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Review

Innate immune cells in tumor microenvironment: A new frontier in cancer immunotherapy

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SUMMARY

Innate immune cells, crucial in resisting infections and initiating adaptive immunity, play diverse and significant roles in tumor development. These cells, including macrophages, granulocytes, dendritic cells (DCs), innate lymphoid cells, and innate-like T cells, are pivotal in the tumor microenvironment (TME). Innate immune cells are crucial components of the TME, based on which various immunotherapy strategies have been explored. Immunotherapy strategies, such as novel immune checkpoint inhibitors, STING/CD40 agonists, macrophage-based surface backpack anchoring, *ex vivo* polarization approaches, DC-based tumor vaccines, and CAR-engineered innate immune cells, aim to enhance their anti-tumor potential and counteract cancer-induced immunosuppression. The proximity of innate immune cells to tumor cells in the TME also makes them excellent drug carriers. In this review, we will first provide a systematic overview of innate immune cells within the TME and then discuss innate cell-based therapeutic strategies. Furthermore, the research obstacles and perspectives within the field will also be addressed.

INTRODUCTION

Innate immune cells are the first line of host defense against external pathogens and infections. Recently, innate immune cells in the tumor microenvironment (TME) such as macrophages, dendritic cells (DCs), granulocytes, myeloid-derived suppressor cells (MDSCs), innate lymphoid cells (ILCs), and innate-like T cells (ILTCs) have become a research focus in tumor immunity. These cells are now recognized as critical components of the TME, contributing to its heterogeneity and plasticity. The TME is a highly dynamic and complex ecosystem, comprising all non-cancer cells (including fibroblasts, stromal cells, adaptive immune cells, and innate immune cells, etc.) and non-cellular components (including the extracellular matrix (ECM), signaling molecules, blood vessels, etc.).[1] Innate immune cells in the TME are highly heterogeneous, with both anti-tumor and pro-tumor functions. Innate immune cells primarily inhibit tumor growth through the nonspecific killing of tumor cells or by invigorating adaptive immune responses.[2] However, in the TME, tumor cells, tumor-associated immune cells, and cytokines can change the phenotype of innate immune cells, suppressing their anti-tumor abilities or converting them to a pro-tumor phenotype. Pro-tumor innate immune cells accelerate the progression of tumor cells by directly acting on the tumor cells, inhibiting immune responses, promoting immune evasion, etc.

Over the past two decades, significant advances in adaptive immune cell-based cancer immunotherapy have positioned it as the fourth mainstream cancer treatment after surgery, chemotherapy, and radiotherapy.[3] Among these, immune checkpoint inhibitors (ICIs) and adoptive cell therapies (ACTs) have been widely applied in the clinical setting.[4,5] These therapies primarily target T cells to harness adaptive immunity's anti-tumor capabilities. However, T cell-based immunotherapies face limitations, as eliminating heterogeneous cancer cells through specific killing is challenging. Cancer is a heterogeneous disease, and under the selective pressure of adaptive immunity, tumor subclones with weaker immunogenicity become the main subclones that evade immune-mediated tumor clearance. Therefore, innate immune cells, with their nonspecific killing capabilities, are being developed as targets for tumor immunotherapy. Given the heterogeneity of innate immune cells in the TME, one common strategy is to stimulate their anti-tumor abilities, as exemplified by the development of novel ICIs,

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STING/CD40 agonists, macrophage-based surface backpack anchoring and *ex vivo* polarization, and DC-based tumor vaccines. Additionally, since innate immune cells are naturally recruited to the TME, they have also been engineered to serve as carriers for anti-tumor drugs to enhance the accumulation of drugs in tumors. Furthermore, CAR-expressing innate immune cells such as macrophages, neutrophils, and natural killer (NK) cells are being actively pursued to improve the tumor-targeting and killing abilities of innate immune cells.

In this review, we systematically explore the various types of innate immune cells, delving into their cellular characteristics, origins, or subgroup classifications and further elucidating their unique contributions and effectiveness in influencing tumor progression within the complex landscape of the TME. Furthermore, from the perspective of clinical treatments, we highlight the significant advantages and potential of innate-immunity-based tumor therapies compared to traditional tumor immunotherapies. This underlines the necessity of continued exploration into the multifaceted roles of innate immune cells within the TME and a reassessment of their significance in this context. Lastly, we will discuss the research bottlenecks and perspectives within the field, aiming to develop strategies to overcome the current limitations of immunotherapy.

MACROPHAGES

Macrophages, vital for innate immunity, contribute to tissue stability, organ development, wound healing, and regeneration. Initially categorized into pro-inflammatory M1 and anti-inflammatory M2 types based on function and metabolism,[6,7] further research reveals their extensive diversity and adaptability.[8] Macrophages respond dynamically to environmental stimuli, leading to a spectrum of activation states beyond M1/M2 classifications, now expanded to include M1, M2a, M2b, M2c, and M2d subtypes.[9] Besides their traditional classification, macrophages function as antigen-presenting cells (APCs) and produce various cytokines to orchestrate adaptive immune responses. For example, macrophages can sample, process, and present antigens via major histocompatibility complex class I/II (MHC I/II) to prime antigen-specific $CD8^+$ and $CD4^+$ T cells.[10] It was also reported that pro-inflammatory M1 macrophages can cross-present antigens to prime naive $CD8^+$ T cells and activate memory $CD8^+$ T cells.[11] During chronic infection, M1 macrophages reactivate effector $CD8^+$ T cells and produce IL-12 and IL-23, targeting and eliminating infected or malignant cells.[12] Furthermore, macrophages secrete a variety of cytokines, which play pivotal roles in activating and modulating T cell responses.[13] For example, chemokines secreted by M1 macrophages such as CCL2 (MCP-1), CCL5 (RANTES), and CXCL10 (IP-10) can facilitate the recruitment of NK cells and Th1 cells. The pro-inflammatory cytokines produced by M1 macrophages, including tumor necrosis factor (TNF), IL-1β, IL-6, IL-12, and IL-23, can drive the differentiation of naive T cells into Th1 cells. Additionally, M1 macrophages are instrumental in pathogen and tumor eradication by generating reactive oxygen species (ROS) and reactive nitrogen species (RNS) and by producing inducible nitric oxide synthase (iNOS), which catalyzes the metabolism of arginine into nitric oxide and citrulline.[13] Conversely, M2 macrophages express chemokines like CCL17, CCL22, CCL24, CCL26, CCL11, CCL2, and CCL5, supporting Th2 cell proliferation. Moreover, M2 macrophages secrete immunosuppressive cytokines like IL-10 and TGF-β to facilitate Th2 and regulatory T cell (Treg) development.[13]

In the TME, tumour-associated macrophages (TAMs) are mainly M2 macrophages, with a small portion of M1 macrophages. They are closely associated with tumor initiation, progression, angiogenesis, and metastasis.[14] However, the heterogeneity of macrophage is amplified within the TME. The "M1-M2" dichotomy of macrophages is overly simplistic and cannot adequately describe the complex roles of TAMs. For example, TAMs exhibit both M1 and M2 traits in early lung cancer, diffuse-type gastric cancer, and prostate cancer.[15] Therefore, better understanding the heterogeneity of TAMs in the TME and their roles in immunotherapy is crucial for exploring innovative immunotherapy strategies.

Within the TME, TAMs are the predominant immune cells, exhibiting heterogeneity with functions ranging from anti-tumor to pro-tumor activities. Anti-tumor TAMs, activated by cytokines like IFN-γ, TNF-α, or granulocyte-macrophage colony-stimulating factor (GM-CSF), promote Type 1 T helper (Th1) responses, express specific surface proteins (CD68, CD80, and CD86), and secrete pro-inflammatory molecules to combat tumors.[16] Conversely, pro-tumour TAMs, stimulated by IL-10 or TGF-β, foster Th2 responses, express different protein markers (CD163, CD204, and CD206), and produce anti-inflammatory cytokines, contributing to tumor growth.[17] Notably, the crosstalk between pro-tumor TAMs and cancer cells greatly influences tumor malignancy, metastasis, immune evasion, and TAM polarization. For example, in colorectal cancer (CRC), TAMs highly express the CD155 molecule, present an immune-suppressive phenotype, and promote the invasion and progression of cancer cells. Subsequently, these cancer cells secrete IL-4, encouraging macrophages to express CD155, forming a positive feedback loop that accelerates tumor progression.[18] Similarly, a comparable feedback loop in triple-negative breast cancer (TNBC) also contributes to cancer promotion.[19] Moreover, immune regulatory proteins are indispensable in coordinating TAM polarization and their cancer-promoting activities within the TME. For example, forkhead box protein M1 (FoxM1), as an essential indicator of poor prognosis in cancer patients, can directly upregulate the expression levels of IL1A/1B, vascular endothelial growth factor A (VEGFA), and IL6 after being phosphorylated by mitotic kinase PLK1, thereby recruiting monocytes and inducing the formation of pro-tumor TAMs, promoting immune escape and metastasis of lung adenocarcinoma (LUAD).[20] Monocarboxylate transporter 1 (MCT-1) can induce TAMs to secrete IL-6, promoting the polarization of THP-1 monocytes into pro-tumor TAMs, thereby increasing the malignancy of TNBC cells.[21] In addition, in cervical cancer, it was observed that cancer cells could induce the production of pro-tumor TAMs by highly expressing TIE2 protein (promoting angiogenesis and balancing the vascular microenvironment) through their exosomes, accelerating vascular generation in the TME.[22] These studies demonstrate the role of the TME in directing macrophages toward a pro-tumor phenotype (Figure 1).

Intriguingly, under the complex influences of the TME, TAMs can transition into states with anti-tumor functions. For example, research indicates that $CD4^+$ T cells activated by specific tumor antigens can induce macrophages to adopt anti-tumor characteristics *in vitro* conditions through interaction with MHC II on pro-tumor TAMs. This process could potentially transform the immune-suppressive TME.[23] D-lactic

