Cellular Oncology (2025) 48:559–590
https://doi.org/10.1007/s13402-025-01051-y

REVIEW

Tumor-infiltrating myeloid cells; mechanisms, functional significance, and targeting in cancer therapy

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Accepted: 20 February 2025 / Published online: 25 February 2025

Abstract
Tumor-infiltrating myeloid cells (TIMs), which encompass tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), and tumor-associated dendritic cells (TADCs), are of great importance in tumor microenvironment (TME) and are integral to both pro- and anti-tumor immunity. Nevertheless, the phenotypic heterogeneity and functional plasticity of TIMs have posed challenges in fully understanding their complexity roles within the TME. Emerging evidence suggested that the presence of TIMs is frequently linked to prevention of cancer treatment and improvement of patient outcomes and survival. Given their pivotal function in the TME, TIMs have recently been recognized as critical targets for therapeutic approaches aimed at augmenting immunostimulatory myeloid cell populations while depleting or modifying those that are immunosuppressive. This review will explore the important properties of TIMs related to immunity, angiogenesis, and metastasis. We will also document the latest therapeutic strategies targeting TIMs in preclinical and clinical settings. Our objective is to illustrate the potential of TIMs as immunological targets that may improve the outcomes of existing cancer treatments.

Keywords Macrophages · Neutrophils · Dendritic cells · Myeloid-derived suppressor cells · Cancer immunotherapy

1 Introduction

Myeloid cells, including monocytes, macrophages, dendritic cells (DCs), and granulocytes, present the major components of the innate immune system. This heterogeneous cell population exerts its anti-tumor activity through a variety of mechanisms, including direct cytotoxicity, phagocytosis, and antigen presentation to adaptive immune cells. However, tumor/stromal-derived factors may impair myeloid cell maturation, differentiation, and function, leading to the formation of a tumor-promoting microenvironment. Tumor-infiltrating myeloid cells (TIMs) are generally categorized into four distinct lineages, including tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), and tumor-associated dendritic cells (TADCs) [1]. Despite the generic discrimination among myeloid populations in the tumor microenvironment (TME), these cells can share common phenotypes and functions. They can even exist in a variety of activation states in response to multiple signals found in their microenvironment. Hematopoietic stem cells (HSCs) from the bone marrow are the source of TIMs. In stressful situations such as cancer, when more myeloid cells are needed, a feature of immune regulation defined as "emergency myelopoiesis" is activated in the bone marrow, giving rise to various mature and immature populations of TIMs with tumor-promoting activities. Some recent evidence suggests that during tumor development, existing differentiated myeloid cells can also undergo functional reprogramming

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towards a tumor-promoting phenotype in response to TME signals [2–4].

TIMs play critical roles in many important processes of cancer, such as immunosuppression, angiogenesis, and metastasis. A close association between TIMs accumulation and unfavorable clinical outcomes in different cancer types has been reported [5–7]. Moreover, TIMs are responsible for resistance to common anti-tumor therapies such as conventional chemotherapy and anti-angiogenic therapy as well as novel therapeutic strategies such as antibody-based and adoptive cellular therapies. Therefore, targeting TIMs present within the TME may provide relevant therapeutic approaches leading to a decrease in the probability of resistance to various cancer therapies [8, 9].

This review will provide a concise overview of the different subgroups of TIMs and discuss their functions in tumor development, Particular emphasis is placed on their roles in immunosuppression, tumor angiogenesis, and metastasis. We will also review the current therapeutic options that target TIMs alone or in combination with other treatment methods for diseases in both preclinical and clinical research. Our goal is to provide an overview of the potential of targeting TIMs for cancer therapy.

2 TIMs subsets

2.1 TAMs

Traditionally, tumor-associated macrophages (TAMs) were believed to arise primarily from the differentiation of hematopoietic progenitor cells. Over the last decade, it has become clear that TAMs arise from multiple sources, have diverse phenotypes, and serve different functions, with embryonic macrophages contributing to TAM formation in the pancreas, brain, lungs, and breast [10]. It is now generally accepted that TAMs can arise from the long-lived placenta or the fetal placenta during organogenesis or from bone marrow myeloid progenitors, which are tissue-resident macrophages (TRMs) and bone marrow-derived macrophages (BMDMs) respectively [11].

TRMs primarily originate from embryonic precursor cells, including yolk sac macrophages and erythro-myeloid progenitors (EMPs). These precursor cells colonize tissues during development and can self-renew independently of circulating monocytes in adults [10]. The distinct embryonic origins give rise to the unique characteristics of TRMs found in different tissues, such as the lung, liver, brain, skin, and intestine. The identity of TRMs is shaped by niche-specific signals that influence their differentiation, survival, and self-maintenance [12]. Additionally, TRMs in the lung, liver, brain, skin, and intestine secrete a variety of cytokines and display distinct markers. Different transcription factors are activated in response to local signals, leading to TRMs adopting tissue-specific properties [13].

They play important roles in maintaining tissue homeostasis, promoting tissue repair after injury, and responding to inflammation. In the context of cancer, TRMs exhibit complex functions and can be pro- or anti-tumor depending on their interactions with other immune cells and the tumor microenvironment (TME) [14]. TRMs may promote tumor cell survival and growth by secreting cytokines and growth factors, thus creating a supportive environment for tumors. For example, in lung cancer, TRMs have been shown to reside near tumor cells in the early stages of the tumor, promoting epithelial-mesenchymal transition (EMT) and invasiveness [15]. These macrophages can induce regulatory T cells (Tregs), which help protect tumor cells from adaptive immune responses. Reduction of TRMs was associated with decreased Treg numbers and increased CD8 + T cell activity, leading to reduced tumor growth. TRMs are involved in the phagocytosis of apoptotic cells and secrete various cytokines that can modulate the immune system to achieve antitumor effects. This dual function complicates their role in cancer therapy. Also, they interact with cytotoxic T cells and other immune cells, influencing whether the immune response is immunosuppressive or cytotoxic [16].

