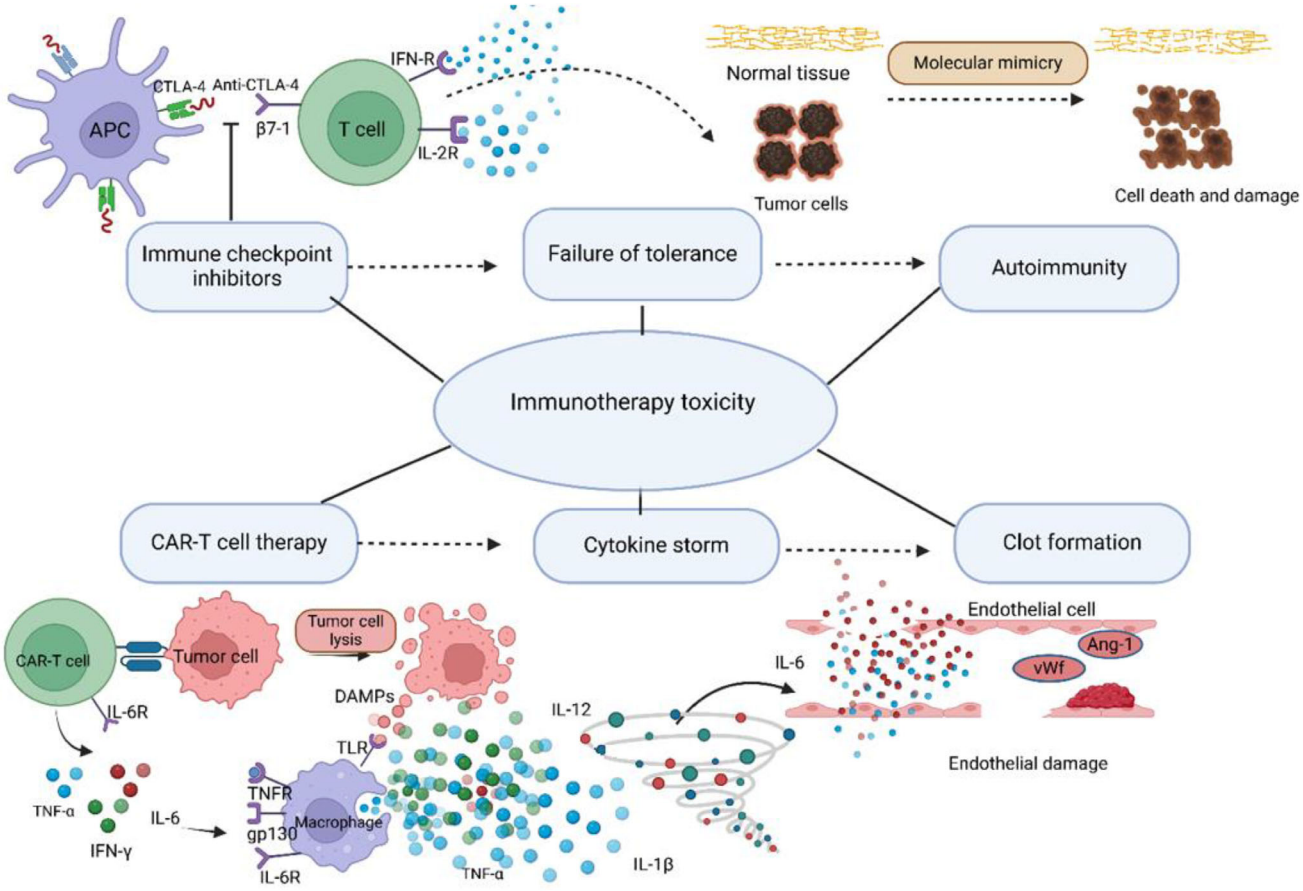

FIGURE 5 Side effects and toxicities of immunotherapy. Illustration depicting the potential side effects and toxicity effects resulting from two cutting-edge cancer immunotherapies ICIs and CAR-T Cell Therapies. ICIs may lead to irAEs characterized by immune dysregulation, affecting non-tumor self-tissues, while CAR-T cell therapies can trigger CRS, and in some cases, thrombosis due to their potent immune activation. These therapies represent promising advances in cancer treatment, yet the management of associated side effects is a crucial aspect of patient care. Abbreviations: Ang-1, angiopoietin-1 APC, antigen-presenting cell; CAR-T cell, chimeric antigen receptor T cell; CTLA-4, cytotoxic T lymphocyte-associated protein 4; DAMPs, damage-associated molecular patterns;gp130, glycoprotein 130; IFN-R, interferon receptor; IFN-γ, interferon-gamma; IL-2R, interleukin-2 receptor; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; IL-12, interleukin-12; IL-1β, interleukin-1 beta; TLR, toll-like receptor; TNF-α, tumor necrosis factor-alpha; TNFR, tumor necrosis factor receptor; vWf, von Willebrand factor.

Additionally, some tissues may already contain autoreactive T cells, which checkpoint molecules normally control. The activation or re-activation of these tissue-resident autoreactive T cells is believed to play a prominent role in the development of irAEs [198, 200]. TCR analysis has revealed that a significant proportion of cytotoxic effector cells observed in ICB-induced colitis originate from tissue-resident $CD8^+$ T cells [200, 201]. The involvement of the humoral immune system and B cells in the development of irAEs has also been proposed. Notably, early alterations in the peripheral B cell repertoire have been linked to treatment-related toxicity [202]. Approximately 25% of patients undergoing ICB therapy for melanoma have been observed to develop new autoantibodies [184]. However, it's worth noting that while autoimmune diseases typically exhibit specific antibody targets, these targets are not consistently observed in irAEs, even when the same tissue or organ is affected [200, 201].

As discussed earlier, CTLA-4 and PD-1 are not exclusive to T cells, and their actions can extend to other components of the immune system. For instance, CTLA-4 is expressed on Tregs, and targeting CTLA-4 could theoretically disrupt or deplete Treg cell function, as seen in mice [203]. However, not all data support this concept in human subjects [200, 201]. PD-1 can also be expressed on certain myeloid cells, and alterations within the myeloid compartment may lead to an influx of inflammatory cells into various distant tissues and organs, potentially inciting organ damage [204, 205]. In cases of ICB-associated colitis and myocarditis, patients have demonstrated a robust and active macrophage infiltrate [200, 201], with macrophages also playing a significant role in ICB-induced diabetes [206].