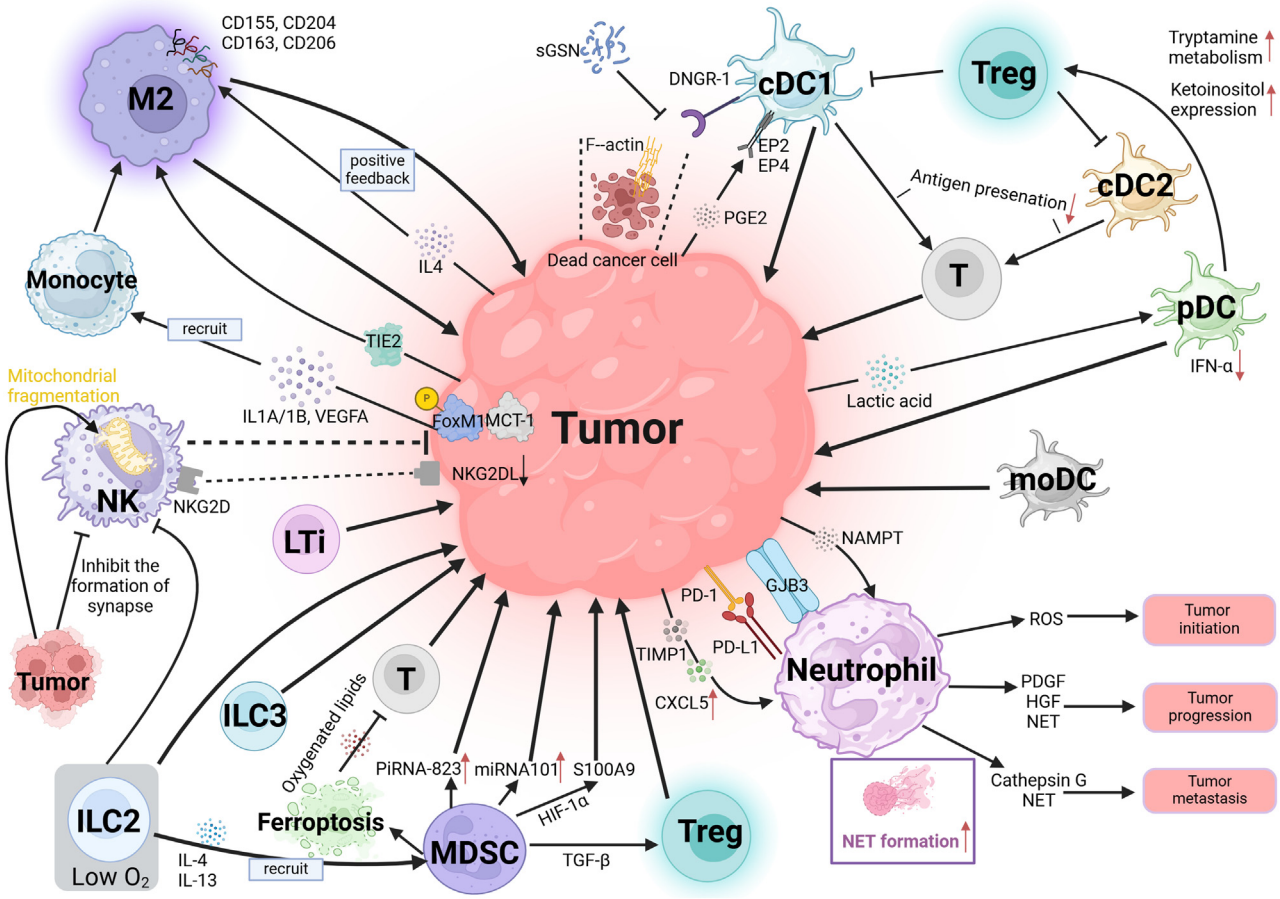

Figure 1. Pro-tumoural roles of innate immune cells within the tumor microenvironment

Macrophages: Pro-tumour TAMs exhibit high expression of specific surface proteins, facilitating tumor progression. Concurrently, tumor cells secrete IL-4, promoting the expression of these surface proteins by macrophages, thus establishing a positive feedback loop. Immune regulatory proteins expressed by cancer cells (such as TIE2, FoxM1, and MCT-1) can induce the formation of pro-tumour TAMs, further enhancing tumor progression. DCs: The sGSN competes with the cDC1 surface receptor DNGR-1 for binding to F-actin exposed to dead cancer cells, inhibiting the cross-presentation of related antigens and impairing the anti-tumor function of cDC1. Similarly, tumor-derived PGE2 operates through a similar mechanism. Tregs can suppress the cross-presentation of antigens by cDC1 and cDC2, promoting tumor progression. Tumor-derived lactic acid, by affecting the amino acid metabolism of pDCs, encourages the production of Tregs while also reducing the expression of IFN-α in pDCs, rendering them an immunosuppressive phenotype. moDCs similarly exhibit pro-tumoral functions in certain tumor types. Neutrophils: Cancer cells interact with neutrophils in various ways, rendering them an immunosuppressive phenotype and inducing the formation of NETs. This interaction allows neutrophils to promote tumor deterioration through the secretion of oxidants, growth factors, Cathepsin G, and NETs. MDSCs: MDSCs can indirectly promote tumor progression by inhibiting T cell activity or fostering the generation of Tregs. Additionally, interactions between MDSCs and cancer cells can directly enhance tumor progression. ILCs: LTi, ILC2s in hypoxic TME, and ILC3s in specific tumor types exhibit pro-tumoural phenotypes. NKs: The TME can suppress NK cell function through alterations in the surface topography, mitochondrial fragmentation, and the absence of ligands for activating receptors, thus facilitating tumor immune evasion. Abbreviations: TME, Tumor Microenvironment; TAMs, tumour-associated macrophages; IL-4, interleukin-4; TIE2, TEK receptor tyrosine kinase; FoxM1, forkhead box protein M1; MCT-1, monocarboxylate transporter 1; DCs, dendritic cells; sGSN, secretory gelsolin; PGE2, prostaglandin E2; Tregs, regulatory T cells; pDCs, plasmacytoid dendritic Cells; IFN-α, interferon Alpha; moDCs, monocyte-derived dendritic cells; NETs, neutrophil extracellular traps; MDSCs, myeloid-derived suppressor cells; ILCs, innate lymphoid cells; LTi, lymphoid tissue-inducer; NKs, natural killer cells.

acid, an intestinal microbe metabolite, and the endogenous immune regulator can transform pro-tumor TAMs to anti-tumor macrophages by regulating the phosphatidylinositol 3-kinase/protein kinase B pathway, hindering the progression of hepatocellular carcinoma (HCC).[24] Additionally, the transcription factor STAT3, known to be overactivated in various cancers, can be targeted and inhibited by miR-506, a microRNA, altering the polarization of macrophages and encouraging the transition from cancer-promoting pro-tumor TAMs to anti-tumor macrophages.[25,26] STING, as a cytoplasmic DNA sensor in the endoplasmic reticulum, decreases endoplasmic reticulum STING content through either its knockdown or activation pathways, which can induce TAM reprogramming to the anti-tumor macrophages, thereby inhibiting the deterioration of gastric cancer cells (Figure 2).[27] These findings underscore reprogramming pro-tumor TAMs into anti-tumor macrophages is a promising therapeutic approach.

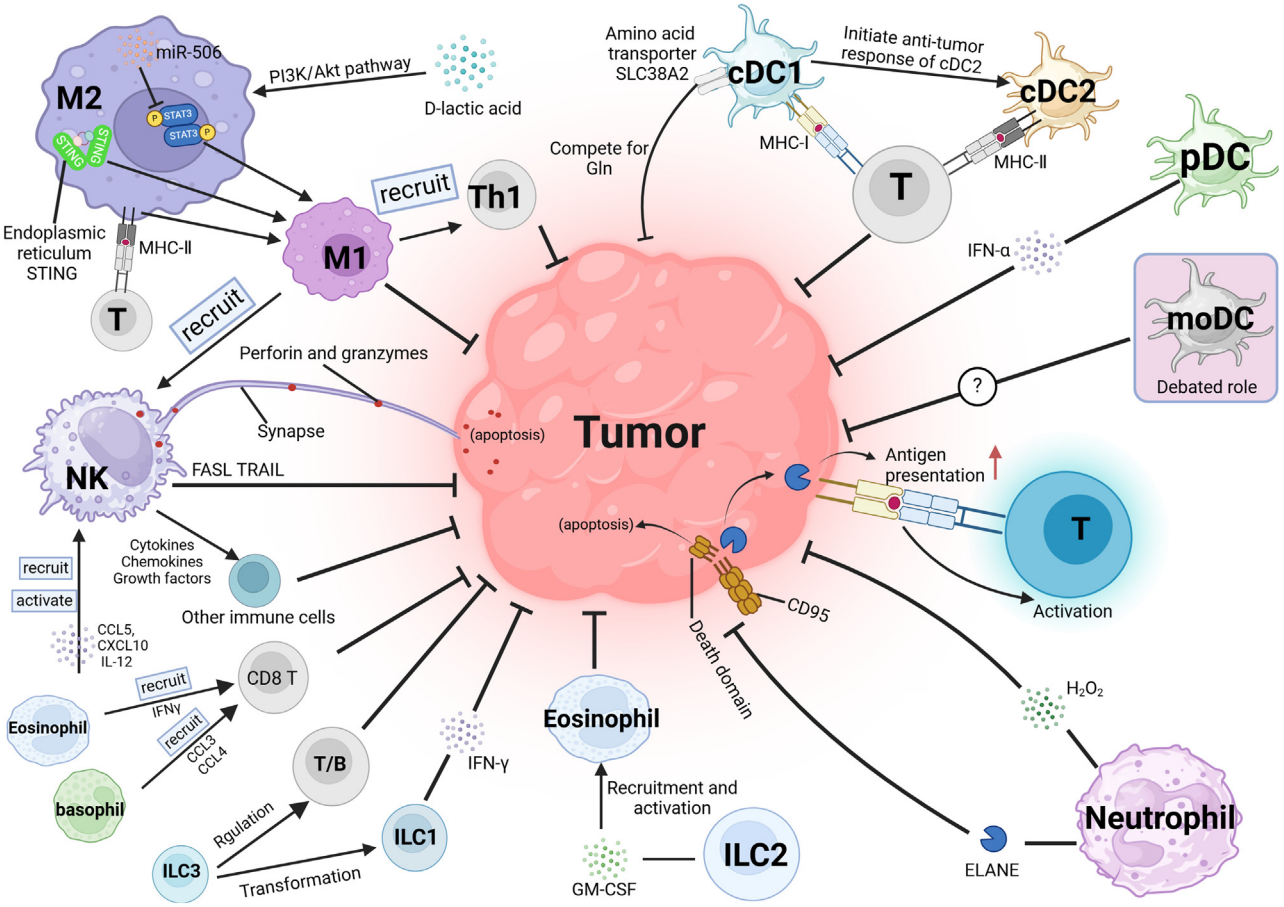

Figure 2. Anti-tumoural roles of innate immune cells within the tumor microenvironment

Macrophages: The polarization of pro-tumor TAMs toward anti-tumor TAMs, which exert anti-tumor functions, can be induced by several factors, including T cells, D-lactate, the suppressed transcription factor STAT3, and a decrease in the endoplasmic reticulum content of STING. DCs: cDC1 competes with tumor cells for glutamate uptake through the amino acid transporter SLC38A2, playing an anti-tumor role. Both cDC1 and cDC2 stimulate the anti-tumor response of T cells through the presentation of tumor antigens. Notably, cDC1 can also induce anti-tumor responses in cDC2. pDCs inhibit tumor progression by expressing IFN-α. However, the anti-tumor potential of moDCs within the TME remains controversial. Neutrophils possess innate cytotoxicity and can exhibit anti-tumor functions by expressing H2O2 and ELANE. ELANE induces apoptosis in cancer cells by hydrolyzing the death domain of CD95 on cancer cells. Additionally, when cancer cells absorb, ELANE can enhance antigen presentation and activate T cells. Innate lymphoid cells: ILC1 and ILC2 can exert anti-tumor effects by expressing relevant factors. Interestingly, ILC3 can limit tumor deterioration by regulating adaptive immune cells and possesses the plasticity to convert into ILC1 for anti-tumor activity. NKs: NKs form synapses with cancer cells and release lytic granules containing perforin and granzymes to activate apoptosis pathways in cancer cells. Similarly, by expressing death receptor ligands (FASL and TRAIL) and binding to death receptors on cancer cells, NKs induce tumor apoptosis. Moreover, NK cells recruit and regulate other immune cells to exert anti-tumor effects by secretion of cytokines, chemokines, and growth factors. Abbreviations: TME, tumor microenvironment; TAMs, tumour-associated macrophages; STAT3, signal transducer and activator of transcription 3; STING, stimulator of interferon genes; DCs, dendritic cells; cDC1, conventional dendritic cell 1; pDCs, plasmacytoid dendritic cells; IFN-α, interferon Alpha; moDCs, monocyte-derived dendritic cells; H2O2, hydrogen peroxide; ELANE, neutrophil elastase; ILCs, innate lymphoid cells; ILC1, innate lymphoid cell type 1; NKs, natural killer cells; FASL, Fas ligand; TRAIL, TNF-related apoptosis-inducing ligand.