Although precise characterization of macrophages remains challenging, two molecularly and functionally distinct subsets have been proposed for them. Classically activated M1 macrophages have a more pronounced pro-inflammatory and anti-tumor properties, characterized by increased levels of antigen-presenting and co-stimulatory molecules, as well as high levels of immunostimulatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-12, and IL-23. The upregulation of interferon regulatory factor 5 (IRF5) by M1 macrophages leads to the promotion of T helper (Th)1 and Th17 responses [17]. In contrast, alternatively activated M2 macrophages have a pro-angiogenic and immunoregulatory phenotype and are stimulated by Th2 cytokines such as IL-4, IL-10, and IL-13. M2 macrophages are characterized by the expression of co-inhibitory molecules such as programmed death-ligand 1 (PD-L1) and the release of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta 1 (TGF-β1) [18–21]. High expression of C-type mannose receptor 1 (MRC1/CD206) and hemoglobin/haptoglobin scavenger receptor (CD163) also indicates the M2 phenotype [22, 23]. In addition, the M2 macrophages release a variety of pro-angiogenic growth factors, like vascular endothelial growth factor (VEGF)-A and are an important source of proteases, including matrix metalloproteinases (MMPs), that lead to tumor invasion, neoangiogenesis, and metastasis [24–27]. Studies have shown that soluble factors (i.e., CSF1, CCL2,

IL-4, IL-10) produced by tumor, stromal, and immune cells, as well as specific physicochemical conditions (such as hypoxia and acidosis) in the TME, promote the accumulation of TAMs and their polarization to the M2 phenotype [28–30].

The M2 macrophages are thought to be the predominant phenotype of TAMs, and in most cases, it indicates a poor prognosis [5, 27]. However, some recent studies on human tumors have shown a more diverse and heterogeneous population of TAMs, which cannot be simply categorized as M1 or M2 macrophages phenotypically and functionally [31, 32]. Zilionis et al., by single-cell RNA sequencing (scRNA-seq), characterized myeloid populations including macrophages in human and murine non-small cell lung cancer. In humans, they did not detect TAMs exhibiting only M1 markers; however, they identified macrophages enriched in markers of the M2 state yet not as a distinct cell state. In mice, TAMs also did not represent a discrete M1/M2 transcriptional signature [31]. Other studies have also used scRNA-seq to show that individual TAMs in various tumor types can simultaneously express M1 and M2 gene signatures [32, 33]. However, due to the limitations of scRNA-seq, Chevrier et al. used mass cytometry to analyze the phenotypic diversity of TAMs in renal cell carcinoma. They demonstrated a total of 17 major TAM phenotypes, of which six phenotypes were considered as the main pro-tumor macrophages and were only present in tumors of grade II and higher. Interestingly, their results showed that some of these pro-tumor macrophages can co-express both anti- and pro-tumor markers [34]. Together, these studies challenge the traditional classification of TAMs as either M1 anti-tumor or M2 pro-tumor subtypes and highlight the importance of the TME in the functional polarization of macrophages. This means that identical TAMs can have either tumor-promoting or tumor-suppressing effects in response to stimulation from different factors [35].

Although the most of TAMs originate from circulating monocytes, some studies have shown that a small proportion of TAMs arise from tissue-resident macrophages that migrate from the yolk sac or mouse fetal liver to peripheral tissues during embryonic development. Tissue-resident macrophages are self-sustaining and do not depend on circulating monocytes for maintenance [36–39]. They express a distinct set of biomarkers from bone marrow-derived macrophages; however, additional research is necessary to determine whether macrophages derived from these independent sources have distinct roles during tumor development [39–42].

A unique and small subset of monocytes, named Tie-2 expressing monocytes (TEMs), has also been shown to be critical promoters of tumor angiogenesis. TEMs are characterized by the expression of the angiopoietin receptor Tie2, which binds to angiopoietins 1–4 (ANGs 1–4) [43, 44]. In humans, three distinct subsets of monocytes have been identified based on the pattern of CD14 and CD16 expression: classical ($CD14^{++}/CD16^{-}$), intermediate ($CD14^{++}/CD16^{+}$), and non-classical ($CD14^{+}/CD16^{++}$) [45]. It has been reported that Tie-2 is predominantly expressed in the intermediate subset; however, further research is required to understand the processes controlling Tie-2 induction in monocytes as well as the origin of TEMs [46].