Lastly, some fewer common effects may be attributed to on-target actions on normal tissue. For example, the proposed mechanism for pituitary dysfunction involves the binding of anti-CTLA-4 agents to CTLA-4 expressed in normal tissue, instigating complement-mediated cell destruction [207]. Interestingly, research has revealed that a polygenic risk score (PRS) designed to assess the risk for conditions like vitiligo, psoriasis, and atopic dermatitis can serve as a predictor of response to ICBs, as demonstrated in bladder cancer cases [208]. Additionally, the detection of immune activation in non-target organs, as indicated by increased metabolic activity observed through positron emission tomography (PET) imaging, has been identified as a predictive factor for response [209].

9.3 | Heterogeneity of tumor response

Genetic heterogeneity within tumors constitutes a significant factor that has been closely associated with suboptimal responses to ICB therapies [210–212]. Tumors are frequently composed of multiple distinct populations of cancer cells, each characterized by a unique repertoire of genetic alterations and phenotypic traits [213–215]. This genetic diversity, often categorized under the umbrella term intratumoral heterogeneity (ITH), is a ubiquitous feature across various cancer types [211]. Extensive research across multiple cancer types has established that tumors characterized by high genetic heterogeneity (high ITH) exhibit a reduced likelihood of responding favorably to ICB treatments [210, 212]. Importantly, studies in murine models have corroborated the notion that heterogeneity can hinder the anti-tumor immune response [216–218].

For example, studies using PDAC models on mice showed that a mix of two different PDAC cell lines – one that makes immune hot tumors and the other that makes immune cold tumors – created an overall immune cold tumor environment. This finding suggests that the immune cold phenotype may dominate in high-heterogeneity scenarios [219]. Additionally, a study in a murine melanoma model demonstrated that high-heterogeneity tumors displayed a notably diminished $CD8^+$ T cell response when compared to low-heterogeneity tumors [219].