Notably, due to the high infiltration of TAMs often associated with poor prognosis in a range of cancers, targeting or eliminating immunosuppressive TAMs can effectively weaken the immune evasion mechanisms of tumors and enhance anti-tumor efficacy. For instance, CD47 (a ubiquitous protein) inhibits the phagocytosis of tumors by macrophages through its interaction with SIRPα (expressed on macrophages). Anti-CD47 antibodies block this interaction, restoring the phagocytic function of macrophages and thereby inhibiting tumor growth and spread. One such anti-CD47 antibody, Hu5F9-G4, has shown promising results in preclinical studies of human acute myeloid leukemia (AML) 41 and pediatric brain tumors.[28] Interestingly, utilizing CAR-T cells to eliminate TAMs are also a promising potential therapy. Recent studies have designed CAR-T cells targeting macrophage markers such as F4/80 and folate receptor β, effectively eliminating TAMs in mouse tumor models and enhancing anti-tumor immunity.[29,30] Moreover, a recent study has highlighted the critical role of TAMs in the dysfunction of mucosal-associated invariant T (MAIT) cells within hepatocellular carcinoma (HCC). By targeting the interaction between TAMs and MAIT cells, particularly the $CSF1R^{+}PD\text{-}L1^{+}$ TAMs, it is possible to reinvigorate the anti-tumor function of MAIT cells.[31]

DENDRITIC CELLS

DCs, critical APCs, bridge innate and adaptive immunity by recognizing tumors and invaders like pathogens and viruses through the membrane or cytoplasmic receptors. They uptake and present non-self-antigens to naive T cells via MHC molecules, stimulating adaptive immune responses. Like macrophages, DCs are heterogeneous and include conventional dendritic cells (cDCs, subtypes cDC1 and cDC2), plasmacytoid dendritic cells (pDCs), and monocyte-derived dendritic cells (moDCs). These classifications are based on tissue localization, phenotypic characteristics, and function. Functionally, cDC1 excels in cross-presenting antigens, which is crucial for processing endogenous and exogenous antigens. It presents tumor and pathogen antigens on MHC I molecules to CD8 T cells, activating anti-tumor and anti-pathogen responses.[32] Conversely, cDC2, with limited cross-presentation capacity, targets exogenous antigens to CD4 T cell subsets (Th1, Th2, and Th17) via MHC II, crucial for responding to extracellular pathogens.[33] In addition, pDCs produce significant type I interferon (IFN-I/α) upon Toll-like receptor (TLR) stimulation, contributing to anti-pathogen and anti-tumor immunity.[34] However, within the TME, the response-ability of pDCs to TLR7/9 activation decreases, impairing IFN-α production and fostering an immunosuppressive environment.[34] Unlike cDCs and pDCs, moDCs are typically not observed under normal conditions but appear in response to inflammation, cancer, or infection. This link to specific conditions leads to their alternative name, inflammatory DCs (inf-DCs).[35]

Immune-tolerant DCs can promote tumor immune evasion and subsequent progression. In the TME, soluble molecules and immunosuppressive factors induce an immune-tolerant phenotype in DCs by regulating transcription and metabolic pathways. For instance, secretory gelsolin (sGSN), as an extracellular protein in animal plasma, can compete with the DNGR-1 surface receptor of cDC1 for F-actin exposed by dead cancer cells, hindering the cross-presentation of dead cell-related antigens dependent on DNGR-1, and damaging the anti-tumor function of cDC1.[36] Moreover, tumor-derived prostaglandin E2 (PGE2), as an immune regulatory factor, upregulates the cAMP signal transduction of cDC1 through its receptors, prostaglandin E2 (EP2) and EP4, diminishing the key cDC1 differentiation factor IRF8 and impairing cDC1 function in tumors.[37] Tregs have immunosuppressive characteristics, and local Treg-DC interactions in the TME are crucial for their immunosuppressive functions. For example, INF-γ, as an immune regulatory factor, increases its expression in the tumor-draining mediastinal lymph nodes (mLN), prompting Treg cells to polarize into TH1-like effector Treg cells, driving them to suppress cDC1 in a spatially coordinated manner, making it unable to induce anti-tumor responses.[38] IFN can also increase the chemokine CXCL9, which is crucial for coordinating immune cells in the TME.[39] The chemokine receptor CXCR3 is expressed on Treg cells, and activated $CXCR3^+$ Treg cells tend to crosstalk with $BATF3^+$ cDC1, which can express CXCL9, thereby inhibiting the cross-presentation of tumor antigen by cDC1 and promoting tumor progression.[40] Despite the predominance of cDC2 in the TME, studies have mainly focused on the cross-presentation of antigens by cDC1, neglecting the tumor-promoting potential of cDC2 due to its lack of distinct membrane markers for identification. However, the significance of cDC2 within the TME should not be overlooked. Similarly to cDC1, the interaction of cDC2 with Treg cells contributes to tumor progression. In the TME of hypoxic HCC, the interplay between Treg cells and cDC2 leads to the loss of the antigen-presenting molecule, human leukocyte antigen-DR isotype (HLA-DR), on cDC2. This loss hinders the activation of T cell anti-tumor functions, promoting an immunosuppressive TME.[41] Similarly, tumor metabolic product lactic acid enhances the tryptophan metabolism and kynurenine expression of pDCs, stimulating the production of immunosuppressive $FoxP3^+$ $CD4^+$ Treg cells. pDCs affected by lactic acid can also undergo pro-tumor reprogramming, causing their IFN-α expression to decrease and presenting an immunosuppressive phenotype.[42] In addition, numerous studies confirm that pDCs usually present an immune-tolerant phenotype and play a pro-tumor role in the TME.[43–45] moDCs, when influenced by the TME, display an immunosuppressive phenotype, leading to tumor malignancy. This has been observed within ovarian cancer, chronic granulocytic leukemia, and chronic lymphocytic leukemia (Figure 1).[46–48]

Immune-activated DCs can promote tumor immune clearance and subsequent suppression. The cDC1 subgroup presents tumor antigens to $CD8^+$ T cells via MHC I, aiming to elicit CTL-guided responses.[49] Research has found that in LUAD, cDC1 maintains the $TCF\text{-}1^+$ $CD8^+$ T cell reserve in the tumor-draining lymph nodes (dLN), exerting anti-tumor functions.[50] Meanwhile, tumor progression correlates with a reduction in cDC1 numbers and functional impairments.[50] It is worth noting that the gene-edited mouse model with Xcr1 defects highlights the significant anti-tumor capabilities of cDC1, exceeding current understanding.[51] This study reveals the crucial role of cDC1 in initiating the anti-tumor response of cDC2 beyond its known cross-presentation activity.[51] In addition to cross-presentation, the co-stimulatory ligands and nutrients of cDC1 are vital for enhancing anti-tumor immunity and tumor rejection reactions. For example, CD40-dependent cDC1 induces the production of co-stimulatory ligands (CD70, 4-1BB) of $CD8^+$ T cells and Bcl2l1 protein that prevents cell death, safeguarding its anti-tumor immunity.[52] In addition, recent studies identify nutrients like glutamine as critical regulators of immune homeostasis, crucial for cDC1 function in the TME.[53] cDC1 competes with tumor cells for the uptake of glutamine through the amino acid transporter SLC38A2, influencing anti-tumor immunity.[53] In the mouse tumor model supplemented with glutamine in the tumor, tumor growth can be inhibited by enhancing the $CD8^+$ T cell immune response mediated by cDC1.[53] Despite its limited capacity compared to cDC1, cDC2 significantly contributes to tumor suppression. For instance, an increase in IL-6 expression in the blood of pancreatic ductal adenocarcinoma (PDAC) patients decreases the number of circulating cDC2s, which is associated with poor prognosis in PDAC patients.[54] Additionally, in HPV16-driven oral cancer, $CD163^+$ cDC2 stimulates type 1 T cell polarization, triggering an anti-tumor response.[55] The anti-tumor function of pDC primarily operates through IFN-α expression, inhibiting tumor proliferation, metastasis, and angiogenesis.[56] For example, studies show $OX40^+$ pDCs, with their immune-stimulating and cytolytic traits, produce IFN-α and collaborate with cDC1 to eradicate head and neck squamous cell carcinomas.[57] Additionally, pDCs can collaborate with NK and $CD8^+$ T cells to combat breast cancer.[58] Despite the debated role of moDCs in tumors like multiple myeloma (MM), research into their anti-tumor potential in the TME continues (Figure 2).[59]

GRANULOCYTES

Granulocytes traditionally include neutrophils, eosinophils, and basophils. Although mast cells contain basophilic granules, they do not originate from the common granulocyte precursor, making their classification controversial. However, given that mast cells share functional similarities with traditional granulocytes in the TME, they are also discussed in this section. The heterogeneity of neutrophils in the TME is a significant focus of tumor immunology research and will be discussed in detail. Additionally, the anti-tumor and pro-tumor roles of eosinophils, basophils, and mast cells will be briefly discussed.

Neutrophils

Neutrophils, the most abundant immune cells in human blood, serve as the first line of defense against microbial infections. Previously, due to the short lifespan and non-differentiation of neutrophils, their role in cancer was overlooked. However, neutrophils are now recognized as critical players in the TME, involved in all cancer development stages. Tumor-associated neutrophils (TANs) show phenotypic diversity in their anti-tumor and tumor-promoting roles. In 2009, Fridlender et al. proposed a binary classification of TANs into anti-tumor ("N1") and tumor-promoting ("N2") types, mirroring the TAMs classification.[60] This classification marked a milestone in TAN research, though recent single-cell analyses suggest it's an oversimplification, with N1 and N2 representing only the extremes.[61,62]

The innate cytotoxic ability of neutrophils is crucial to their anti-tumor capabilities. Tumor-entrained neutrophils (TENs) prevent metastatic seeding in the lungs by producing H_2O_2.[63] Neutrophil elastase (ELANE) released by neutrophils can hydrolyze the death domain of CD95 in cancer cells, inducing their apoptosis. At the same time, when ELANE is taken up by breast cancer cells, it can enhance antigen presentation and activate cytotoxic T cells. These anti-tumor effects can be regarded as an extension of the antibacterial effect of neutrophils (Figure 2).[64]

