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Review article

Innate immune cells: Key players of orchestra in modulating tumor microenvironment (TME)

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ABSTRACT

The tumor microenvironment (TME) with vital role in cancer progression is composed of various cells such as endothelial cells, immune cells, and mesenchymal stem cells. In particular, innate immune cells such as macrophages, dendritic cells, myeloid-derived suppressor cells, neutrophils, innate lymphoid cells, γδT lymphocytes, and natural killer cells can either promote or suppress tumor progression when present in the TME. An increase in research on the cross-talk between the TME and innate immune cells will lead to new approaches for anti-tumoral therapeutic interventions. This review primarily focuses on the biology of innate immune cells and their main functions in the TME. In addition, it summarizes several innate immune-based immunotherapies that are currently tested in clinical trials.

1. Introduction

A tumor is not merely a groups of cancer cells, but rather a heterogeneous gathering of host tissue cells, immune-infiltrating cells, extracellular matrix (ECM), and secretory mediators. Together, they generate the TME, which is a complex and continuously evolving entity [1,2]. The TME is predominantly regulated by cancer cells, which control cellular and molecular processes within its structure and surrounding tissues through different signaling pathways [3,4]. Intimate intercellular cross-talk has a key role in the evolution and hemostasis of the TME which is mostly mediated by production of chemokines, cytokines, growth factors and matrix-remodeling enzymes [5]. Cellular components of the TME include stromal cell (such as cancer-associated fibroblasts (CAFs)), endothelial, and malignant, as well as innate and adaptive immune cells which play essential roles in the development of different tumor. Also, noncellular components of the TME include exosomes and the ECM [5–10]. These interactions consequently result in the organization of the tumor, and the TME actively contributes to the progression and maintenance of cancer cells [11].

Immune cells are major components of the TME, and recently it has been reported that tumors are infiltrated by both adaptive and innate immune cells [12–14]. Moreover, there is mutual crosstalk between cancer cells and the TME that result in the recruitment and activation of immune cells in the extracellular space. It has been well documented that cancer progression and proliferation are controlled by the immunosuppressive functions of host immune cells [15,16]. Moreover, several lines of studies have demonstrated

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that immune responses by innate cells not only affect the TME indirectly by regulating T cells functions, but also influence the formation of the TME [3]. Therefore, histopathological findings and biomarkers of the TME and immune system components, particularly the innate part, are crucial for cancer diagnosis and assessment of patients' response to treatment [17].

This review primarily explores the different functions of innate immune cells within the TME as well as the reciprocal crosstalk between these tumor-infiltrated innate cells and other TME components. We additionally examine how these cells may either suppress or promote tumor growth and metastasis. Lastly, it provides a summary of several innate immune-based clinical trials for improving patients' antitumor immunity.

2. Macrophages

Monocyte-derived macrophages are well-known phagocytes with various functions in immune system. Exposure to stimuli signals in TME triggers their differentiation into two phenotypes-inflammatory or classically activated M1 and anti-inflammatory or alternatively activated M2 [18–22]. These cells are necessary for immune homeostasis through various functions such as antigen presentation, pathogen phagocytosis, tissue repair, and wound healing [23]. M1 macrophages polarization is associated with lipo poly saccharide (LPS) and IFNγ that promote antitumor activity. While M2 polarization is related to IL-4 and IL-13 cytokines, which have tumor-promoting effects by producing growth factors, angiogenic mediators, and immunosuppressive agents [24]. Furthermore, M2 macrophages have been categorized into subsets called M2a, M2b, M2c, and M2d. Each subset depends on its specific inducer: for M2a the inducers are IL-10, IL-13, and IL-4; M2b is induced by agonists of TLR; glucocorticoids, TNFα, and IL10 induce M2c; and M2d is induced by adenosine A2A receptor and TLR [25].

The main population of leukocytes infiltrating TME are tumor-associated macrophages or TAMs, that share many properties with M2 macrophages [26]. Many studies have reported that an increased TAM recruitment is associated with a weak prognosis in various cancers such as breast, prostate, ovarian, and thyroid [27–30]. However, the other experiments on prostatic, lung, and colorectal cancers have demonstrated a positive correlation between TAMs and elevated overall patient survival [31–33]. TAMs show characteristics of both M2 and M1 phenotypes within the TME, although the M2 phenotype is more prevalent depending on the type of tumor [3,34]. Multiple lines of evidence have confirmed that the phenotype of TAMs is not fixed, and they can be targeted by different approaches to repolarize into M1 macrophages, which can improve antitumor capacities [35].

There are ample documentation to suggest that macrophages in TME with a high percentage of M2 macrophages exhibit practically no killing activity. Indeed, TME induces a wound-healing subset of M2 macrophages which subsequently result in tumor progression, metastasis, and epithelial-mesenchymal transition (EMT) [34]. Recently, it has been demonstrated that CCL18+ M2 macrophages abundantly found in brain and liver metastatic breast cancer [36].Many features of TME, including cytokine secretion and hypoxia can orchestrate the macrophage polarization and function [37]. For example, TME triggers immunosuppressive responses from M2 macrophages via producing of mediators like IL-4 cytokines. In addition, it has been observed that tumor cells participate in a cross-talk with macrophages by releasing Hedgehog ligands [38]. All of these events lead to a feed-forward loop which retains alternatively activated M2 macrophages within the TME. Thus, interfering with this interaction reprograms the complex entity of TME to a more reactive immune response and reduces the rate of metastasis [39].