2.2 TANs

Neutrophils are the most abundant phagocytic polymorphonuclear cells producing immune cells [47]. High numbers of neutrophils in the blood or an increased ratio of neutrophils to lymphocytes (NLR) have been associated with unfavorable outcomes in a variety of cancers [6, 47, 48]. Soluble factors derived from tumor/stromal cells promote neutrophil recruitment to tumor sites and modify their phenotype and function. Similar to the macrophage paradigm, TANs have been categorized into N1 or N2 in tumor-bearing mice. The N1 TANs exhibit a proinflammatory and anti-tumorigenic phenotype (i.e., $TNF\alpha^{high}$ and $Arginase^{low}$), while N2 TANs are characterized by a protumorigenic and immunosuppressive profile (i.e., $CCL2^{high}$, $CCL3^{high}$, and $Arginase^{high}$) [49]. Pro-tumorigenic TANs facilitate tumor angiogenesis and metastasis through the secretion of proangiogenic factors such as VEGF-A and Bv8, as well as matrix remodeling factors such as MMP-9 [47, 50–53]. However, it is worth noting that the classification of TANs as N1/N2 has only been observed in mouse cancer models, and the phenotype and role of TANs in the TME, especially in human tumors, have yet to be fully explored. Zilionis et al. demonstrated through scRNA-seq that neutrophils in human and murine lung tumors represent a continuum of states, ranging from populations expressing canonical neutrophil marker genes to subsets exhibiting tumor-associated phenotypes. In humans, the depiction of these subsets varied between patients. However, they found significant differences in the proportions of these subpopulations in tumor-free and tumor-bearing mice. In both humans and mice, they have also identified neutrophil subpopulations that express type I interferon response genes, which were highly enriched in marker genes associated with poor patient survival [31]. These findings support the view that the binary N1/N2 classification system represents an oversimplification of the phenotypic and functional spectrum of TANs.

Further complications in TAN studies arise due to their phenotypic and functional similarities with polymorphonuclear (PMN)-MDSCs. It is unclear whether these are analogous or separate populations [54]. We will discuss this issue in more detail in the next section.

As mentioned, neutrophils are known to show significant heterogeneity and recent studies have identified several neutrophil subpopulations that play critical roles in the cancer microenvironment. These subsets exhibit diverse functions, including promoting tumor progression and suppression [55]. Key points about neutrophil subsets and their roles including:

1. **Neutrophil Progenitors**: These are immature neutrophils that can differentiate into mature neutrophils. They contribute to the myeloid heterogeneity in the tumor microenvironment and can be recruited to tumor sites where they can promote tumor growth and metastasis.
2. **Senescent Neutrophils**: These are long-lived neutrophils and mediate immunosuppression and therapeutic resistance. They are defined as a tumor inducing population that promote cancer progression by creating an immunosuppressive environment.
3. **Tumor-Associated Neutrophils (TANs)**: TANs can be divided into two major subgroups according to their functional properties: **N1 Neutrophils** that exert antitumor activity, mainly due to releasing pro-inflammatory cytokines that facilitate the recruitment and activation of CD8 + T cells. They stimulate the immune response against tumor. **N2 Neutrophils** have strong immunosuppressive and tumor-promoting activities. They promote tumor angiogenesis, invasion, and metastasis through the release of various factors such as hepatocyte growth factor (HGF), oncostatin M, reactive oxygen species (ROS), and matrix metalloproteinases (MMPs) [56].
4. **High Density Neutrophils (HDNs)**: These neutrophils are functionally similar to N1 neutrophils, which exhibit antitumor activity.
5. **Low Density Neutrophils (LDNs)**: These neutrophils are functionally similar to N2 neutrophils, which exhibit protumor activity. They are often associated with immunosuppressive environments and poor prognosis in cancer patients.
6. **Neutrophil Extracellular Traps (NETs)**: Neutrophils can release NETs, which are web-like structures composed of DNA and cytotoxic proteins. NETs can promote tumor progression by facilitating metastasis, and protecting tumor cells from cytotoxic immune cells.
7. **Metabolic Crosstalk**: Recent data have shown that neutrophils have metabolic interactions with cancer cells. For example, neutrophils can take up lipids from the tumor microenvironment, which may influence their function and promote tumor progression [57].
8. **Antigen-Presenting Neutrophils (APNs)**: Single-cell RNA sequencing analyses of neutrophils from 225 samples in 17 types of cancers identified HLA-DR + CD74 + neutrophils that are particularly remarkable for their anti-tumor potential. HLA-DR + CD74 + neutrophils have been identified as antigen-presenting cells that can activate antitumor T cells [58]. This activation increases the efficacy of immunotherapy by stimulating stronger immune response against cancer cells. Also, the antigen-presenting program in neutrophils is associated with favorable survival in most types of cancers [59]. This can be caused by leucine metabolism and subsequent histone H3K27ac modification, which helps in invoking both antigen-specific and antigen-independent T cell responses. In addition, by presenting tumor antigens to T cells, APNs help in re-shaping the T cell immune repertoire and enhancing antigen-specific responses. This function is crucial for the effectiveness of various immunotherapies [60]. Furthermore, they can modulate the immune response by altering tumor antigens from the tumor site to the lymph nodes, thus organizing pervasive immune attack on the tumor. Given their dual role in promoting and suppressing tumor growth, neutrophils are considered as potential therapeutic targets. Strategies to enhance their antigen-presenting abilities could improve cancer treatment outcomes significantly [61].

Overall, studies using pan-cancer single-cell analysis has emphasized that neutrophils involved in inflammation, angiogenesis, and antigen presentation. Their ability to modulate immune responses makes them as key players in enhancing the effectiveness of immunotherapies, such as anti-PD-1 treatments [58]. Studies suggest that the manipulation of neutrophils could improve cancer treatments. For example, delivering activated neutrophils or adjusting dietary leucine levels can enhance the immune response and increase the effectiveness of treatment in the mouse model. The presence of these antigen-presenting neutrophils is associated with better patient outcomes and the formation of a “hot tumor” microenvironment, that is favorable for immunotherapy [62]. Despite their potential, studying neutrophils in cancer is complicated by their short half-life and the dynamic nature of their functions. The recruitment and activation of neutrophils can vary significantly depending on the tumor microenvironment and the presence of specific cytokines, leading to tumor growth or suppression [63].