Multiple aspects of the TME regulate the phenotypic transformation of neutrophils from anti-tumor to pro-tumor. Meng et al. found that cancer cells can secrete nicotinamide phosphoribosyltransferase (NAMPT) to induce $CD10^+ALPL^+$ neutrophils in the TME to stay in an immature state and show immunosuppressive ability, inducing $CD8^+$ T cell exhaustion.[65] In addition to secreting cytokines, cancer cells can also change the phenotype of neutrophils through direct interaction with neutrophils. In PDAC, cancer cells and neutrophils can form a channel through gap junction protein Beta 3 (GJB3), through which cancer cells transfer cAMP to neutrophils, supporting the survival and polarization of neutrophils.[66] In addition, PD-1 expressed by cancer cells can interact with PD-L1 expressed by neutrophils to inhibit the cytotoxicity of neutrophils.[67] Non-cancer cells can also regulate the phenotype of neutrophils. Gong et al. found that lung mesenchymal cells can make infiltrating neutrophils show immunosuppressive manifestations, which can strongly inhibit T cells and NK cells, thereby promoting breast cancer metastasis.[68] The TME can also drive neutrophils to form neutrophil extracellular traps (NETs), a net-like structure with DNA as the scaffold and loaded with cytotoxic proteins. Recent studies have found that NETs play an essential role in tumor development. The tissue inhibitor of metalloproteinases-1 (TIMP1) secreted by the tumor interacts with CD63 of neutrophils in PDAC, triggering the downstream ERK signaling pathway, thereby inducing the formation of NETs.[69] The metabolic transformation induced by tumors enhances the glycolysis and pentose phosphate pathway of neutrophils, which indirectly promotes the production of NETs.[70] In addition, fibroblasts in the TME can secrete collagen to activate the membrane receptor DDR1 of cancer cells, thereby up-regulating CXCL5 expression. CXCL5 will promote the recruitment of neutrophils and the formation of NETs.[71] In addition, TME hypoxia also induces NETs formation (Figure 1).[72]

Following phenotypic transformation, pro-tumour neutrophils facilitate tumor initiation, development, and metastasis via multiple pathways. During inflammation, oxidants secreted by neutrophils will cause DNA damage to epithelial cells and further lead to cancer initiation.[73,74] After cancer initiation, neutrophils can promote the survival and proliferation of tumor cells. Neutrophils can release a series of growth factors, such as platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), etc., promoting cancer cell growth and countering senescence. NETs-DNA can interact with the membrane protein CCDC25 of cancer cells and activate the downstream pathway of cell proliferation.[75,76] NET-associated proteins like MMP9 and NE can remodel the ECM, and the matrix protein after enzymatic remodeling can activate tumor cell proliferation signaling pathways.[77–79] Moreover, neutrophils and the contents related to NETs can secrete pro-angiogenic factors, promoting tumor vasculature formation and nourishing tumor growth.[79] When the tumor grows to a particular stage, neutrophils can increase the invasiveness of the primary tumor. Cathepsin G derived from neutrophils can hydrolyze the ECM of cancer cells to increase the flexibility of cancer cells, which is conducive to the occurrence of metastasis.[76] In addition, in CRC, NETs have also been found to promote the formation of pseudopodia of cancer cells and their movement.[80] When cancer cells enter the circulating blood, NETs released by neutrophils can dilate blood vessels, facilitating cancer cell migration.[81] When the NETs in the blood vessels capture the circulating tumor cells, it can enhance the migration ability and stemness of cancer cells, thereby further promoting tumor metastasis.[82] In addition, neutrophils have been found to accumulate in the lung pre-metastatic niche.[83] On the one hand, the NETs in the pre-metastatic niche can act as a chemokine to recruit cancer cells, and on the other hand, the metastatic cancer cells will enter a dormant state.[75] NETs help to activate dormant cancer cells and promote cancer cells to re-enter the cell cycle (Figure 1).[78]

Eosinophils

Traditionally studied in parasitic infections and allergies, eosinophils also infiltrate various tumors, playing complex roles in the TME.[84] Eosinophils in the TME can exhibit both anti-tumor and pro-tumor activities. Under the influence of IL-5, IL-33, CCL11, IFNγ, and TNF, eosinophils secrete cytotoxic proteins (MBP, ECP, EDN, granzymes, etc.) to induce tumor cell death directly.[85] Eosinophils can also exert anti-tumor functions by promoting NK cell migration and activation by secreting CCL5, CXCL10, and IL-12 and recruiting $CD8^+$ T cells through secreting IFNγ.[84] Conversely, eosinophils can support tumor growth by attracting Treg cells via CCL22 and suppressing effector T cells

through 2,3-dioxygenase (IDO)-mediated tryptophan degradation.[85] Current research on eosinophil function in cancer and cancer therapy is limited, as eosinophils are often "absent" in most single-cell RNA sequencing analyses, hindering the discovery and identification of eosinophil subsets.[84] Future studies are needed to overcome these limitations.

Basophils

Basophils, comprising only 0.5–1% of circulating white blood cells, are vital participants in IgE-mediated responses.[86] Basophils infiltrating various human cancers play dual roles in tumor development. Regarding anti-tumor activities, intratumoral basophils secrete CCL3/CCL4, which recruits $CD8^+$ T cells into the TME, indirectly suppressing melanoma in mouse models.[87] Additionally, basophils secrete TNFα and granzyme B, which can exert direct cytotoxic effects on tumor cells.[86] Conversely, in pro-tumor activities, cancer cells overexpressing galectin-3 (Gal-3) can activate basophils to secrete large amounts of IL-4 and IL-13,[88] promoting macrophage polarization toward M2-like macrophages,[86] indirectly facilitating cancer progression. Moreover, basophil-derived VEGF-A can enhance angiogenesis and promote tumor growth and metastasis.[89]

Mast cells

Mast cells also contain basophilic granules in the cytoplasm and have long been associated with the pathogenesis of allergic and autoimmune diseases. Recent studies suggest that as tissue-resident myeloid cells, mast cells can shape the TME through their potent inflammatory mediators, playing either promotive or suppressive roles in tumor progression.[90] In terms of anti-tumor activities, mast cells act as sentinel immune cells, releasing chemokines such as CXCL10, CCL3, and CCL5, which recruit $CD8^+$ and $CD4^+$ T cells to the TME, further regulating T cell activity through secreting TNF-α. Depending on the stimulated receptors, histamine released by mast cells can induce specific helper T cell subsets or T cell regulatory responses.[90] Activated mast cells have also been shown to upregulate MHC II and co-stimulatory molecules, functioning as local APCs for T cells.[90,91] On the pro-tumor side, mast cells can support angiogenesis, inflammation, and homeostasis, promoting cancer development.[90,92] Mast cells release proteases like tryptase and chymase, which activate matrix metalloproteinases, degrading ECM and surrounding tissue, thus facilitating tumor growth, angiogenesis, and metastasis.[92] Additionally, mast cells secrete VEGF, PDGF-β, and IL-6 to promote angiogenesis, cancer cell proliferation, and tumor growth.[90]

MDSCs

In recent years, MDSCs have become a significant regulator of immune responses in cancer and other pathological conditions. In advanced cancer stages, a subset of mononuclear phagocytes (MNPs) and granulocytes are commonly characterized by immature morphology, markers, and immunosuppressive functions.[93] Fifty years ago, researchers discovered that bone marrow cells could suppress T cell function, leading to their characterization as natural suppressor cells. In the early 2000s, these cells were renamed myeloid suppressor cells (MSCs), associated with immunosuppression in late-stage cancer patients.[93,94] In 2007, the term MDSCs was formally proposed to describe immature and heterogeneous myeloid cells within pathological environments.[95] However, the initial purpose of introducing this term was not to define a new group of myeloid cells but to provide a term that could summarize the function, origin, and heterogeneity of this group of cells.[96] With the development of molecular biology, the definition of MDSCs has been further refined. In mice, MDSCs have consistently been characterized by the simultaneous expression of Gr-1 (anti-Gr-1 monoclonal antibody recognizes common epitopes of Ly6C and Ly6G) and CD11b. Subsequently, based on morphology and molecular biology characteristics, MDSCs were further differentiated into two cell groups: polymorphonuclear-MDSCs (PMN-MDSCs): $CD11b^+$ $Ly6G^+$ $Ly6C^{low}$, accounting for more than 75%; mononuclear-MDSCs (M-MDSCs): $CD11b^+$ $Ly6G^-$ $Ly6C^{high}$, accounting for about 10%–20%.[96] Notably, M-MDSCs have a more vital immunosuppressive ability than PMN-MDSCs. Despite the MDSCs group having heterogeneity and overlap with traditional cell classifications, the significance of MDSCs in clinical and scientific research remains undiminished, underlining the continuous efforts to understand their role, especially within the TME.[93]

MDSCs are crucial in immune suppression and are significantly linked to poor clinical cancer outcomes. MDSCs can release a variety of substances to enhance the stemness of cancer cells and inhibit T cell activity to promote tumor development. PMN-MDSCs can induce the upregulation of piRNA-823, activate DNA methyltransferases (DNMTs), and enhance the growth and stemness of MM cells. The silencing of piRNA-823 in MM cells reduces the stemness of MM stem cells maintained by PMN-MDSCs, potentially reducing tumor burden and angiogenesis in the body.[97] Furthermore, M-MDSCs suppress IL-2 secretion, CD25 expression, and STAT-5 phosphorylation in T cells in a nitric oxide-dependent manner, aiming to inhibit T cell proliferation and activation.[98] Moreover, M-MDSCs induce the generation of immunosuppressive Foxp3 Tregs by releasing TGF-β.[99] Similarly, MDSCs can also cause the expression miRNA101 in cancer cells. miRNA101 then inhibits the co-repressor gene C-terminal binding protein-2 (CtBP2), leading to the upregulation of stem cell core gene expression, and increased cancer cell stemness, metastasis, and tumorigenic potential.[100] In addition, PMN-MDSCs can secrete exosomes containing S100A9 to promote the progression of mouse CRC cells. Under hypoxic conditions in TME, PMN-MDSCs release more exosomes in a dependent manner of a hypoxia-inducible factor 1α (HIF-1α). Clinical data show that human MDSCs enhance the stemness and growth of colorectal cancer cells through exosomal S100A9, with significantly higher levels of exosomal S100A9 in the plasma of colorectal cancer patients compared to healthy subjects.[101] Another study shows that MDSCs can promote tumor progression through "suicide". PMN-MDSCs in the TME will undergo spontaneous death through ferroptosis. Although the presence of PMN-MDSCs is reduced, ferroptosis induces the release of oxygenated lipids. These lipids then inhibit T cell activity, further facilitating tumor progression (Figure 1).

INNATE LYMPHOID CELLS

ILCs lack adaptive antigen receptors produced through genetic recombination and are the innate counterparts of T lymphocytes, primarily residing in tissues.[102,103] ILC1, ILC2, and ILC3 functionally mirror Th1, Th2, and Th17, respectively, while NK cells reflect the function of CD8 cytotoxic T cells. ILCs act in the early immune response, whereas T cell responses take several days due to their clonal expansion process. After several days of immune response, ILCs and T cells can work together and cross-regulate each other. For example, ILCs can express MHC II and present antigens, modulating antigen-specific T cell activity, while interleukin-2 produced by T cells can enhance ILC activity. These cells form a positive feedback loop to amplify the response and inhibit each other by competing for survival factors.[103]

The terminology for ILCs and ILC subsets 2013 grouped ILCs into three categories based on cytokine production and the transcription factors required for their development and function. Group 1 includes NK cells and ILC1s, which depend on the T-box transcription factor T-bet and produce IFN-γ. Group 2 provides ILC2 cells, which rely on GATA3 and RORα and produce type 2 cytokines, mainly IL-5 and IL-13. Group3 includes ILC3 and lymphoid tissue-inducer (LTi) cells, which depend on the transcription factor RORγt and can produce IL-17 and IL-22.[104] With further exploration of ILC heterogeneity and more detailed molecular data on ILC development, the latest classification divides ILCs into five subsets: NK cells, ILC1, ILC2, ILC3, and LTi cells.[103] All five subsets of ILCs have been found to play roles in tumor development, with the most extensive research focused on NK cells. In the following texts, we will discuss the role of NK cells in tumor progression in detail and provide a brief overview of the roles of the other four ILC subsets in cancer.