3. Neutrophils

Neutrophils, the first responder to different pathogens, are the most abundant leukocytes in circulation and play an essential role in the acute phase of inflammation [40,41]. During tissue damage and infection, they enter the damaged site, release neutrophil extracellular traps (NETs), produce pro-inflammatory mediators and phagocyte the pathogens [42]. Within the TME, neutrophils or TANs (tumor-associated neutrophils) interact with other immune cells and tumor cells through various pathways and have a dual role; serving both an anti-tumoral and pro-tumoral function [43]. Moreover, finding neutrophils in TME is one of the principal indicators of inflammation, which is a major hallmark of cancer [44]. Numerous studies have demonstrated that the TME influences neutrophil differentiation, causing the emergence of different subsets, including pro-tumoral (N2-neutrophil) and anti-tumoral (N1-neutrophil) [43]. In the TME, neutrophils' anti-tumoral or pro-tumoral function depends on the stage and type of tumor. It has been shown that neutrophils possess anti-tumoral and inflammatory properties in the early stages of the disease. However, as the tumor progresses, neutrophils often acquire an immunosuppressive and pro-tumoral phenotype [45,46].

Neutrophils facilitate tumor initiation, growth and metastasis by secretion of VEGF, MMP9/8, and myeloperoxidases ROS [47–49]. In addition, these cells produce arginase 1 (ARG1), ROS, and inducible nitric oxide synthase (iNOS) which reduce the $CD8^+$ T cytotoxic cells [50] and natural killer cells (NKs) [51] function in the TME. Neutrophils also release neutrophil extracellular traps (NETs) within the TME which contain MMPs, neutrophil elastase (NE), and cathepsin G (CG) [52,53]. These mediators decrease the secretion of pro-inflammatory cytokines and enhance the progression and metastasis of tumors [54].

The process of NET formation is known as NETosis. Numerous studies have showed the direct involvement of the TME in NETosis in several cancers including pancreatic and triple-negative breast cancer cells. Indeed, the impact of NET and NETosis on tumor progression is linked to the function of NE, CG, and MMP-9, which are found in NET contents [55,56]. In addition, it has been shown in various studies that NETs can trap the circulating tumor cells, preventing their movement to metastatic site [56–58]. Another pro-tumoral property of NETs was described by Yang et al. They found that the DNA of NETs can attach to a specific receptor on breast cancer cells, enhancing their adhesive capacity, along with their proliferation and invasive potentials [59]. Another study by Teijeira et al. showed that chemokines, released by human colorectal adenocarcinoma cell line, remarkably can promote NETs formation. As a result, NETs trap the tumor cells preserving them from cytotoxicity activity of $CD8^+$ T lymphocytes [60]. Furthermore, it has been

elucidated that NETs can trigger the prometastatic phenotype in the MCF7 cell line by inducing EMT [61]. Collectively, neutrophils have vital role in the TME; thus, targeting or reprogramming these cells can improve antitumor responses in cancer immunotherapy.

4. Myeloid-derived suppressor cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) are heterogeneous population of immature myeloid cells which infiltrate the TME, playing a key role in tumor angiogenesis and progression [20]. MDSCs show immunosuppression capacity, especially on T lymphocytes, thereby abolishing acquired immune responses [62]. Immature myeloid cells, including both MDSCs and DCs, are typically represented as regulatory DCs [63]. It has been shown that constitutive overexpression of STAT3 in these cells disrupts the differentiation process, and subsequently inducing immature phenotype of these cells [64,65].

Based on functional, molecular, and phenotype differences, MDSCs are categorized into two distinct types: polymorphonuclear/granulocytic (PMN-MDSCs or G-MDSCs) and monocytic MDSC (M-MDSC). M-MDSCs are charachtrized by a $CD11b^{+}Ly6C^{high}Ly6G^{low}$ phenotype, while PMN-MDSCs are recognized by a $CD11b^{+}Ly6C^{low}Ly6G^{high}$ phenotype [64,66]. Both types of MDSCs are present in the TME and are recruited by various tumor-derived mediators such as colony-stimulating-factor (CSF) 3, IL-6, and IL-1β. These factors contribute to induce the expression of STAT3 in immature MDSCs, turning them into immunosuppressive cells [67].

Several lines of evidence have been identified that MDSCs in lymphoid organs are mostly constituted of PMN-MDSCs with immunoregulatory features and participate in the suppression of T cells. In the TME, M-MDSCs are the main population of MDSCs and exhibit greater inhibitory activity. Additionally, they are capable of differentiating into TAMs [20]. Recently, a study has showed that tumor-induced hypoxia increased CD45 tyrosine phosphatase activity in MDSCs, leading to decrease differentiation of MDSCs into TAMs through downregulating the expression of STAT3 [67].