2.3 MDSCs

MDSCs are considered the most important cell population contributing to the formation of a pro-tumorigenic and immunosuppressive TME. High levels of MDSCs have been found to act as a negative prognostic factor for many cancers [7, 64]. MDSCs are a diverse combination of immature myeloid cells that can be divided into two main categories: PMN-MDSCs

and monocytic (M-MDSC) groups. In tumor-bearing mice, PMN-MDSCs can be defined as $CD11b^{+}Ly6G^{+}Ly6C^{lo}$ and monocyte/M-MDSCs as $CD11b^{+}Ly6G^{-}Ly6C^{hi}$ [65]. In humans, a consolidated phenotypic marker for the MDSC population still poses a challenge as they share surface markers with other cells in the myelocytic lineage [66]. Regardless of the variability between laboratories in describing the phenotype of MDSCs, PMN-MDSC is usually described as $CD11b^{+}$ $CD14^{-}$ $CD15^{+}$ $CD33^{+}$ $CD66b^{+}$ $HLA\text{-}DR^{-}$ Lin^{-} (including CD3, CD19, CD20, CD56), while M-MDSC is characterized as $CD11b^{+}$ $CD14^{+}$ $CD15^{-}$ $CD33^{+}$ $CD66b^{+}$ $HLA\text{-}DR^{-/low}$ Lin^{-}. A population of "early stage MDSCs" or eMDSCs comprising more immature progenitors is also identified through the Lin^{-} $CD11b^{+}$ $CD33^{+}$ $CD14^{-}$ $CD15^{-}$ $HLA\text{-}DR^{-}$ profile [67]. In humans, the major histocompatibility complex (MHC) class II molecule, HLA-DR, is used as a marker to differentiate monocytes from M-MDSCs. However, no marker has been identified yet that allows for the clear separation of PMN-MDSCs from neutrophils [68]. One common method that can help to isolate PMN-MDSCs from normal neutrophils is by using a Ficoll density gradient. While normal high-density neutrophils (HDNs) are separated at the lower end of the density gradient, a subpopulation of neutrophils, termed low-density neutrophils (LDNs), can be located within the interphase of plasma and Ficoll in the low density (LD) fraction. LDNs have been isolated, in small numbers, from the peripheral blood of healthy individuals; however, increased numbers of LDNs with immunosuppressive functions are found in cancer patients [51, 69, 70]. It has been proposed that PMN-MDSCs with immunosuppressive functions are enriched in the LD fraction; however, small subsets of LDNs displaying an anti-tumor immunity profile, mature neutrophils with protumor activity, and activated neutrophils have also been identified in the LD fraction [51, 71, 72]. Several studies have proposed that N2 TANs with immunosuppressive and tumor-promoting functions are actually PMN-MDSCs. However, other studies suggest that PMN-MDSCs are a distinct subpopulation of granulocytes that can infiltrate the TME and acquire an N2 phenotype [51, 64, 70, 72, 73]. In a study of tumor-bearing mice, Youn et al. identified PMN-MDSCs as a distinct population with significantly higher expression of CD115 and CD244 markers and limited phagocytic properties compared to neutrophils [74]. More recently, Condamine et al. identified lectin-type oxidized LDL receptor 1 (LOX-1) as a potent marker of PMN-MDSCs, which can be used to distinguish them from neutrophils [75].

In summary, despite some differences between PMN-MDSCs and neutrophils, more studies are needed to determine whether PMN-MDSCs are a distinct subset of granulocytes or simply neutrophils with a different activation or polarization state.

2.4 TADCs

Naive antigen-specific $CD4^{+}$ and $CD8^{+}$ T cells are stimulated by dendritic cells, which are highly skilled at presenting antigens. Multiple DC subsets with specific immune functions have been distinguished in lymphoid organs, peripheral tissues, and blood [76]. In both mouse and human tissues, two primary DC subsets have been recognized: conventional DCs (cDCs), also called myeloid DCs, and plasmacytoid DCs (pDCs). The cDCs are further subdivided into cDC1 and cDC2 by unique expression of surface markers and reliance on various transcription factors for their development and/or function. During inflammation, an additional subset of DCs, monocyte-derived DCs (moDCs), also referred to as inflammatory DCs (infDCs), differentiate from monocytes. The ontogeny and classification of DCs have been extensively reviewed elsewhere [77, 78].

The pDCs are characterized by their ability to secrete significant quantities of type I interferons (IFN-1) through the recognition of viral RNA and DNA via toll-like receptors (TLRs) 7 and 9 expressed in their endosomal compartments. The cDC1s mainly induce potent CTL responses by cross-presenting internalized exogenous antigens onto MHCI to $CD8^{+}$ T cells, whereas cDC2s preferentially present internalized antigens on MHCII to $CD4^{+}$ T cells and induce Th2 or Th17 responses. It is worth noting that cDC2s have also been shown to cross-present soluble antigens to $CD8^{+}$ T cells; however, unlike cDC1s, they are not critical for directing CTL responses [79–83].

DCs display different phenotypes and activities (immunostimulatory or immunosuppressive) at the tumor site, suggesting the plasticity of these cells in response to a wide spectrum of signals in the TME. The role of pDCs in cancer has been considered tolerogenic, and pDC infiltration indicates a poor prognosis in many tumors [84–86]. cDC1s are essential in tumor immunity by generating significant quantities of IL-12, which facilitates the recruitment of $CD8^{+}$ effector T cells and $CD4^{+}$ Th1 cells to the tumor microenvironment. In the tumor-draining lymph nodes, cDC1s could also initiate $CD8^{+}$ T cell responses. An increased presence of cDC1s within human tumors indicate a better clinical outcome, and these cells are crucial for the response to anti-immune checkpoint therapy [84, 85, 87–89]. Although many studies have shown that the dominant role of cDC1s in tumor immunity, many studies have addressed the tumor suppressor function of cDC2s via MHC-II presentation of tumor antigens to $CD4^{+}$ T cells [85, 90–92]. The abundance of cDC2 in the TME has been demonstrated to plays pivotal function in the quality of $CD4^{+}$ T cell responses and responsiveness to anti-immune checkpoint therapy [90].