10 | CURRENT AND FUTURE DIRECTIONS

For much of the last century, research has primarily been concentrated on exploiting various classes of therapeutics with a sole focus on targeting cancer cells [104]. However, in the past decade, our comprehension of the immune system's pivotal role in orchestrating anti-tumor responses has deepened significantly [220]. This paradigm shift has sparked a revolution across the realms of preclinical, translational, and clinical research, with a dedicated focus on harnessing the immune system's potential for the advancement of novel immunotherapeutic approaches in the field of cancer medicine [220]. Immunotherapy represents a transformative milestone in the realm of oncology, signifying a crucial juncture where the prospect of long-term survival and even lasting cures has become attainable for patients grappling with metastatic solid tumors. Nevertheless, the prevailing reality underscores a significant challenge: a substantial proportion of patients present with immune cold tumors upon seeking medical care. These tumors, regrettably, exhibit poor or even negligible responsiveness to the existing arsenal of checkpoint therapies [221]. In these cancers, immune suppression operates as a formidable barrier, resisting reversion through checkpoint blockade [222]. This resistance stems from the multi-faceted nature of immune suppression, which encompasses factors such as the presence of suppressive cytokines, deficient antigen presentation, induction of T cell apoptosis, and the establishment of hostile metabolic conditions with nutrient deprivation [222]. These levels of immune privilege for tumors are a big problem that needs to be fixed therapeutically in order to get the full benefits of T cell checkpoint blockade, which could eventually lead to tumor regression. As such, a combination of multiple immune interventions becomes imperative to overturn the immune cold tumor state. However, a notable hurdle is that many of the established backbone immunotherapies have already approached the limits of tolerability, even when administered at doses well below their maximum efficacy thresholds [222]. This complexity underscores the pressing need for innovative strategies to enhance the effectiveness of immunotherapies and broaden their applicability in the pursuit of durable responses in patients with immune-resistant tumors [222]. Enhancing our understanding of the intricate mechanisms governing both the response to immunotherapies and the development of resistance represents the pivotal next phase in the advancement of immunotherapeutic strategies for the future. This deeper insight is fundamental to the development of more effective and targeted approaches, ultimately striving for improved outcomes in the field of cancer immunotherapy.

10.1 | Combination therapies

In more recent times, the advent of ACT, exemplified by approaches like CAR-T cells, has emerged as a highly effective therapeutic option, particularly in hematological

malignancies [223]. The way ICBs work is by boosting anti-cancer immunity that has been weakened. On the other hand, CAR-T cells work differently because they don't need to present antigens or prime T cells. Instead, they directly target cancer cells, offering a potent and precise means of attacking malignancies. However, even after administration, ACT remains subject to the challenges posed by downstream resistance mechanisms, particularly within the TME [223]. Along with ICBs and ACT, researches are also looking into new immunotherapeutic strategies that might help treatments work better and/or lessen the harmful effects on the immune system. These innovative approaches hold promise for expanding the scope and impact of immunotherapy in the ever-evolving landscape of cancer treatment [223].