MDSCs exert their immunosuppressive activities by different mechanisms and trigger the induction of the premetastatic site. In particular, MDSCs promote angiogenesis and metastatic process via increasing EMT through secretion of IL-6, [68,69]. TME in turn influence the MDSCs and increase their suppressive function. For instance, some factors in TME alter the metabolic program of MDSCs towards fatty acid oxidation, resulting in high secretion of Arg1 and NOS2 [70]. MDSCs show high expression of NADPH oxidase, which plays a crucial role in the generation of ROS, thereby contributing to immunosuppression within the TME [71]. It has been revealed that both PMN-MDSCs and M-MDSCs isolated from colon tumor cells have overexpressed Arg1, iNOS, TGFβ, MMP9, and S100A9 [72]. Thus, targeting these cells through blockade or depletion might lead to successful outcomes in the treatment of cancer.

5. Dendritic cells (DCs)

DCs comprise multiple cell subsets which possess potent antigen-presenting functions and are essential for the activation of the adaptive immune system. Particularly, they play a vital role in T cell antitumor responses [73,74]. Within TME, these cells uptake antigens by pattern recognition receptors (PRRs) in response to damage-related molecular patterns (DAMPs) released from tumor cells. These signals help DCs to trigger tolerance and immunogenicity features in a subset-specific manner [75].

Conventional dendritic cells (cDCs), specially cDC1, participate in the phagocytosis of exogenous and tumor-released antigens, present them on MHC I, and activate $CD8^{+}$ T cells [76]. Moreover, through secretion of IL-15 and IL-12, these cells interact with natural killer (NK) cells to enhance anti-tumor capacity [77]. In turn, NK cells release XCL1 and CCR5 to recruit cDC1 to the TME [78]. The plasmacytoid dendritic cells (pDCs) subset can stimulate the expression of programmed cell death protein 1 ligand 1 (PD-L1) and granzyme B on transformed cells, leading to immune tolerance induced by regulatory T cells [79,80]. Another subset, MoDC or monocytic dendritic cells, cross-present tumor-associated antigens and significantly increase the proliferation of CTL in a mouse model of melanoma [81]. Nevertheless, tumor-associated DCs or regulatory DCs (regDCs) exhibit immunosuppressive features in the TME including low expression of co-stimulatory molecules, elevated expression of metastatic factors, and attenuated cross-presentation abilities. These alterations arise due to the release of IL-10, prostaglandin E2 (PGE2), adenosine, and increased lactate production and hypoxia [82–84].

Previous studies have shown that DCs can induce either tumor progression or immunosurveillance, depending on the microenvironment. For instance, CCR6+ cDCs infiltrate the TME abundantly and become activated to produce proangiogenic mediators in response to tumor vascular endothelial growth factor (VEGF) [85]. In an ovarian mouse model, a decrease in DC number at early stages of cancer is related to tumor progression [86]. As the tumor advances, the hypoxia-activated regDCs obtain tolerogenic features and proangiogenic capacities, such as the release of galectin-1. Galectin-1 eventually binds to neuropilin-1 and VEGFR2, therefore boosting angiogenesis [73,87,88]. Another mechanism of regDCs is Treg activation and expansion via TGFβ production [89,90]. In addition, hypoxia stimulates DCs to induce a Th2 phenotype, preserve an M2 macrophage phenotype, and promote tumor angiogenesis [91]. Even though MDSCs and regDCs have specific activity, their abilities to regulate tumor angiogenesis within the TME are similar to those of N2 neutrophils and M2 macrophages, leading to the generation of several molecules like MMP9, VEGF, and fibroblast growth factor 2 (FGF2) [92]. Overall, targeting MDSCs in the TME provides an opportunity to improve antitumor responses in cancer therapy.

6. Natural killer cells (NK) and natural killer T cells (NKT)

NK cells are effector lymphocytes of the innate immune system which can eliminate virus-infected cells or transformed cells with their cytotoxic function [93,94]. These cells classified as a subtype of innate lymphocyte cell (ILC)-1 [95]. Through process called ADCC (antibody-dependent cell cytotoxicity), these cells produce granzymes and perforin to induce apoptosis in target cells. Also, they secret IFNγ and TNFα to enhance antitumor responses [96]. Generally, two main population of NK cells are identified in human:

$CD56^{dim}CD16+$ and $CD56^{bright}$ $CD16^{-}$. The $CD56^{dim}CD16+$ NK cells comprise 90–95% of the total number of peripheral NK cells population and are characterized by their secretion of perforin, granzymes, and ADCC. These cells play a major role in eliminating transformed cells and suppressing tumor growth and metastasis. Another subtype of NK cells are the $CD56^{bright}$ $CD16^{-}$ NK cells which account for 5–10% of the total circulating NK population and release cytolytic mediators [97,98].

The effect of NK cells on malignant cells is associated with the receptors expressed on the cell surface. The receptors involved in the regulation of NK activation can be broadly classified into two types: inhibitory receptors (like KIRs) and activating receptors (like NKRs). While normal cells do not express ligands for activating receptors, virus-infected or transformed cells express ligands for activating receptors, which ultimately results in NK cells activation [99,100].