Despite the presence of TADCs with significant antigen-presenting capabilities within the TME, DCs often exhibit

impaired antigen-presenting and/or inhibitory functions in advanced solid tumors. It has been proposed that the TME keeps the majority of TADCs in an immature state. However, it is important to emphasize that the immunoregulatory function of DCs cannot simply be limited to immature DCs since various factors and pathways can influence the polarization, activation status, and capacity of DCs to invoke immunostimulating or immunosuppressive responses within the TME [82, 87, 93, 94].

3 Mechanism of immune suppression and immune tolerance by TIMs

The TIMs can directly suppress the function of $CD8^+$ T cells through the secretion of various cytokines and enzymes with immunosuppressive activity or by expressing surface markers that restrict $CD8^+$ T cell activities. TIMs may also indirectly control T cell responses by recruiting and expanding regulatory T (Treg) cells or by suppressing the anti-tumor functions of other immune cells like DCs (Fig. 1). Macrophages and MDSCs are the major immunoregulatory cells that inhibit T cell function in the TME [95, 96].

Both express high levels of inducible nitric oxide synthase (iNOS) and arginase 1 (Arg-1), leading to increasing L-arginine catabolism and producing of several reactive oxygen species (ROS) and reactive nitrogen species (RNS). Since L-arginine is an essential nutrient for T cell activation and growth, L-arginine deficiency results in the downregulation of the expression of TCR/CD3 complexes and inhibition of cytotoxic T-cell responses [97–100]. Moreover, ROS inhibits T cells by nitration of T-cell receptors, thereby preventing recognition between TCR and MHC-peptide complex [101, 102]. RNS also blocks tumor infiltration of antigen-specific T cells by nitration of T cell-specific chemokines [102]. Both MDSCs and TAMs produce IL-10 that plays a pivotal role in the immunosuppressive function of Treg cells and inhibition of cytotoxic T-cell responses [97,