Unlike T cells, which specifically recognize tumor antigens, the cytotoxicity of NK cells is unique and nonspecific. NK cells identify tumor cells based on the "missing self" principle. NK cells possess two types of receptors on their surface: inhibitory and activating. Inhibitory receptors bind to tumor ligands such as MHC I molecules, which show signals of "self" and prevent NK cell activation. Activating receptors, on the other hand, bind to stress-induced ligands on tumor cells, leading to NK cell activation. A balance between signals regulates NK cell activation from activating and inhibitory receptors. When activating signals are present and inhibitory signals are absent or reduced, NK cells become activated and mediate cytotoxicity against the tumor cells.[105,106]

NK cells primarily inhibit primary tumor growth via apoptosis. Upon recognizing tumor cells, NK cells form synapses, which transport lytic granules from NK cells to tumor cells.[107–109] Lytic granules contain two main killing molecules: perforin and granzymes. Perforin can be inserted into the target cell's plasma membrane and form pores, leading to the osmotic lysis of cancer cells. Meanwhile, granzymes enter cancer cells through the pores, activate caspase signaling pathways, and ultimately trigger cancer cell apoptosis.[108,109] NK cells can mediate targeted cancer cell apoptosis by expressing death receptor ligands FASL and TRAIL, binding to death receptors on cancer cells.[110,111] Beyond apoptosis, NK cells also initiate anti-tumor responses through pyroptosis. For example, NK cells release granzyme A into targeted tumor cells to cleave gasdermin B, releasing its pore-forming activity and mediating cancer cell pyroptosis.[112] Apart from their cytotoxicity, NK cells can also exert anti-tumor effects by secreting cytokines (IFN-γ, IL-13, TNF, etc.), chemokines (CCL3, CCL4, CCL5, CXCL1, etc.), and growth factors (FMS-like tyrosine kinase 3 ligand (FLT3L), GM-CSF, etc.). This helps NK cells recruit and regulate other immune cells. For instance, NK cells release FLT3L in the TME to activate DCs and increase T cell activity, triggering anti-tumor immune responses (Figure 2).[113]

However, tumor cells can escape the surveillance of NK cells by regulating surface ligands. As mentioned before, the recognition of tumor cells is based on the balance between inhibitory and activating ligands presented by cancer cells. Upregulating inhibitory ligands are a theatrical strategy for tumor cells to escape NK surveillance. In most cases, tumor cells reduce MHC I expression to evade T cell-mediated killing. The downregulation of MHC I in melanoma has been shown to be a significant cause of anti-PD-1 immunotherapy resistance.[114] However, when NK cells are co-cultured with melanoma cells, the tumor cells upregulate MHC I to escape NK cell surveillance.[115] Additionally, downregulating activating ligands is another strategy. NKG2D is an activating receptor that binds to tumor cell NKG2D ligands (NKG2DLs), triggering tumor cell destruction.[116] Studies have found that AML stem cells evade NK cell killing by lacking NKG2DL expression.[117] In glioblastoma multiforme (GBM), the overexpression of EZH2-92aa encoded by circular EZH2 coding protein inhibits NKG2DLs, inducing GBM stem cells (GSCs) to evade NK cells (Figure 1).[116]

In addition to suppressed recognition ability, the killing efficiency of NK cells toward cancer cells is also severely affected in the TME. Research has revealed that within the TME, a disruption in serine metabolism precipitates a decline in sphingomyelin (SM) levels in intratumoral NK cells. This metabolic imbalance reduces the number and length of NK cell membrane protrusions, hindering immune synapse formation with HCC cells. This metabolic dysregulation reduces the number and length of cell membrane protrusions, thereby impeding the formation of immune synapses with HCC cells. Consequently, this hampers the cytotoxic capabilities of NK cells.[118] Mitochondrial fragmentation induced by the TME in NK cells is also an essential immune escape mechanism. Hypoxic tumor areas enhance the key signal mTOR-Drp for mitochondrial fragmentation and apoptosis of tumor-infiltrating NK cells (TINK). This leads to NK cell loss and weakened cytotoxicity, thereby driving tumor immune escape.[119]

Research on the role of ILCs in tumor development is less extensive than that on NK cells. As part of group ILCs, ILC1 inhibits the organ metastasis of disseminated cancer cells and shows an anti-tumor phenotype similar to that of NK cells. However, the phenotypes of the other two groups of ILCs exhibit heterogeneity.

Moral et al. reported that ILC2s can infiltrate PDACs to activate tissue-specific tumor immune responses.[120] Furthermore, ILC2s can promote lung cancer metastasis by inhibiting NK cells through IL-5-dependent eosinophils.[121] However, in highly infiltrated melanomas, ILC2s can coordinate the recruitment and activation of eosinophils by expressing GM-CSF, which enhances anti-tumour immune responses.[122] Ye et al. found that in hypoxic TME, ILC2s play an immunosuppressive role in PDACs through reprogramming.[123]

LTi cells can promote the growth of lymphatic vessels in the TME and coordinate the expression of lymphoid cytokines, leading to tumor metastasis within the lymphatic system.[124,125] ILC3s play different functions in various types of tumors. ILC3s in CRC can regulate adaptive

immune cells and the intestinal immune environment, limiting tumor deterioration.[126] Similarly, in the melanoma TME, tumor-infiltrating ILC3s have been found to have the plasticity to transform into ILC1s, have cytotoxicity in humans and mice, and can inhibit tumor progression in mouse tumor models.[127] Preliminary, non-systematic studies have suggested a potential role for ILC3s in accelerating the progression and tissue metastasis of pancreatic cancer, HCC, and breast cancer.[124,128,129] However, understanding the functions and impacts of ILC3s in the progression and metastasis of other tumor types remains limited (Figures 1 and 2).

INNATE-LIKE T CELLS

ILTCs, like ILCs, are tissue-resident lymphocytes that can rapidly respond to environmental changes. ILTCs consist of three key subsets: invariant natural killer T (iNKT) cells, MAIT cells, and γδ T cells. These cells have multifunctional capabilities and rapidly respond to non-peptide antigens through their conserved T cell receptors (TCRs).[130] iNKT cells possess a semi-invariant TCR composed of an invariant α-chain paired with a limited number of TCR β-chains. This TCR is reactive to both self and foreign glycolipid ligands, including α-galactosylceramide (α-GalCer) presented by the MHC I-like molecule CD1d.[131] MAIT cells have a highly restricted TCRα chain paired with a limited set of TCRβ chains and can detect microbial metabolites derived from vitamin B2 (riboflavin) or vitamin B9 (folic acid) presented by MR1.[132] γδ T cells express TCRs consisting of γ and δ chains instead of the conventional αβ chains. They can respond rapidly in an innate-like manner, indicating their potential role as first responders in immune responses.[130]

Although the importance of NK cells in cancer has been known for many years, ILCs and ILTCs have only recently been recognized as significant regulators in cancer immunology. ILTCs can have both pro-tumour and anti-tumor effects, depending on the environment, as the pro-inflammatory cytokines released in the TME induce unique transcriptional profiles in these cells.[130] Regarding anti-tumor activity, unlike ILCs, ILTCs can exert direct tumor-killing effects through TCRs. iNKT cells can be activated by the glycolipid ligand α-GalCer to mediate anti-tumor effects in a CD1d-restricted manner both *in vitro* and *in vivo*. TCR agonists can activate 166 MAIT cells to reduce tumor burden in lung and liver metastasis models.[133] γδ T cells and iNKT cells can recognize tumor cells either through their TCRs or by expressing activating receptors such as NKG2D, NKp30, or NKp44.[134] Additionally, ILTCs can lyse cancer cells by releasing granzyme B and perforin or induce tumor cell apoptosis by expressing TRAIL.[130] Conversely, regarding pro-tumor effects, chronic secretion of IL-16 by ILTCs and ILCs contributes to tumor initiation and progression.[130,135] ILTCs, such as γδ T and MAIT cells, can also secrete TGF-β, promoting tumor immune evasion and poor responses to anti-tumor therapies when perturbed in the TME.[136] Moreover, within the TME, ILTCs can be polarized into a tumor-promoting phenotype in a TCR-dependent manner.[130]

TUMOR IMMUNOTHERAPIES ARE BASED ON INNATE IMMUNE CELLS

Innate immune cells, as crucial components of the TME, can be recruited by tumor cells and possess plastic phenotypes, making them significant targets for cancer therapy. As previously mentioned, innate immune cells within the TME are generally heterogeneous, possessing both anti-tumor and pro-tumor potential. The standard strategy is to stimulate the anti-tumor capabilities of these immune cells or to relieve them from the immunosuppressive effects exerted by tumor cells. Therapies based on this strategy include ICIs, STING/CD40 agonists, macrophage-based surface backpack anchoring and *ex vivo* polarizing, and DC-based tumor vaccines. Taking advantage of the recruitment and proximity of innate immune cells to cancer cells within the TME, these cells can be transformed into carriers of anti-tumor drugs to enhance the targeting and efficiency of the drugs. Additionally, innate immune cells with CARs can further improve the targeting specificity of immune cells, accurately exerting tumor-killing effects.

Immune checkpoint inhibitors

Currently, ICIs have emerged as a frontline therapeutic strategy for both solid tumors and hematological malignancies, marking a breakthrough in the field of cancer immunotherapy.[137] Classic ICIs activate T cells by removing their inhibitory signals, rebuilding anti-tumor responses, and preventing tumor cells from evading immune surveillance. Immunotherapeutic agents, specifically antibodies that inhibit the classical immune checkpoints CTLA-4, PD-1, and its ligand PD-L1, are extensively utilized in the medical field.[137] While classic ICIs show some clinical efficacy, primarily targeting T cells, many patients develop primary or acquired resistance, restricting benefits to a small minority.[137,138] Furthermore, a practical approach to combat drug resistance involves the alteration of drug targets. This leads to the prospect of developing ICIs that specifically target non-T cells. The initiation, progression, and maintenance of T cell effector functions rely on the innate immune system. Therefore, screening out immune checkpoints that consider innate immune cells as the basis may be instrumental in enhancing the clinical treatment efficacy.

Lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin (Ig) and mucin domain-3 (TIM-3), and T cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif (ITIM) domain (TIGIT) are the second wave of immune checkpoints discovered after CTLA-4 and PD-1/L1.[139] Following these, NK Group 2A (NKG2A) and signal regulatory protein alpha (SIRPα) were identified as additional immune checkpoints (Figure 3).