The function of NK cells in the TME is impaired, because tumors employ various mechanisms to escape from eliminating by NK cells. These mechanisms include covering themselves in collagen to activate inhibitory receptors and utilizing platelets as a shield to block detection by NKs [101]. Another tumor immune escape mechanism is the down-regulation of activating receptors like natural killer 2 member D (NKG2D) [102]. As a result, these cells are less efficient in destroying tumor cells within TME compared to circulatory NK cells. In addition, both NK populations exhibit decreased secretion of inflammatory mediators and cytotoxic activity in TME and both populations considered as TINK or tumor-infiltrating natural killer cells. Cytokines secreted in the TME can attenuate the antitumor function of NK cells, eventually result in suppression of T cells expansion and an increased pro-tumoral capacities [3]. In addition, many chemokines, such as CCL3, CCL4, CCL5, CXCL8, and XCL1, can be secreted by NK cells, thereby promoting the infiltration of other immune cells to the tumor site to suppress or enhance tumor development [103].

NKT cells, another type of innate immune cells within the TME, express both NK cell markers (like CD56 and CD16) and αβ-T cell receptors for identification of antigens [104]. There are two types of NKT cells, NKT I and NKT II, which are identified by their specific T cell receptor and cytokines. These cells also recognize lipid antigens presented by CD1 molecules. Several lines of experiments have revealed the essential role of NKT cells in defensing against tumors [105,106]. In the context of the TME, NKT cells can have both inflammatory and anti-inflammatory effects. Type I NKT cells have been found to exert anti-tumoral functions, while type II NKT cells have pro-tumoral capacities. For instance, studies have reported that NKT I cells can inhibit the metastasis of cancer cells in breast tumor [107]. While NKT II cells may support MDSCs in a mouse model of B cell lymphoma [108]. In conclusion, targeting NKT and NK cells within TME may provide a novel approach for cancer immunotherapy in the future.

7. Innate lymphoid cells (ILCs)

Innate lymphoid cells (ILCs) are a heterogeneous group of mononuclear cells found in the TME with properties similar to those of NK cells and have recently been recognized as cells associated with tumor suppression and progression [109,110]. These cells can be categorized into three subtypes, namely ILC1, ILC2, and ILC3, based on their secretion of specific cytokines and expression of transcription factors [111,112].

ILC1s have diverse functions, including macrophage activation, cytotoxicity, and immunity to cancer and viruses [113]. ILC1s are also characterized by their antitumor function, which stems from the production of certain inflammatory cytokines, in particular IFN-γ, and the expression of Tbet. Moreover, there are two distinct ILC1 cells including NK ILC1 and non-NK ILC1, based on the presence or absence of eomesodermin, respectively [114,115]. Based on *in vivo* and clinical documents, non-NK ILC1 are involved in either antitumor responses or protumor responses. These cells have tumorigenic capacity and do not express perforin and granzyme. Moreover, non-NK ILCs inhibit tumor cell proliferation and induce tumor apoptosis through the production of TNF-α and IFN-γ [116].

ILC2s have an essential role in defense against helminthes and in the induction of allergy-associated inflammation. ILC2s need retinoic acid receptor-related orphan receptor-***α*** (ROR***α***) and GATA3 for their maintenance and development. These cells are also induced by thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 [117]. Furthermore, ILC2s play an important role in the intestine and lung inflammation by secretion of Th2-related cytokines including IL-5, IL-4, and IL-13 [118]. These cells have been shown to have exhibit either pro-tumoral or anti-tumoral properties depending on the tumor type. Bie et al. revealed that the elevated number of ILC2 in subjects with gastric tumor is associated with immunosuppressive responses mediated by MDSCs, Th2, and macrophages [119]. Similarly, another study suggested that secretion of IL-13 by ILC2 improves MDSCs function to express nitric oxide synthase and arginase, resulting in a suppressive microenvironment characterized by enhanced numbers of regulatory T cells and dimnished numbers of activated NK cells, which eventually leads to tumor development and invasion in a mouse model of breast tumor [120]. In contrast to the above mentioned studies, Ikutani et al. demonstrated that administration of rIL-33 stimulated the induction of IL-5-secreting ILC2, which subsequently increased the migration of eosinophils to the tumor site, therefore inhibited tumor metastasis and augmented tumor cell apoptosis [121].

ILC3s have 3 subgroups including ILC3-lymphoid tissue inducer cells (LTi), NCR- ILC3, and NCR + ILC3, which require RORγt for their function and development [116]. ILC3s release IL-22 and/or IL-17, and functionally promote tumor growth [114]. It has been shown that IL-17 and IL-22 produced by ILC3s induce tumor progression in colon cancer [122]. In addition, ILC3s stimulate the recruitment of Treg, M2 macrophages, and MDSC to establish a pro-tumoral microenvironment in various tumor types [123,124]. Interestingly, ILCs have a high plasticity capacity and can transform into different phenotypes depending on various stimuli and tumor type [125]. For example, ILC3s differentiate into ILC1s upon IL-12 exposure, and ILC1 may convert into ILC3s in response to IL-23 and retinoic acid [126]. For different tumor types, ILC3s are frequently found in colon cancer, ILC2s are implicated in gastric and breast tumor, and ILC1s exert anti-tumoral activity in melanoma cancer [111,120,127]. This plasticity suggests a novel therapeutic approach based on reprogramming of ILC1s and ILC3s.