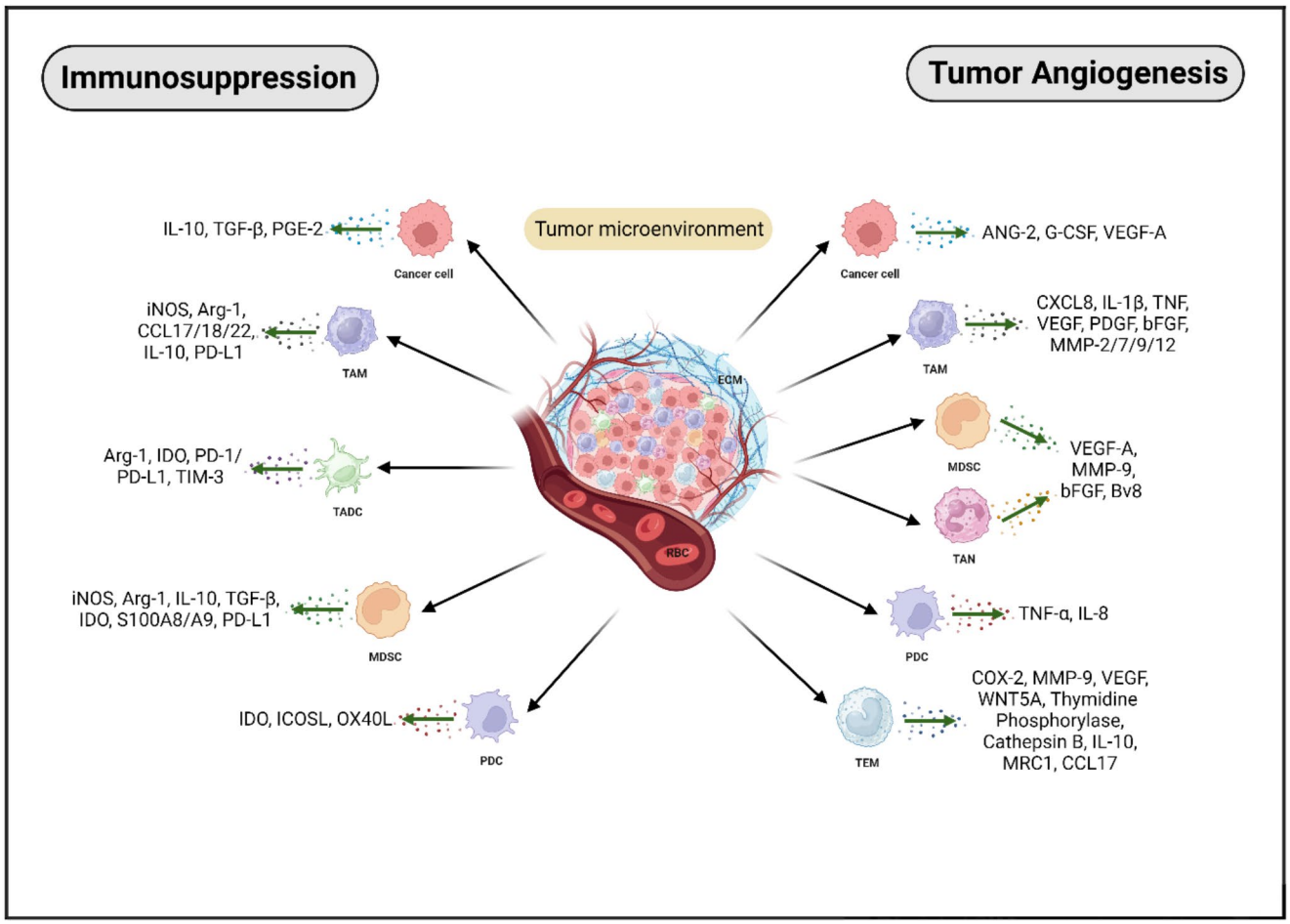

Fig. 1 Tumor-promoting factors produced by various populations of myeloid cells in the tumor microenvironment induce immune suppression and tumor angiogenesis. Abbreviations: MDSC, Myeloid-derived suppressor cell; TAM, Tumor-associated macrophage; TAN, Tumor-associated neutrophil; TADC, Tumor-associated dendritic cell; TEM, Tie-2 expressing monocyte; PDC, Plasmacytoid dendritic cell; ECM, Extracellular matrix. This figure was created using www.BioRender.com

103]. TGF-β and indoleamine 2,3-dioxygenase (IDO) are known to be responsible for the development of Tregs by MDSCs [104, 105]. TAMs directly stimulate the recruitment of Tregs to TME through the secretion of chemotactic factors such as CCL17, CCL18, and CCL22 [106, 107]. MDSCs can suppress T cell responses through the secretion of S100 calcium-binding proteins A8 and A9 (S100A8 and S100A9, also known as myeloid-related protein 8, MRP8, and myeloid-related protein 14, MRP14). These proteins have been shown to inhibit DC maturation and promote MDSC migration and accumulation [108]. High levels of PD-L1 expression by activated MDSCs and monocytes inhibit cytotoxic T lymphocyte responses [19]. MDSCs and macrophages also impair the cytotoxic capacity of NK cells and cytokine secretion through different mechanisms [109, 110].

TEM has been shown to exert immunosuppressive effects by producing known anti-inflammatory cytokines such as IL-10 and VEGF. It also inhibits the proliferation of tumor-specific T-cells, increases the ratio of $CD4^+$ T-cells to $CD8^+$ T-cells, and increases the number of $CD4^+CD25^+FOXP3^+$ Treg cells [111, 112].

TADCs are a subset of TIMs that often exhibit immunosuppressive and tolerogenic properties within the TME. Several factors, such as IL-10 and TGF-β produced by tumor cells and/or TME cells, have been shown to inhibit DC maturation and reduce the capacity of DCs in antigen presentation and T cell activation through various mechanisms [87, 113–115]. Treatment of DCs with IL-10 has been shown to induce anergy in cytotoxic $CD8^+$ T cells. Tumor-produced TGF-β reduces the effectiveness of DCs to present antigens, stimulate tumor-specific cytotoxic T lymphocytes, and migrate to draining lymph nodes [116]. It has been shown that the TME converts a specific DC subset of immature mDCs to regulatory DCs that secrete TGF-β and selectively promote the proliferation of $CD4^+CD25^+FOXP3^+$ Treg cells [117]. Several factors, such as Arg-1 and IDO produced by TADCs, have been considered to play important functions in mediating the suppression of T cell responses [94, 118, 119]. Treg cells subsequently induce immunosuppression and DC dysfunction through different mechanisms [117, 120]. The expression of inhibitory molecules such as PD-L1 (and its receptor PD-1) and T-cell immunoglobulin and mucin domain 3 (TIM-3) is another mechanism by which DCs exert their immunosuppressive effects [121, 122]. Tumor-infiltrating DCs expressing PD-1 have been found to suppress $CD8^+$ T cell activity and decrease T cell infiltration in advancing tumors in mouse models of ovarian cancer [77, 123]. PDL-1 expressing DCs have also been shown to induce Treg generation in the presence of TGF-β [78, 124]. TIM-3 prevents DCs activation and maturation and reduces the anti-tumor responses as well as the efficacy of cancer treatments [125].

Tumor-infiltrating pDCs represent another subset of DCs with immunosuppressive and tolerogenic activity that favors tumor progression. Although properly stimulated pDCs have been shown to induce immunogenic anti-tumor responses, pDCs are mostly defective in their functions within the TME. High densities of tumor-infiltrating pDCs indicate a poor prognosis in many tumors [86, 126–132]. Several factors in the TME, such as IL-10, TGF-β, and prostaglandin E2 (PGE-2), have been known to be responsible for the impaired function of pDCs [133, 134]. Moreover, pDCs have been found to induce Treg generation through various mechanisms, including the inducible T cell co-stimulator (ICOS) and ICOS-ligand (ICOSL) pathway, IDO expression [135, 136], and the OX40/OX40L pathway [126].

4 TIMs and tumor angiogenesis

Tumor angiogenesis is a crucial phase in the progression and spread of tumors. Although tumor cells can directly stimulate angiogenesis, recent research indicates that TIMs significantly contribute to the process of tumor angiogenesis (Fig. 1) [112, 137].

M2 macrophages promote angiogenesis through various mechanisms, including secretion of several potent pro-angiogenic factors including VEGF, TNF-α, IL-1β, IL-8 (CXCL8), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF), as well as production of different classes of matrix remodeling factors (i.e., urokinase plasminogen activator (uPA), MMP-2, MMP-7, MMP-9, MMP-12, and elastase) [138, 139]. The hypoxic TME have pivotal function in inducing the proangiogenic phenotype of TAMs. High densities of TAMs have been found in hypoxic and/or necrotic areas of many human tumors [140, 141]. Hypoxia has been shown to upregulate the expression of hypoxia-inducible factors 1 and 2 (HIF1 and HIF2) in TAMs, leading to subsequent activation of many genes involved in cell proliferation, angiogenesis, and metastasis [142, 143].