LAG-3 is an inhibitory immune checkpoint protein expressed by $CD4^+$ and $CD8^+$ T cells, NK cells, NKT cells, pDC cells, and B cells under antigen stimulation.[140] LAG-3 can inhibit the cytokine secretion and anti-tumor effects of $CD4^+$ T cells by competing with its highly homologous CD4 to bind MHC II.[141] In addition, LAG-3 can also stimulate the immune suppression function of Treg cells and directly inhibit $CD8^+$ T cells through signal transduction, ultimately exerting an immune suppression function.[142,143] It is worth noting that LAG-3 expressed by pDC is a potential molecular target for restoring anti-tumor immune responses in melanoma.[144] In a phase II/III clinical trial of unresectable or

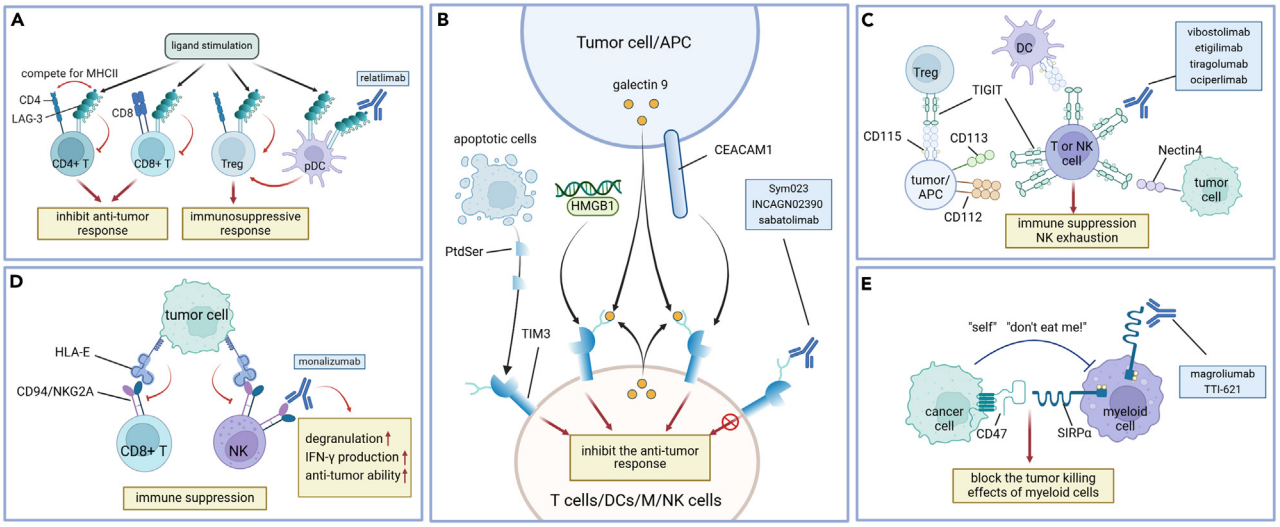

Figure 3. Immune checkpoint inhibitors based on innate immune cells

(A) Upon binding to its ligand, LAG-3 inhibits anti-tumor responses from $CD4^+$ and $CD8^+$ T cells; it can also activate immunosuppressive responses from Tregs directly or through pDC-mediated pathways. Relatlimab is an antibody targeting LAG-3.

(B) TIM3, an inhibitory immune checkpoint receptor expressed on T cells, DCs, macrophages, and NKs, interacts with ligands such as PtdSer, HMGB1, galectin-9, and CEACAM1, leading to the suppression of anti-tumor responses. Antibodies that block TIM3 include Sym023, INCAGN02390, and sabatolimab.

(C) TIGIT, a receptor found on the surface of T or NK cells, interacts with ligands such as CD112, CD113, CD155, and nectin-4, which are present in tumor cells and APCs. This interaction results in immune suppression and NK cell exhaustion. Antibodies that inhibit TIGIT include vibostolimab, etigilimab, tiragolumab, and ociperlimab.

(D) Expressed in $CD8^+$ T cells and NK cells, NKG2A can form a heterodimer with CD94 and bind to HLA-E on tumor cells, leading to immunosuppression. Monalizumab, an NKG2A-blocking antibody, enhances NK cell degranulation and IFN-γ production, thereby strengthening their anti-tumor activity.

(E) Cancer cells express CD47, which binds to the SIRPα receptor on myeloid cells, conveying a "don't eat me" signal that inhibits the tumor-killing capacity of myeloid cells. Magroliumab and TTI-621 are antibodies designed to disrupt the SIRPα-CD47 interaction. Abbreviations: LAG-3, lymphocyte-activation gene 3; DCs, dendritic cells; MDSCs, myeloid-derived suppressor cells; ILCs, innate lymphoid cells; NKs, natural killer cells; pDC, plasmacytoid dendritic cell; Treg, regulatory T cell; TIM3, T cell immunoglobulin and mucin-domain containing-3; M, macrophages; PtdSer, phosphatidylserine; HMGB1, high-mobility group box 1; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; APCs, antigen-presenting cells; NKG2A, natural killer group 2A; HLA-E, human leukocyte antigen E; ICIs, immune checkpoint inhibitors; ACTs, adoptive cell therapies; SIRPα, signal regulatory protein Alpha.

metastatic melanoma, the combination therapy of anti-LAG-3 antibody relatlimab and nivolumab (anti-PD-1 antibody) achieved positive results.[145] Significantly, for patients with primary resistance to anti-PD-1/PD-L1 therapy, the combination of relatlimab and nivolumab plays therapeutic efficacy in the neoadjuvant treatment environment for advanced melanoma and non-pulmonary visceral metastasis (Figure 3).[146]

TIM-3, as an inhibitory immune checkpoint receptor, accelerates tumor proliferation and metastasis by inhibiting the activation of innate immune cells or adaptive immune cells through binding with its ligands (galectin 9, phosphatidylserine [PtdSer], carcinoembryonic antigen cell adhesion molecule 1 [CEACAM1], and high-mobility group box 1 [HMGB1]).[139] TIM-3 is expressed on $CD4^+$ and $CD8^+$ T cells and on tumor-related DCs, macrophages, and NK cells.[147] Although there is currently a lack of understanding of the role of TIM-3 in the previous non-T cells, more studies have shown that TIM-3 still plays a suppressive role in these cells. To date, clinical trials of three anti-TIM-3 antibodies have been completed: Sym023 (NCT03489343, NCT03311412), INCAGN02390 (NCT03652077), and sabatolimab (NCT04812548). They have achieved initial success in the safety and tolerance of monotherapy or combination therapy with other drugs for specific advanced solid tumors or hematological malignancies. In addition, in phase I clinical trial AMBER (NCT02817633), the combination therapy of the novel anti-TIM3 antibody cobolimab and the anti-PD-1 antibody dostarlimab achieved preliminary anti-tumor effects and acceptable tolerance in NSCLC, skin cancer, and peritoneal mesothelioma (Figure 3).[148]

TIGIT is a widely overexpressed inhibitory receptor on $CD4^+$ and $CD8^+$ T cells and is highly expressed in NK cells.[149] TIGIT binds to its ligands CD155 (primary ligand, also known as PVR), CD112, CD113, Nectin4, and Fab2, which are expressed on tumor cells and APCs, causing overall immune suppression of cells.[150,151] TIGIT mediates the exhausted phenotype characteristics of NK cells in the TME, specifically manifested as weakened killing ability, reduced cytokine production, and decreased proliferation function,[152] and has been found to mediate T cell exhaustion in HCC,[153] cervical cancer,[154] and colorectal cancer.[155] At present, clinical trials of monotherapy or combination therapy with anti-TIGIT antibodies and anti-PD-1 antibodies are being explored. It is worth noting that anti-TIGIT antibodies (vibostolimab, etigilimab, tiragolumab, ociperlimab) in the treatment of advanced solid tumors, and these anti-TIGIT antibodies combined with other immunotherapeutic agents (such as pembrolizumab, nivolumab, atezolizumab, and tislelizumab) have shown some clinical benefits.[156–159] However, the efficacy and safety profiles of these anti-TIGIT antibodies necessitate further validation through large-scale clinical trials. Moreover, two

distinct Phase III clinical trials were conducted for lung cancer, one targeting small cell lung cancer (SCLC) and the other NSCLC. These trials investigated the therapeutic effects of the anti-TIGIT antibody, tiragolumab, specifically in combination therapy regimens. Regrettably, the anticipated clinical outcomes were not achieved (NCT04256421 for SCLC, NCT04294810 for NSCLC) (Figure 3).

NKG2A, as a novel immune checkpoint, is an inhibitory receptor on the surface of NK cells. It forms a heterodimeric receptor with CD94 and binds to the non-classical MHC I molecule HLA-E to exert an inhibitory effect on the activity of NK cells.[160–162] Importantly, widespread expression of HLA-E has been found on the surface of several types of human tumor cells.[163] Therefore, monalizumab, as a humanized anti-NKG2A blocking monoclonal antibody, can promote the degranulation of NK cells (a way for NK cells to kill target cells) and stimulate the production of IFN-γ, increasing the anti-tumor effect of NK cells after blocking NKG2A.[164] Interestingly, monalizumab can also amplify the therapeutic effect of other tumor immunotherapies, showing encouraging potential. For example, combining monalizumab and the anti-PD-L1 antibody durvalumab can increase the effector function of NK cells and $CD8^+$ T cells.[163] In addition, in a phase II clinical trial of head and neck squamous cell carcinoma, a combination therapy of monalizumab and cetuximab (an anti-epidermal growth factor receptor (EGFR) antibody) was carried out (NCT02643550). The interim report showed that compared to the overall response rate (ORR) of 13% in early studies of cetuximab monotherapy, the ORR showed a higher 27.5% after combination therapy in 40 evaluable patients (Figure 3).[163,164]

SIRPα is an inhibitory immune receptor carrying ITIM, expressed in myeloid cells (monocytes, granulocytes, DCs, especially macrophages).[165] CD47 is overexpressed not only in normal cells but also in tumor cells. When SIRPα binds to CD47, it produces an immune suppression signal, preventing the immune system from mistakenly attacking itself and helping cancer cells evade immune cells.[166,167] Therefore, blocking or disrupting the CD47/SIRPα pathway, which enhances the phagocytic activity against tumor cells, is currently a research hotspot in tumor immunotherapy and is being actively explored in a clinical context. For example, recently, there have been multiple treatments targeting the CD47/SIRPα pathway for monotherapy or combination therapy with other anti-cancer therapies, such as anti-CD47 antibodies, including magrolimab (NCT04599634) and recombinant fusion protein TTI-621 (NCT02663518) (Figure 3).

Chimeric antigen receptor innate immune cells

Chimeric Antigen Receptor (CAR)-T cells, as a type of engineered immune cell, are created by modifying T cells extracted from patients through *ex vivo* genetic engineering. This enables T cells to express CAR that specifically recognize and attack tumor cells with specific antigens. Currently, CAR-T cell therapy has emerged as a prominent clinical strategy for cancer immunotherapy, achieving significant results in treating hematological malignancies (such as MM, B cell lymphoma, B cell lymphocytic leukemia).[168,169] However, elevated off-target risks, solid tumor physical barriers, and immunosuppressive TME lead to the poorer performance of CAR-T cell therapy in treating solid tumors. At the same time, distinct adverse effects associated with CAR-T cell therapy, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenia, and graft versus host disease (GvHD), pose significant clinical challenges.[170,171] Consequently, these challenges have motivated exploring alternative strategies in immune cell engineering, such as CAR-NK and CAR-macrophage (CAR-M) therapies (Figure 4).