Table 1
Clinical trials of targeting innate immune cells for cancer immunotherapy.

Innate immune cell	Mechanism of action	Agents	Combination partners	Type of cancer	Main clinical/laboratory findings	Identifier	Ref.
Macrophages	Reducing the number	Anti–CSF–1R antibody (emactuzumab)	Anti-PD-L1 antibody	Patients with advanced tumors	CD8 + TILs increased and TAMs reduced	NCT02323191	[148]
		Anti–CSF-1R antibody (LY3022855)	–	Patients with advanced tumors	TAMs and $CD14^{dim}CD16^{bright}$ levels reduced	NCT01346358	[149]
		Anti–CSF–1R (LY3022855)	–	Patients with metastatic breast cancer or metastatic castration-resistant prostate cancer	Increased level of CSF1 and IL-34.	NCT02265536	[150]
		Anti–CSF–1R antibody (AMG 820)	–	Patients with advanced tumors	Remarkably decreased CD163+, CD68+, and CD206+ skin macrophages	–	[151]
		Anti–CSF–1R antibody (Cabiralizumab)	Nivolumab	Advanced pancreatic ductal adenocarcinoma	Reduced TAM and increased pro-inflammatory cytokines	NCT03336216	[152]
		Anti-TREM2 mAb (PY314)	Pembrolizumab	EOC	Lack of evidence	NCT04691375	–
		Anti–CSF–1 R and VEGFR2 (Chiauranib)	–	Hepatocellular carcinoma	Lack of evidence	NCT03245190	–
	Blocking recruitment	CCR2 inhibitor (PF-04136309)	Gemcitabine and nab-paclitaxel	Metastatic pancreatic ductal adenocarcinoma	Number of CD14+CCR2+ monocytes reduced	NCT02732938	[153]
		CCR2 inhibitor (PF-04136309)	FOLFIRINOX	Pancreatic cancer	Reduced TAM numbers	NCT01413022	[154]
		CCR2/5-inhibitor (BMS-813160)	–	Hepatocellular carcinoma	Lack of evidence	NCT04123379	–
		Anti-CCL2 (Carlumab or CNTO 888)	–	Metastatic castration-resistant prostate cancer	Did not have any effect on the CCL2/CCR2 axis or reveal antitumor capacity	NCT00992186	[155]
		Anti-Ang2 antibody (trebananib or AMG-386)	–	Advanced ovarian cancer	Did not improve progression-free survival	NCT01493505	[156]
		Anti-VEGF/Ang2 bispecific antibody (vanucizumab)	Anti-PD-L1	Patients with advanced solid tumors	Decrease tumor vascularity and increase antitumor activity	NCT01688206	[157]
	Improving the phagocytic killing capacity	CD47 inhibitor (Hu5F9-G4)	Rituximab	Non-Hodgkin's lymphoma	Resulted in a roughly 100% CD47-receptor occupancy on circulatory red and white cells	NCT02953509	[158]
		CD47 inhibitor (Hu5F9-G4)	–	Patients with solid tumors	Full saturation of CD47 on the surface of RBCs	–	[159]
		Agonistic CD40 antibody (selicrelumab)	–	Pancreatic ductal adenocarcinoma	CXCL10 and CCL22 elevated, M2-like TAMs reduced, intratumoral dendritic cells were more mature, and T cell proliferation was increased in TME and circulatory	NCT02588443	[160]
		Agonist CD40 antibody (CP-870,893)	Gemcitabine	Pancreatic ductal adenocarcinoma	Increased recruitment of inflammatory monocytes via CCL2, enhanced IL-12 and IFN-γ secretion	–	[161]
		Selicrelumab (RO7009789)	Atezolizumab	Patients with advanced solid tumors	Lack of evidence	NCT02304393	–
	Inducing macrophage reprogramming	TLR7 agonist (RO7119929)	–	Hepatocellular carcinoma	Stimulate pro-inflammatory polarization in TAM	NCT04338685	[162]
		TLR8 agonist (motolimod)	Pegylated liposomal doxorubicin	EOC	Increased overall survival, and activated innate immunity by increasing inflammatory mediators	NCT01666444	[163]

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Table 1 (*continued*)