TEMs have been reported as a highly pro-angiogenic subpopulation of monocytes and express pro-angiogenic factors such as MMP-9, VEGF, cyclooxygenase-2 (COX-2), and wingless-type MMTV integration site family member 5a (WNT5A). TEMs found in mouse and human peripheral blood are recruited into solid tumors mainly by ANG-2 produced by tumor endothelial cells [43, 144]. ANG-2 has also been shown to enhance the angiogenic activity of TEMs by upregulating several proangiogenic enzymes such as

thymidine phosphorylase and cathepsin B. Additionally, ANG-2 upregulates three "alternatively activated" (M2-like) macrophage markers in TEMs: IL-10, mannose receptor (MRC1), and CCL17 [145]. Moreover, hypoxia upregulates Tie2 expression on TEMs and, together with ANG-2, downregulates their anti-tumor functions [146]. Overall, although circulating TEMs are pro-angiogenic in nature, exposure to tumor-derived ANG-2 induces these cells to display a broader, tumor-promoting phenotype [145].

TANs and MDSCs are potent promoters of tumor angiogenesis. Both have been shown to induce angiogenesis by upregulating VEGF-A, MMP-9, bFGF, and BV8. Human neutrophils contain VEGF-A-rich granules that can be rapidly released upon stimulation [147, 148]. It has been shown that MDSCs upregulate the production of VEGF and bFGF, and promote angiogenesis in a signal transducer and activator of transcription 3 (STAT3)-dependent manner [149]. The blockade of STAT3 signaling with IFN-β has been found to suppress the production of VEGF-A and MMP-9 by neutrophils, and limit the growth and angiogenesis of tumors in a mouse tumor model [150]. MDSCs produce high levels of MMP-9, which are essential for their angiogenic properties and regulate the bioavailability of VEGF in tumors [151]. Neutrophils are a key source of the MMP-9 proenzyme, which is not in complex with the tissue inhibitor of metalloproteinase (TIMP). TIMP inhibits the angiogenic function of both the MMP-9 proenzyme and mature MMP-9 through the formation of a complex with them. The proteolytic cleavage of the extracellular matrix (ECM) by neutrophil-derived TIMP-free MMP-9 proenzyme has been found to release ECM-sequestered bFGF and promote angiogenesis [152]. Granulocyte-colony stimulating factor (G-CSF), as the main regulator of granulopoiesis, has been demonstrated to have a significant impact on MDSC-induced tumor angiogenesis. G-CSF produced by the tumor or stromal cells upregulates the expression of the proangiogenic factor Bv8 in $CD11b^+Gr1^+$ cells, which subsequently induces endothelial cell proliferation and tumor angiogenesis [153].

Besides the major role of DCs in immune suppression/tolerance, there is now substantial evidence that immature DCs, in contrast to mature DCs, actively promote tumor angiogenesis [154]. It has been shown that β-defensin promotes tumor vasculogenesis through the recruitment of immature DCs from the peripheral blood in the presence of increased VEGF-A expression. High levels of VEGF-A in the TME induce endothelial-like differentiation of DCs and their migration to vessels through VEGF receptor-2 [155]. pDCs derived from human ovarian tumor ascites induce tumor angiogenesis in vivo through the production of TNF-α and IL-8 [156].

5 TIMs and tumor metastasis

Metastasis is still the primary contributor to mortality in solid tumors. For tumor cells to metastasize, they must migrate to other areas and form metastatic nodules [157]. Recent evidence suggests that primary tumors can affect the microenvironment of distant organs prior to the arrival of metastatic tumor cells, providing a supportive metastatic microenvironment called the premetastatic niche (Fig. 2) [158]. Both circulating and tumor-infiltrating myeloid cells have been demonstrated to have significant roles in different aspects of metastasis, including premetastatic niche formation, tumor cell intravasation into the blood vessels and extravasation at the secondary site, and finally tumor cell colonization.

Neutrophils are the central cell population that promotes tumor metastasis (Fig. 2a) [159]. While initial studies suggested that $CD11b^+$ $VEGFR1^+$ bone marrow-derived hematopoietic progenitor cells were the major component of the pre-metastatic niche [160], recent studies have suggested that neutrophils are a major cell type in the premetastatic microenvironment and can migrate in response to primary tumor-derived factors [49, 161]. Tumor-derived G-CSF has been shown to be accountable for the recruitment of bone marrow-derived $CD11b^+Gr1^+$ $Ly6G^+Ly6C^+$ granulocytes (immunosuppressive neutrophils) and their homing into the lungs prior to the tumor cells arrive [162]. G-CSF induces the expression of Bv8 by $Ly6G^+Ly6C^+$ cells, which is a chemoattractant for the homing of bone marrow-derived $Ly6G^+Ly6C^+$ cells into pre-metastatic lungs [162, 163]. Studies have demonstrated that in mice with mammary tumors, stimulation with IL-17 derived from γδ T cells induces expansion and polarization of immunosuppressive neutrophils in a G-CSF-dependent manner. These population of neutrophils promote lung metastasis of tumor cells by blocking the antitumor activity of $CD8^+$ T cells [164]. Neutrophils have also been considered as major sources of some pro-metastatic proteins, such as MMP-9, S100A8, S100A9, and leukotrienes [163, 165, 166]. Neutrophil-released neutrophil extracellular traps (NETs) can also contribute to cancer metastasis by trapping circulating tumor cells [167]. TGF-β produced by TANs has been indicated to trigger the epithelial-mesenchymal transition (EMT) of tumor cells, which, in turn, promotes metastasis [168]. MDSCs can also promote tumor metastasis through infiltration into the pre-metastatic niche. Some soluble factors secreted by primary tumor/stromal cells have been shown to induce migration and activation of MDSCs in the pre-metastatic niche (Fig. 2b). In a mouse model of colorectal cancer, VEGF-A produced by primary tumor cells induced the formation of a pre-metastatic niche and liver metastasis by MDSCs through the upregulation of CXCL1 in TAMs.