Compared to CAR-T cells, CAR-innate immune cells have shown preliminary success against hematological malignancies in clinical research and have also shown advantages in treating solid tumors. For example, although CAR-T cells target specific cancer antigens through chimeric antigen receptors, they still express their native TCRs. When CAR-T cells are derived from allogeneic sources, they may recognize the MHC of the recipient as foreign. This recognition triggers an immune response against the recipient tissues, leading to GvHD. In contrast, CAR-engineered innate immune cells such as CAR-M, CAR-NK, and CAR-engineered innate T cells do not rely on MHC molecules to recognize and attack target cells, bypassing the primary trigger for GvHD. This characteristic enables the production of off-the-shelf CAR-engineered innate immune cell therapies that can be prepared and made available to multiple patients, enhancing safety and accessibility.[172] Additionally, CAR-NK cells can utilize target-specific killing and innate anti-tumor abilities, killing target-expressing cancer cells through CAR-mediated killing mechanisms and killing target-lacking cancer cells through CAR-independent or innate NK cell toxicity-mediated mechanisms.[173] CAR-M cells rely on phagocytosis, tumor antigen presentation, and tumor infiltration abilities. Therefore, both can effectively kill solid tumors. Currently, clinical trials of CAR-NK are mainly focused on targeting these markers of hematological malignancies: CD19 (NCT05410041, NCT05645601, NCT05667155, NCT05673447, NCT05739227), CD123 (NCT06006403, NCT05574608, NCT06201247), and BCMA (NCT05652530, NCT06045091). At the same time, some clinical trials are actively exploring the application of CAR-NK cells in the treatment of metastatic or recurrent/refractory solid tumors, mainly targeting NKG2D (NCT05528341, NCT05248048, NCT05213195, NCT05776355) and PSMA (NCT03692663). Finally, it is worth noting that two ongoing clinical trials recently registered on clinicaltrials.gov aim to explore the safety and effectiveness of CAR-M cell therapy for HER2-overexpressing solid tumors (NCT06224738, NCT04660929). The conduct of these clinical trials provides valuable experience for us to deeply understand the feasibility and potential of CAR non-T cells in the treatment of cancer (Figure 4).

STING/CD40 agonists

Currently, agonists targeting the immune system have demonstrated significant promise as cancer immunotherapies. Notably, STING and CD40 agonists are crucial in bridging innate and adaptive immune responses, showcasing substantial potential in tumor treatment. Tumor-specific adaptive immune responses, exemplified by $CD8^+$ T cells, rely on IFN-I signaling within APCs. The cGAS/STING pathway, a critical regulator of IFN-I signaling, activates various anti-tumor functions in adaptive immune cells by triggering innate immune signaling pathways.[174] The cGAS/STING pathway responds to pathogenic infections, DNA damage, abnormal cellular replication, and senescence. These processes generate abnormal double-stranded DNA, which is recognized by cGAS, subsequently catalyzing the production of cyclic

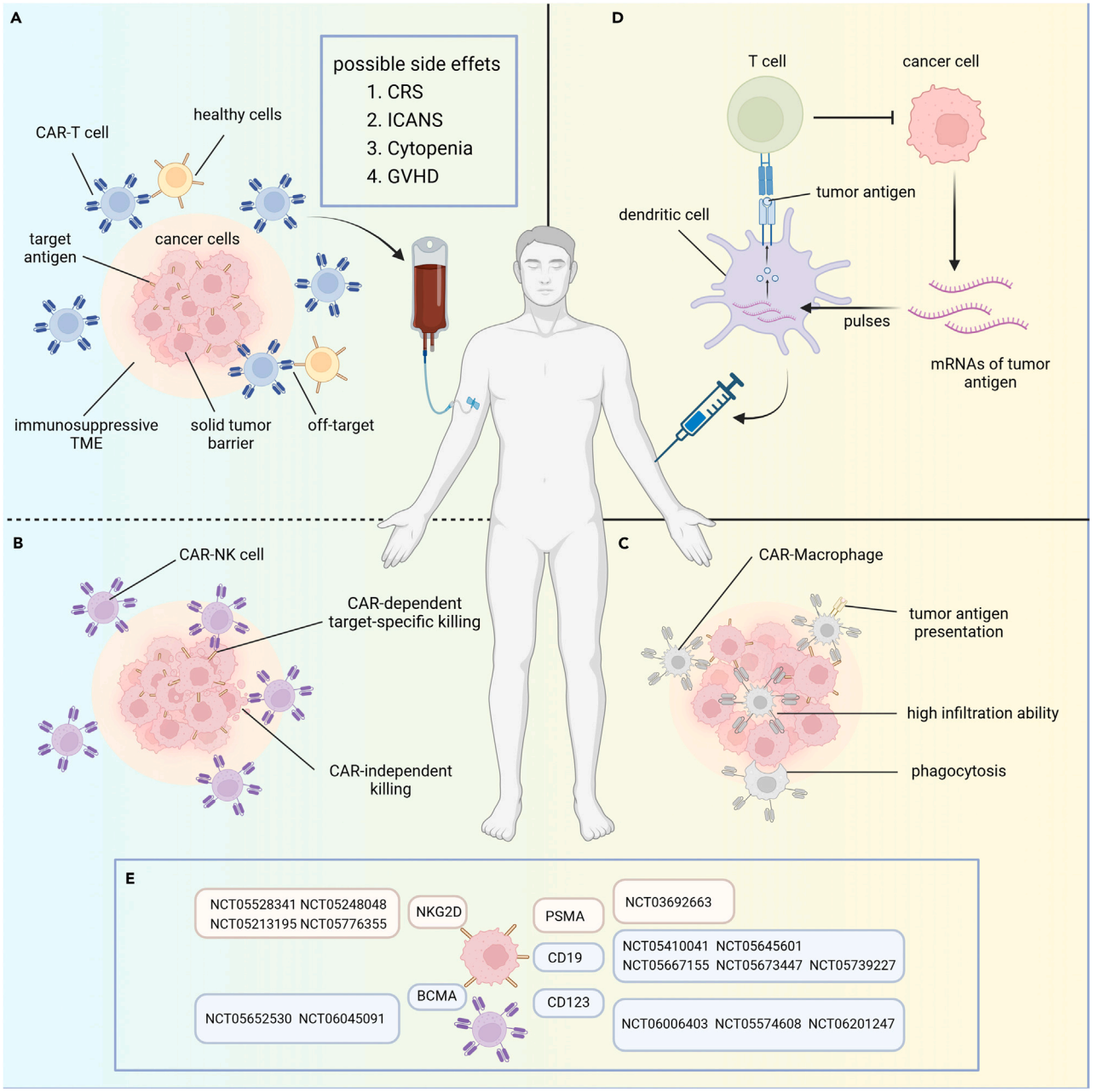

Figure 4. The working principle of novel immunotherapies based on innate immune cells

(A) The efficacy of CAR-T cells against solid tumors is limited due to the immunosuppressive effects of the TME, solid tumor barrier, and off-target risks.

(B) CAR-NK cells exert tumor-killing effects through both CAR-dependent and independent mechanisms.

(C) CAR-macrophages exhibit high infiltration capability and exert anti-tumor effects through tumor antigen presentation and phagocytosis.

(D) Working model of DC cancer vaccines. Tumor antigen-expressing mRNA is pulsed into DCs. The antigen-presenting DCs can activate anti-tumor immunity after being injected into patients.

(E) CAR-NK clinical trials target different tumor antigens. NKG2D and PSMA are antigens of solid tumors, while BCMA, CD19, and CD123 are antigens of hematological malignancies. Abbreviations: CAR-T, chimeric antigen receptor T cell; TME, tumor microenvironment; DCs, dendritic cells; CAR-NK, chimeric antigen receptor natural killer cell; CAR-macrophages, chimeric antigen receptor macrophages; mRNA, messenger RNA; NKG2D, natural killer group 2D; PSMA, prostate-specific membrane antigen; BCMA, B cell maturation antigen; CD19, cluster of differentiation 19; CD123, cluster of differentiation 123.

GMP-AMP (cGAMP). cGAMP binds to the endoplasmic reticulum membrane receptor STING, inducing STING oligomerization and translocation to the Golgi apparatus, thereby recruiting and activating downstream TBK1/IRF3/IFN-I or TBK1/NF-κB signaling cascades.[174,175]

DCs are considered the primary innate immune cells in the TME that produce IFN-I. STING agonists enhance DC-mediated tumor antigen presentation and subsequent anti-tumor $CD8^+$ T cell responses.[174] Additionally, novel STING agonists, such as di-ABZI, MSA-2, and manganese, can enhance the expression of costimulatory molecules and MHC on DCs and improve the ability of DCs to prime and properly activate antigen-specific $CD8^+$ T cells, demonstrating significant anti-tumor potential in tumor models and are currently in clinical trials.[175–179] Notably, manganese, as an STING agonist, can also promote macrophage maturation and tumor-specific antigen presentation, enhancing $CD8^+$ T cell and NK cell activation, thus boosting cytotoxicity mediated by $CD8^+$ T cells and NK cells.[177] Overall, STING agonists mobilize innate immune sensors within the TME for immune surveillance and activate tumor-targeting T cell responses.[2]

CD40, a member of the TNF receptor superfamily, is expressed by various types of immune cells, including B lymphocytes, DCs, and monocytes.[178,179] CD40 activation modulates the TME independently of innate immune sensors such as Toll-like receptors (TLRs) and STING. The ligand of CD40, CD40L (CD154), primarily located on activated T cells, triggers critical immune responses through $CD40^-$CD40L interactions, including licensing DCs to activate $CD8^+$ T cells.[179] It was also reported that $CD8^+$ T cells can upregulate IL-12 expression in DCs via CD40L-CD40 interactions, promoting their proliferation and differentiation and forming a positive feedback loop for anti-tumor activity.[180] Moreover, in epithelial cancers and melanoma, the binding of CD40L to CD40 can mediate immunogenic cell death, activating DCs within the TME.[181,182] Similarly, CD40L stimulation leads to increased secretion of IL-12 by DCs and macrophages, which perpetuates Th1 responses and activates NK cell anti-tumor activity.[183] In macrophages, CD40 receptor ligation increases IFN-γ, TNF-α, T cell-dependent nitric oxide production, and antibody-dependent cellular cytotoxicity (ADCC), contributing to tumor suppression.[179] Additionally, CD40-activated macrophages can induce apoptosis in tumor cells *in vitro*, such as in mouse lymphoma cells (L5178Y).[184] Notably, selicrelumab, one of the most extensively studied CD40 agonists in clinical trials, modulates the TME by inducing DC maturation and macrophage polarization.[185] Although CD40 agonists are still developing, their critical role in activating antitumor immune responses within the TME makes them promising targets for cancer immunotherapies.