Innate immune cell	Mechanism of action	Agents	Combination partners	Type of cancer	Main clinical/laboratory findings	Identifier	Ref.
					including, IL-6, IL-1β, and TNFα.		
		IL-12 (GEN-1)	Paclitaxel and carboplatin	EOC	Increased IL-12, IFN-γ, and number of $CD8^+$ T cells. Reduced immunosuppressive condition in TME	NCT02480374	[164]
		PI3K- inhibitor IPI-549	–	Head and neck squamous cell carcinoma	Lack of evidence	NCT03795610	–
		Arginase inhibitor (INCB001158)	Pembrolizumab	Metastatic/ advanced solid tumors	Increased overall survival	NCT02903914	–
		CCR5 antagonist (Maraviroc)	–	Advanced colorectal cancer	Increased IFN-α2 and IFN-γ.	NCT01736813	[165]
		IDO inhibitors (Epacadostat) versus tamoxifen	–	EOC	No significant difference in efficacy between epacadostat and tamoxifen	NCT01685255	[166]
	–	CAR Macrophages	–	HER2 overexpressing solid tumors	Lack of evidence	NCT04660929	–
Neutrophils	Blocking recruitment	Reparixin or CXCR1/2 antagonist	Paclitaxel	Metastatic triple-negative breast cancer	Improve progression-free survival. There was no significant change in inflammatory cytokines including IL-6, IL-1β, TNF-α, and GM-CSF. But IL-8 levels reduced.	NCT02370238	[167]
		Anti-CXCL12 (Olaptesed pegol or NOX-A12)	Pembrolizumab	Pancreatic and colorectal cancer	Had good safety and increased IL-2, IFN-γ, and IL-16.	NCT03168139	[168]
		PGE2 inhibitor (CR6086)	AGEN2034 (PD-1 inhibitor)	Colorectal cancer	Lack of evidence	NCT05205330	–
	Reducing the number	TRAIL-R2 (DR5) antibody (DS-8273a)	–	Advanced colorectal cancer	Lack of evidence	NCT02991196	–
		TRAIL receptor 2 agonists (Tigatuzumab)	Carboplatin/ paclitaxel	Non-small cell lung cancer	Did not affect the efficacy of carboplatin/paclitaxel	NCT00991796	[169]
	Neutrophil differentiation	C/EBPα activator (MTL-CEBPA small activating RNA)	–	Hepatocellular Carcinoma	Had good safety	NCT02716012	[170]
	Inducing neutrophil reprogramming	LY2157299 monohydrate (a TGFβ inhibitor)	Lomustine	Glioblastoma	Had good safety and efficacy	NCT01582269	[171]
		PI3K inhibitor (Copanlisib)	Nivolumab	Colorectal cancer	Lack of evidence	NCT03711058	–
	Blockade of the immune checkpoint	STAT3 inhibitors (Napabucasin or BBI608)	–	Colorectal cancer	Did not enhance overall survival or progression-free survival. But in pSTAT3-positive patients, overall survival was longer in the napabucasin group compared to placebo group.	NCT01830621	[172]
DCs	–	DC vaccine	–	Glioblastoma	Increased overall survival	NCT00045968	[173]
		FLT3 ligand	Pembrolizumab	Non-Hodgkin's lymphoma, metastatic breast cancer, and head and neck squamous cell carcinoma	Lack of evidence	NCT03789097	–
	Increasing DC activation	TLR9 agonist (SD-101)	–	B-cell lymphoma	Had good efficacy and increased the function of DCs and $CD8^+$ cells	NCT02266147	[174]
		TLR-9 agonist (CMP-001)	Pembrolizumab	Advance melanoma	Increase CXCL10 level in serum	NCT02680184	[175]

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Table 1 (*continued*)

Innate immune cell	Mechanism of action	Agents	Combination partners	Type of cancer	Main clinical/laboratory findings	Identifier	Ref.
		TLR7/8 agonist (NKTR-262)	NKTR-214 and nivolumab	Metastatic or advanced solid tumors	Increased antigen presentation reduced PD-1, and increased number of $CD8^+$ cells	NCT03435640	[176]
		TLR7/8 agonist (MEDI9197)	–	Patients with solid tumors	Increased CXCL11, CXCL10, and IFN-γ.	NCT02556463	[177]
NKs	Improving killing capacity	IL-15 superagonist complex ALT-803	–	Patients with hematologic malignancy	Increased the activation, and proliferation of NK cells	NCT01885897	[178]
		Anti-NKG2A antibody (monalizumab)	–	Head and neck squamous cell carcinoma	Revealed good safety	NCT03088059	[179]
		Anti-NKG2A antibody (monalizumab)	Cetuximab	Head and neck squamous cell carcinoma	Revealed good safety and favorable duration response	NCT02643550	[180]
		Anti-KIR antibody (Lirilumab)	Nivolumab	Bladder cancer	Was safe and well tolerated	NCT03532451	[181]
	–	NK cell adoptive immunotherapy	–	Patients with recurrent/refractory brain tumors	The level of NK cells elevated in CSF	NCT02271711	[182]
		NK cell adoptive immunotherapy	–	Non-small cell lung cancer	Increased the number of NK cells in peripheral blood	–	[183]
	–	CAR NK	–	Acute myeloid leukemia	In vitro cytotoxicity assay revealed the moderate improvement of CD33-CAR NK-92 cytotoxicity against HL60. Did not demonstrate obvious clinical efficacy.	NCT02944162	[184]
MDSCs	Stimulating MDSCs differentiation	Retinoic acid receptor targeting (ATRA)	Pembrolizumab	Advanced melanoma	Decreased the frequency of circulating MDSCs and increased overall survival	NCT03200847	[185]
		STAT3 inhibitor (TTI-101)	–	Advanced solid tumors	Reduced MDSC	NCT03195699	[186]
	Inducing MDSC reprogramming	IL-12 gene therapy (veledimex)	Nivoluman	Recurrent glioblastoma	Reprograms MDSCs into APCs and increased IL-12 production	NCT03636477	[187]
	Blocking recruitment	MET/VEGFR inhibitor (cabozantinib)	–	Advanced melanoma	Decreased MDSC infiltration into TME	NCT00940225	[188]