At the China Cancer Immunotherapy (IO) Meeting 2020, Dr. Charles Drake from Columbia University and Dr. James Gulley from the National Institute of Health engaged in discussions regarding strategies to target cytokines and explore various combinations for cancer immunotherapy. Dr. Drake initially highlighted serendipitous findings from a clinical trial involving an anti-IL-1β monoclonal antibody, canakinumab. This antibody, administered at 300 mg every three months, demonstrated a notable reduction in the relative risk of overall cancer incidence (0.49) and fatal lung cancer (0.23) when compared to the placebo cohort [224]. These findings suggested a potential protective effect of canakinumab. His team further confirmed that an anti-IL-1β antibody, particularly in conjunction with an anti-PD1 antibody, led to a significant increase in M1 macrophages and the M1/M2 macrophage ratio within the TME [225]. Subsequently, a pilot clinical trial was initiated to assess the efficacy and molecular correlates of kidney cancer (ClinicalTrials.gov Identifier: NCT04028245). Dr. Drake also covered how androgen deprivation therapy (ADT) in prostate cancer can have a significant impact on cytokines, opening the door to targeted cancer therapy. In mice, ADT notably increased the expression of CXCL15, which is analogous to human IL-8. Neutrophils and polymorphonuclear MDSCs (PMN-MDSC) are thought to get into the immunosuppressive TME through this cytokine pathway [223]. Building on these findings, a clinical trial was initiated, combining the anti-PD1 antibody nivolumab with an anti-IL-8 antibody to synergize with ADT in prostate cancer (ClinicalTrials.gov Identifier: NCCT03689699) [226]. Recently, there has been substantial interest in cytokine-based bifunctional molecules. These molecules take advantage of the immunoregulatory properties of cytokines while adding extra parts that carry the cytokine to where it needs to be to work. For instance, RO6874281 has a different type of IL-2 (IL-2v) that doesn't bind to the high-affinity IL-2 receptor α but does bind to IL-2R$\beta\gamma$. IL-2v is conjugated to a human monoclonal antibody directed against fibroblast activation protein-alpha (FAP-α) on CAFs [227]. Both RO6874281 and bintrafusp alfa have shown clinical activity with reduced toxicity. In a phase I trial with bintrafusp alfa as a second-line treatment for non-small cell lung cancer (NSCLC), an overall response rate of 21.3% was observed in the study population [228].

10.2 | Personalized immunotherapy approaches

Personalized medicine, also known as individualized medicine, is a medical approach that involves tailoring specific treatments and therapeutics to suit the unique characteristics of an individual patient. This consideration encompasses both genetic and environmental factors that influence how a person responds to therapy [229]. The term precision medicine is often used because it signifies that diagnostic, prognostic, and therapeutic strategies are precisely customized to meet the specific requirements of each patient. However, it is important to note that personalized medicine extends beyond genomic and proteomic technologies; it also incorporates other advanced techniques, such as metabolomics. Personalized medicine, which is driving the integration of various biotechnologies into medicine, improves patient management and deepens our understanding of the underlying mechanisms of the disease. Cancer stands out as a particularly crucial field for the application of personalized medicine. This is not only due to the significant variations observed among individual patients but also because tumors with the same histological diagnosis can exhibit diverse characteristics that necessitate tailored treatment approaches [229].

Anti-PD-1/PD-L1 therapy can help predict how different types of cancer will respond by looking at a number of important factors connected to neoantigens, immune checkpoints, and immune responses. To achieve this, comprehensive data from whole-exome and RNA sequencing of patients sourced from the publicly available Cancer Genome Atlas, combined with objective response rate data from a collection of clinical trials, have been rigorously examined [230].

Out of these factors, the number of $CD8^+$ T cells was found to be the most accurate predictor of how well anti-PD-1/PD-L1 therapy would work in different types of cancer. The TMB and the high expression of the PD-1 gene followed this closely. When these three variables are combined, they exhibit a strong correlation with over 80% of the variation in treatment response observed across diverse tumor types [229].

10.3 | Role of neoantigens in personalizing cancer vaccines

Neoantigens are mutated proteins that are exclusively expressed in cancer cells and can be recognized by the immune system. These tumor-specific neoantigens are essentially foreign proteins not found in normal human organs or tissues. They become targets for recognition by neoantigen-specific TCRs when presented in conjunction with MHC molecules [231].

Neo antigens are very important for getting tumor-specific T cells to fight the tumor, which is a key part of how well cancer immunotherapies work. Neoantigen-based personalized therapeutic vaccines and adoptive T cell transfer are two exciting new developments in the field of cancer immunotherapy. The early results from both of these methods are very positive [231]. Instances of mutation-induced neoantigen-specific activation of T cells have been observed in various cancer types, such as lung cancer, head and neck squamous cell carcinoma, colorectal cancer, breast cancer, and lymphomas [232].

Researches can find possible neoantigens in individual cancer cases thanks to the genetic makeup of human cancer and the large amount of genomic information they can get from next-generation sequencing (NGS). The future of cancer vaccines will likely involve a high degree of personalization, involving the identification of both patient-specific immunosuppressive mechanisms and the target neoantigens [233].