Drug delivery based on innate immune cells

Using innate immune cells to deliver anti-tumor drugs is an emerging drug delivery method. Innate immune cells naturally tend to migrate to sites of tissue damage and inflammation, which is the feature of TME. As a result, immune cells are continuously recruited to tumor sites. Additionally, self-recognition signals on innate immune cells ensure that the drugs they carry are not rapidly cleared, thereby improving drug efficacy, extending half-life, reducing immunogenicity, and minimizing off-target effects and related adverse reactions.[186] These characteristics make innate immune cells potentially excellent drug delivery carriers. The application of macrophages and neutrophils in drug delivery has been extensively explored, so this section focuses on these two cell types.[186,187]

As anti-tumor drug carriers, macrophages have natural advantages. They circulate in the bloodstream like red blood cells and neutrophils and target tumor tissues through their α4 and β1 integrins, which bind to vascular cell adhesion molecule 1 (VCAM-1) of cancer cells.[187] Drugs can be directly loaded in macrophages or incorporated into nanoparticles before loading into macrophages.[188] As directly loaded drugs may kill macrophages, the latter approach is more often deployed for macrophage-based drug delivery systems. For example, Choi et al. developed peritoneal macrophages loaded with DOX-liposomes (doxorubicin-loaded liposomes), which showed higher tumor metastasis inhibition than DOX-liposomes alone.[189] Additionally, macrophages can cross the blood-brain barrier (BBB) to deliver drugs to brain tumors. However, challenges such as large-scale production difficulties and quality control issues of human macrophages hinder the clinical translation of engineered macrophages.[188] The strategy of using neutrophils as anti-tumor drug carriers is similar to that of macrophages, including using neutrophils directly as drug carriers and indirect drug carriers (encapsulating drugs in nanoparticles such as liposomes),[190] and using neutrophil-derived exosomes for drug delivery.[191] Neutrophils can also cross the BBB, making them potential drug carriers for treating brain tumors.[192] However, due to their short lifespan and the potential damage caused to healthy tissues through degranulation, the application of neutrophils as drug delivery carriers has certain limitations.[186]

Surface backpack anchoring

In recent years, various strategies have been proposed to regulate the phenotypes of adoptively transferred macrophages to treat tumors, autoimmune disorders, and inflammatory diseases. Recent studies have shown that engineered particles containing IFN-γ, defined as "backpacks", can evade phagocytosis for days and adhere firmly to macrophages, inducing their polarization. This allows the macrophages to maintain their cytotoxicity deep within the immunosuppressive TME, enhancing anti-tumor responses.[193] Similarly, another study developed IFN-γ-modified backpacks to control monocyte differentiation, effectively slowing solid tumor progression due to the intense tumor tissue infiltration of monocytes.[194] Using a similar approach, immunogenic bacteria were used as backpacks to attach to macrophages for the reprogramming of TAMs to provide a more sustained and robust immune response, leading to the inhibition of tumor progression with reduced side effects.[195]

Ex vivo polarization of macrophage

Notably, due to the high heterogeneity and plasticity of TAMs in the TME, altering TAM behavior *in situ* is difficult to control and predict. Alternatively, macrophages are polarized *ex vivo* and then adoptively transferred for tumor control. The first attempt dates back to 1990, when blood monocytes were isolated, cultured with autologous serum, and induced with INF-γ to differentiate into autologous M1

macrophages for tumor therapy.[196] These macrophages effectively targeted and killed tumor cells without harming normal cells *in vivo*. Subsequent studies on activated macrophages using similar principles demonstrated high efficacy against lymphoma, ovarian cancer, and other types of cancer.[197] Importantly, *in vitro* polarized macrophage therapy appears safe, with minimal severe adverse events reported.[198]

Cancer vaccines

Compared to traditional prophylactic vaccines, therapeutic cancer vaccines are designed to target established cancers. They induce an immune response to specific antigens to eliminate tumors and maintain a lasting immune effect to prevent cancer recurrence. Currently, cancer vaccines that are based on the APCs of patients have demonstrated significant potential in the field of tumor immunotherapy. For example, the therapeutic cancer vaccine sipuleucel-T (Provenge) became the first FDA-approved autologous *ex vivo* APC-based cancer vaccine in 2010. It was successful in a phase III clinical trial (NCT00065442) for the treatment of metastatic castration-resistant prostate cancer, ushering in a new era for cancer immunotherapy. Notably, in a recent phase II clinical trial for metastatic castration-resistant prostate cancer, researchers further explored whether the combination of sipuleucel-T and novel hormone drugs (NHAs) could enhance the activation of APCs (NCT05751941).

DCs, as the most effective APCs in the immune system, are used to prepare DC cancer vaccines by loading cancer antigens or transfecting antigen genes. For instance, mRNA *ex vivo* pulsed DC vaccines represent an innovative approach in tumor immunotherapy. The working principle involves using pulses to introduce mRNA, which encodes cancer antigens, into DCs *ex vivo*. This allows the DCs to encode and present the cancer antigens. Subsequently, the DCs mature under *ex vivo* conditions and are reintroduced into the patient's body, triggering an anti-tumor immune response.[199] This method effectively harnesses the immune system of patients to fight against cancer. This type of vaccine has been successfully validated in clinical trials for various types of cancer, especially glioblastoma (NCT00846456, NCT02808364, NCT02366728) and malignant melanoma (NCT01278940, NCT00243529). In current research trends, it is worth noting that clinical trials of DC cancer vaccines are exploring combination treatment strategies with chemotherapy (NCT02649829, NCT02649582), traditional prophylactic vaccines (NCT03615404, NCT03334305), antibody-targeted therapy (NCT00626483, NCT02366728, NCT01876212, NCT00626483), and ICIs (NCT05767684, NCT02529072, NCT0130249) (Figure 4).

CONCLUSION AND PERSPECTIVES

Innate immune cells, tumor cells, adaptive immune cells, and other TME components interact to form a complex ecosystem. This review provides a comprehensive and systematic analysis of the heterogeneity and plasticity of various subgroups of innate immune cells within the TME. We also integrate the current innovative cancer immunotherapies associated with innate immune cells, exploring their clinical features and potential. This emphasizes the importance of expanding our current understanding of the role of innate immune cells in anti-tumor therapy.

Innate immune cells within the TME exhibit significant heterogeneity. In terms of their pro-tumor and anti-tumor phenotypes, except for NK cells, which predominantly have anti-tumor functions and MDSCs, which predominantly have pro-tumor functions, other cell types display both pro-tumor and anti-tumor phenotypes. At the molecular level, nearly all cell types demonstrate heterogeneity. How is heterogeneity generated? From the perspective of immune cells themselves, the transcriptome undergoes continuous changes during their developmental processes. The inflammatory environment of the TME not only recruits mature innate immune cells but attracts immature innate immune cells through various chemokines. These immature immune cells generally activate immunosuppressive signaling pathways, manifesting as pro-tumor phenotypes. Furthermore, the phenotype of immune cells is highly dynamic and susceptible to environmental influences. Interactions between cells (including interactions between immune cells, immune cells and tumor cells, and between immune cells and tissue cells), regulation by cytokines and chemokines, and the chemical environment (such as oxygen concentration, pH, and metabolic products) all contribute to this process. Different environmental stimuli activate different signaling pathways, activating distinct transcription factors, ultimately leading to diverse gene expression patterns. The heterogeneity of immune cells is found not only in their pro-tumor and anti-tumor phenotypes but also at the molecular level, with the development of single-cell resolution techniques. Phenotypic differences fundamentally arise from variations in gene expression, which are reflected in the RNA and protein expression levels. Current techniques for studying heterogeneity include RNA expression analysis (such as scRNA-seq and spatial transcriptomics) and membrane/cytoplasmic protein level analysis (such as flow cytometry, CyTOF, immunohistochemistry, and mass spectrometry). It is important to note that molecular data do not always perfectly correlate with phenotypes. For instance, $CD163^+$ and $CD206^+$ macrophages, typically considered pro-tumor at the molecular level, can stimulate T cell activity in gastrointestinal tumors.[200] Another example is MDSCs, which were initially defined based on their functional phenotypes and later characterized by molecular markers. The PMN-MDSC marker $CD11b^+$ $Ly6G^+$ Ly6Clow does not distinguish them from neutrophils.[96] High-throughput experimental data have shown that MDSC populations exhibit extreme heterogeneity, making molecular definition challenging and leading to skepticism about the existence of MDSC subtypes.[201]

Numerous innate immune cells in the TME form an interconnected system. Cellular interactions are a crucial factor contributing to the heterogeneity of innate immune cells and a key focus and challenge in TME research. Studying cellular interactions involves several key aspects: (1) identifying specific cell types, (2) observing spatial relationships, and (3) determining interaction patterns and pathways. Due to heterogeneity, research on interactions often requires single-cell resolution molecular information.[202] The most relevant samples for studying the TME are surgical specimens obtained from patient tumors. However, dynamic studies cannot be conducted on fixed or frozen tumor tissues.[202] Organoids can partially address the limited availability of patient tumor samples, making genetic manipulation and high-throughput analysis feasible.[203] *In vitro* cancer cell lines are commonly used models for studying cellular interactions in the laboratory. Co-culturing tumor cell lines with innate immune cells allow exploration of their interactions. However, the limited types of co-cultured cells and the inability to

replicate the conditions within the TME do not fully reflect the *in vivo* situation. To mimic the *in vivo* environment, tumors can be subcutaneously transplanted into immunocompromised mice. However, the TME established by transplanted tumors is not as well-developed as that of primary tumors. Additionally, the compromised immune system of these mouse models does not recapitulate the clinical conditions. Traditional microscopy techniques, such as IHC, focus on analyzing the spatial location of cells but are poor at molecular profiling. Techniques based on cell sorting can achieve high-throughput molecular analysis but lose spatial information due to the need for dissociation. New technologies, such as imaging mass spectrometry, cyclic IHC, and imaging-based transcriptomics, can integrate spatial and molecular expression patterns, potentially providing new insights into the interactions of innate immune cells within the TME.[202]

In humans, adoptive cell therapy typically involves primary cells isolated from peripheral blood. However, the limited availability of primary cells and the difficulty in *ex vivo* expansion pose significant challenges to the large-scale clinical application of primary cell-based therapies. Additionally, the variability among donors, the difficulty in isolating tissue-resident cells, and the insufficient number of cells for screening all impact cellular therapy development and drug invention.[204] One common approach to overcome these limitations is using tumor or immortalized cell lines such as THP-1. However, these continuously dividing cells have limited capacity to simulate *in vivo* conditions, typically used for drug screening.[204] Another approach is using human pluripotent stem cells (hPSCs), including human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), which possess self-renewal capabilities and pluripotency, providing an unlimited supply of immune cells.[205] Using hESC or iPSC-derived engineered cell products allows for individual clone isolation and off-target genome alteration detection through whole-genome sequencing. This method also permits the effective addition of multiple genetic modifications to enhance the cytotoxicity of immune cells.[206] Especially, iPSC technology enables the generation of hPSCs without human embryos, addressing tissue incompatibility and ethical issues associated with human ES cells.[207]

iPSC-derived innate immune cells have been studied in therapies involving macrophages, NK cells, and DCs. Zhu et al. engineered a high-affinity, non-cleavable variant of CD16a (hnCD16) into iPSCs to create hnCD16-iNK cells with enhanced ADCC. When combined with therapeutic antibodies, these hnCD16-iNK cells showed significantly improved efficacy against B cell lymphoma and ovarian cancer in xenograft models.[208] The proliferation capacity of myeloid cells, such as macrophages, is quite limited. Haruta et al. transduced genes involved in cell growth or senescence inhibition (e.g., c-MYC, BMI1, MDM2, or EZH2) to generate human iPSC-derived proliferative myeloid cells. These cells can increase for several months and function as iMacs cell[209] or differentiate into iDCs within 2–3 days[210] Engineered iNK and iMacs can not only act directly but also serve as targets for CAR editing to produce CAR-iNKs[211] or CAR-iMacs.[212] iPSC-derived iDCs can be used as precursor cells for DC vaccines.[213] Overall, iPSC-derived innate immune cells offer the opportunity to produce large amounts of well-controlled and ready-to-use products, heralding a new era in tumor immunotherapy.

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AUTHOR CONTRIBUTIONS

J.L. and S.M. designed, supervised, and supported the whole project. C.Li. wrote the manuscript. X.Y., X.H., C.Lian., Z.W., S.S., F.S., and H.W. revised the manuscript. X.Y. contributed to some figures and a few parts of the manuscript. All authors contributed to the review and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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