Abbreviation: **TAM,** tumor-associated macrophages; **TILs,** tumor infiltrating T lymphocytes; **TREM2**, transmembrane protein triggering receptor expressed on myeloid cells 2; **EOC**, epithelial ovarian cancer; **IDO**, indoleamine 2,3-dioxygenase; **Ang2**, angiopoietin-2; **CSF-1R,** colony stimulating factor-1 receptor; **VEGF**, vascular endothelial growth factor; **CAR**, chimeric antigen receptor; **HER2,** human epidermal growth factor receptor 2; **TRAILR2,** TNF-related apoptosis-inducing ligand receptor 2; **DR5**, death receptor 5; **NK**, natural killer cell; **MDSC**, myeloid-derived suppressor cell; **DC**, dendritic cell; **CSF**, cerebrospinal fluid; **KIR**, killer-cell immunoglobulin-like receptor; APCs, antigen presenting cells.

8. Gamma delta (γδ) T lymphocytes

These cells recognize both protein and non-protein antigens on the surface of stressed cells. Also, they contribute to adaptive immunity by inducing clonal expansion and developing memory cells [128,129]. During the early phase of immune responses, γδ T lymphocytes secrete pro-inflammatory mediators like IL-17, TNFα, and IFNγ to activate other immune cells against bacteria, viruses, and transformed cells [20].

γδ T lymphocytes are categorized into two main subsets, Vδ1 and Vδ2 subtypes, which are founded in tissue and peripheral blood, respectively [130,131]. Both subsets possess inhibitory and activating receptors. The activating receptors NKG2D and DNAM-1 (DNAX Accessory Molecule-1) identify ligands on cancer cells to killing them. On the contrary, like Killer Ig-like receptors and C-type lectin receptors function as inhibitory ones that regulate the killing function of γδ T cells [131–133]. Collectively, the balance between activating and inhibitory signals during the interaction of γδ T lymphocytes with tumor cells facilitates the removal of target cells. It has been shown that Vδ2 cells derived from peripheral blood can eliminate ovarian cancer cells *in vitro* and *in vivo* [134].

Another subset of these cells, named γδT17, play a key role in angiogenic process in TME through producing IL-17 [128,135]. IL-17 secretion leads to increased expression of CXCL8 and/or VEGF by malignant cells [136]. Research has revealed the potential of γδT17 cells to maintain MDSCs [137]. On the other hand, mice lacking IL-17 exhibited reduced tumor progression and vascularization rates in TME [138]. In addition, it has been confirmed that IL-17 induces STAT3 and exposure of human umbilical vein endothelial cells (HUVECs) to IL-17 enhanced the generation of microvessels. This study also showed that STAT3 activation resulted in VEGF secretion from non-small cell lung carcinomas (NSCLC) cells in a GIV-associated manner. GIV (Gα-interacting vesicle-related protein) or Girdin, is a protein that involved in processes such as wound healing, macrophage chemotaxis, and tumor metastasis [139]. In addition, it has

been observed that γδT cells are the main source of IL-17 within the TME [138]. Therefore, targeting γδ T lymphocytes may provide a novel therapeutic approach in combination with other common treatments for cancer immunotherapy.

9. Effect of antibody-drug conjugates (ADCs) on the innate immune cells

The concept of antibody–drug conjugates (ADCs) was initially proposed to extend the therapeutic range of monoclonal antibodies (mAb) in combination with cytotoxic drugs. One of the targets of ADCs is neoantigens, which can be described as a self-antigen produced in tumor cells in response to mutagenic factors expressed exclusively by tumor cells [140].

The mechanism of action of ADCs begins when the mAb of ADC binds specifically to cancer cells' antigens. The cells then endocytose the ADC and fuse it to the lysosomes. When the cytotoxic payload is released from the lysosomes by chemical or enzymatic means, apoptosis or cell death is triggered via DNA or microtubule damage [141]. The release of these drugs can cause an alteration in the TME, which may enhance the killing ability of ADCs [142].

It has also been shown that ADCs are implicated in antibody-dependent cell cytotoxicity (ADCC) and antibody-dependent cell phagocytosis (ADCP). These antibodies bind to antigenic epitopes found on tumors or virus-infected cells, whereas FC segments bind to the killer cell FCRs [143]. The Fab portion of the carrier binds to the epitope on the transformed cell, but the Fc fragment can activate ADCC and ADCP by interacting with the FcR on macrophages and NK cells [144].