To overcome the challenges of immune evasion and resistance in cancer treatment, there is a need to identify novel TAAs and develop innovative strategies. Because mRNA technology is modular by nature, it could be used to make personalized neoantigen vaccines that can boost the immune system's ability to fight tumors. However, selecting the precise neoantigens remains a challenge, requiring the sequencing of the tumor genome, identification of mutations, and prediction of mutations likely to bind effectively to MHCs [234].

One significant advantage of mRNA technology is its capacity to generate patient-specific neoantigen-encoding mRNA directly from sequencing data, eliminating the need for *ex vivo* cell culture or protein engineering. This approach allows for the encoding of multiple neoantigens within a single mRNA molecule, thereby enhancing the vaccine's potency [235]. While there's still a need for definitive studies on cross-species variations in mRNA delivery efficacy and cellular responses to lipid nanoparticles (LNPs), recent research has made strides in addressing these differences and introducing engineered animal models with predictable clinical outcomes to tackle challenges related to cross-species variations [236]. Identifying the factors contributing to low transfection rates in lymphocytes or monocytes and developing strategies to enhance them is crucial for advancing LNP-based mRNA delivery systems in cancer immunotherapy [236].

Through the successful implementation of LNP-based mRNA delivery strategies, there is significant potential to transform the cancer treatment landscape. As research and development in this field progress, it is anticipated that more effective, personalized, and safer therapeutic options will emerge. Ultimately, these advancements aim to not only enhance treatment outcomes but also improve the quality of life for individuals affected by cancer [236].

11 | CONCLUSIONS

The landscape of cancer immunotherapy is dynamic, filled with remarkable breakthroughs, complex challenges, and a promising future. Immunologic modulators, particularly ICIs, have ushered in a new era of cancer treatment, offering renewed hope to patients battling malignancies. However, as we have explored in this comprehensive overview, there are significant hurdles that demand our attention and innovative solutions.

The TIME plays a pivotal role in determining the effectiveness of ICIs. Cold tumors, characterized by a lack of TILs and an abundance of immunosuppressive cells, pose a considerable challenge to immunotherapy. Resistance to ICIs, whether primary or acquired, remains a significant limitation. Host-intrinsic and host-extrinsic factors, including environmental exposome factors, contribute to resistance and necessitate a deeper understanding. irAEs are a complex issue in immunotherapy. Managing these adverse events is crucial for patient safety, and ongoing research aims to develop more targeted therapeutic strategies. Genetic heterogeneity within tumors is associated with suboptimal responses to ICIs. High ITH can hinder the anti-tumor immune response, highlighting the importance of personalized approaches. The future of immunologic modulators in treating cold tumors is bright, with several exciting avenues for exploration. (1) Personalized immunotherapy approaches: precision medicine holds the key to tailoring treatments to individual patients based on their unique genetic and environmental factors. Predictive factors such as $CD8^+$ T cell abundance, TMB, and PD-1 expression are guiding the way towards personalized therapies. (2) Role of neoantigens in personalizing cancer vaccines: neoantigens, tumor-specific mutated proteins, offer promising targets for personalized cancer vaccines. mRNA technology and LNPs are emerging as powerful tools in designing patient-specific neoantigen vaccines. (3) Combination therapies: the synergy of ICIs with ACT and other innovative approaches like cytokine-based bifunctional molecules holds great

promise in enhancing treatment efficacy, particularly in the challenging cold tumor environment.

As we continue to unravel the intricacies of the immune response in cancer, the collaboration of researchers, clinicians, and multidisciplinary teams becomes ever more critical. With ongoing advances in understanding and innovative strategies, we are poised to transform the landscape of cancer immunotherapy. The future holds the potential for more durable responses, improved patient outcomes, and a brighter outlook for those facing the formidable challenge of cold tumors.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Gholam-Reza Khosravi, Samaneh Mostafavi, Narges Ebrahimi, Sanaz Bastan, Roya Safari Gharibvand, and Nahid Eskandari conceptualized the study and wrote the manuscript. Gholam-Reza Khosravi, Samaneh Mostafavi, Sanaz Bastan, and Nahid Eskandari contributed to the drafting of the manuscript. Gholam-Reza Khosravi and Sanaz Bastan edited the final draft of the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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