A study was conducted by Tai et al. on multiple myeloma (MM). There was evidence that an ADC, J6M0-mcMMAF (GSK2857916) with defucosylated Fc targeting B-cell maturation antigen (BCMA), promoted NK-mediated cell lysis against patient cells and MM cell lines. The increased potency of J6M0-mcMMAF was observed even in MM cells that are relatively resistant to ADCC: The maximum lysis rate of J6M0-mcMMAF was between 85% and 100%. Additionally, treatment with J6M0-mcMMAF remarkably improved macrophage recruitment. This may provide a potential involvement of FcγR-expressing monocytes or macrophages in J6M0-mcMMAF-induced anti-MM activity *in vivo*. In antibody-dependent cellular-mediated phagocytosis (ADCP) assays, J6M0-mcMMAF notably enhanced the phagocytosis capacity of MM cells [145].

10. Therapeutic approaches based on innate immune cells

Since, innate immune cells contribute to modulation of TME, there are several strategies based on innate cells to increase the antitumor responses. On the other hand, TME controls its surroundings to enhance tumor survival, growth, and progression through reprogramming immune cells, particularly innate cells. Therefore, beside common approaches for cancer immunotherapy including cancer vaccines, monoclonal antibodies, T cell therapies, and using immune checkpoint inhibitors [146,147], reprogramming cells in innate immunity is a promising approach to improve antitumor therapies. Table 1 provides a summary of several clinical trials which target innate immune cells for cancer immunotherapy.

11. Conclusion

The TME plays a crucial role in cancer development and metastasis. Both innate and adaptive immune cells are key components of

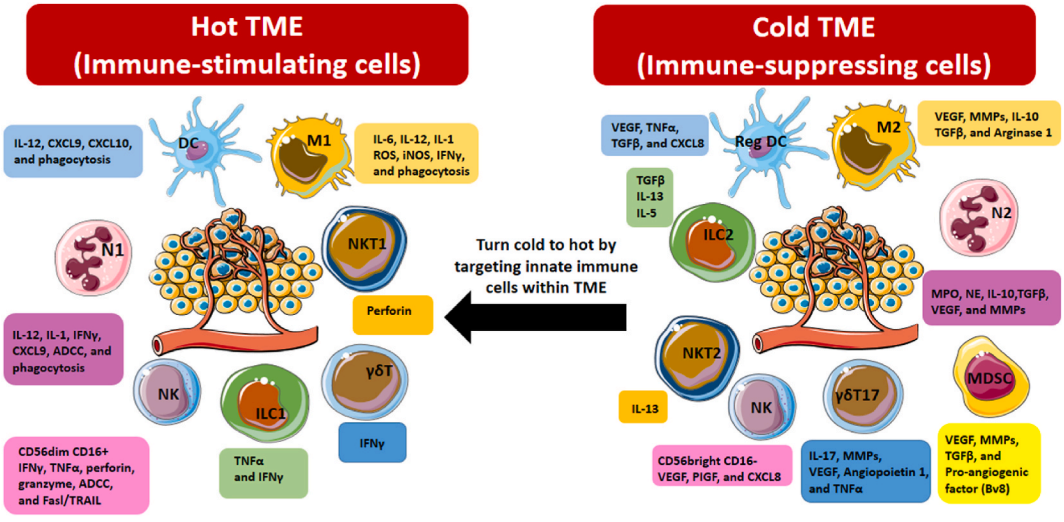

Fig. 1. Schematic presentation of pro-tumoral and anti-tumoral function of innate immune cells in the TME. **Abbreviation**: **VEGF**, vascular endothelial growth factor; **MMPs**, Matrix metalloproteinases; **MPO**, myeloperoxidase; **NE**, neutrophil elastase; **PlGF**, placental growth factor. **ROS**, reactive oxygen species; **iNOS**, inducible nitric oxide synthase; **ADCC**, antibody-dependent cellular cytotoxicity; **Fasl**, Fas ligand; **TRAIL**, TNF-related apoptosis-inducing ligand.

the tumor stroma and can participate in either tumor suppression or progression. The interplay between immune cells and tumor cells finally leads to a microenvironment that can promote tumor metastasis and progression. Innate immune cells, such as neutrophils, macrophages, DCs, ILCs, γδT lymphocytes, MDSCs, and NK cells play an essential role in modulating the TME through various mechanisms. These cells either can inhibit or enhance the antitumor immune responses by secreting mediators (Fig. 1). Understanding the nature of the TME, its role in cancer progression and also its crosstalk with innate immune cells is necessary for developing effective therapeutic strategies. Novel immunotherapeutic interventions are under development to target immune cells within the TME and enhance antitumor immune responses. In addition to innate immune cells, other components of TME including adaptive immune cells (T and B lymphocytes), stromal cells (mesenchymal stromal cells, cancer-associated fibroblasts, and pericytes), extracellular matrix (ECM), secreted factors (chemokines, cytokines, extracellular vesicles, and growth factors), and lymphatic and blood vessels represent promising targets for cancer immunotherapy within the TME. By targeting these components, it may be possible to hinder and obstruct antitumor immune responses, leading to better outcomes for cancer patients.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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