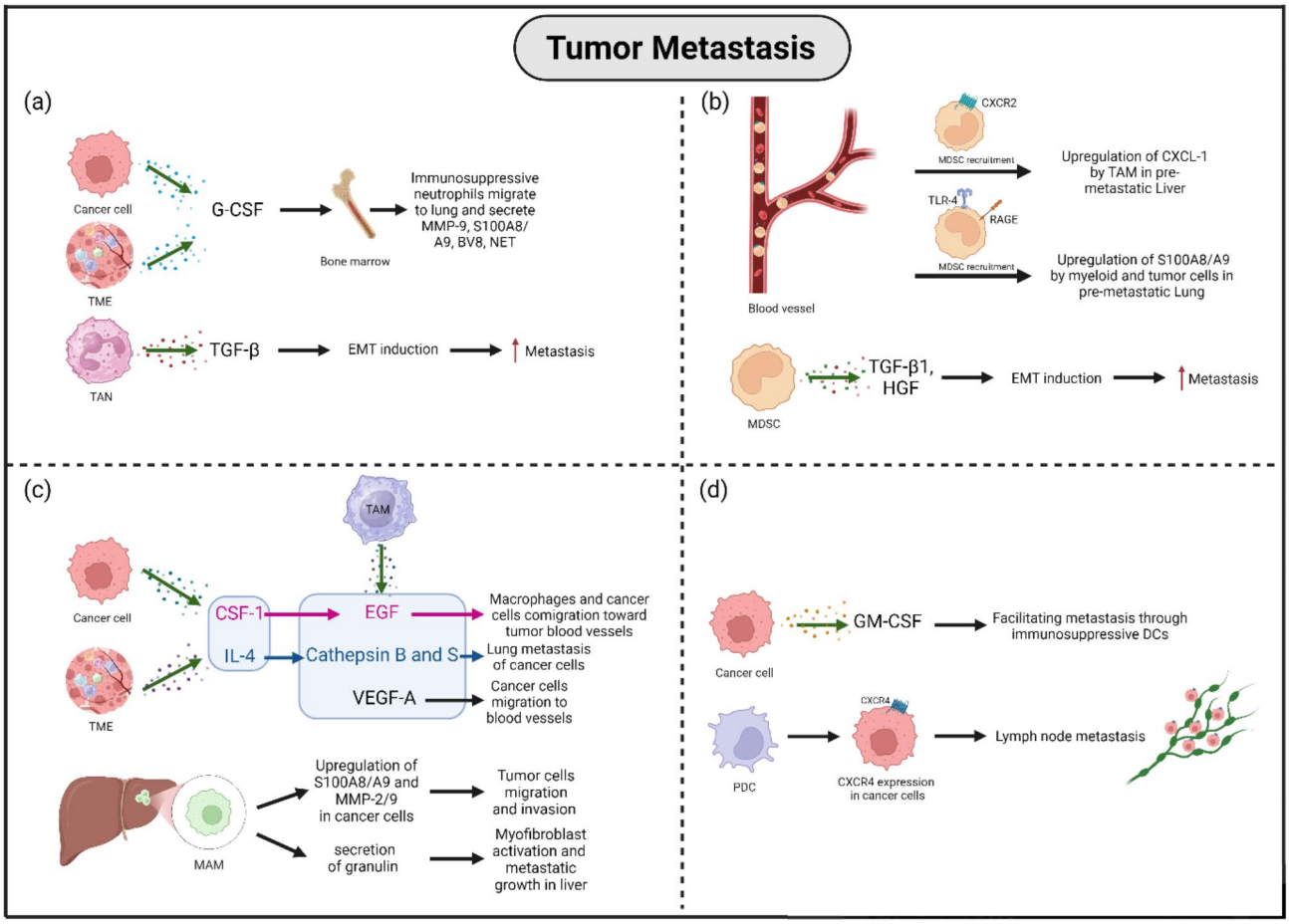

Fig. 2 Some of the main mechanisms used by tumor-infiltrating myeloid cells to induce tumor metastasis. **a**) Neutrophils: Neutrophils are one of the major cell types that respond to primary tumor-derived factors. Cancer cells produce granulocyte-colony stimulating factor (G-CSF), which is responsible for the mobilization of immunosuppressive neutrophils from the bone marrow and the formation of a premetastatic niche that ensures the survival and growth of tumor cells. Pro-metastatic proteins produced by neutrophils also promote cancer cell metastasis. Additionally, neutrophils trigger metastasis through the induction of epithelial-mesenchymal transition (EMT) in cancer cells. **b**) MDSCs: MDSCs can potentially encourage tumor metastasis through infiltration into the pre-metastatic niche. Upregulation of CXCL1 by TAMs and secretion of pro-metastatic proteins such as S100A8 and S100A9 by myeloid and tumor cells in pre-metastatic organs induce recruitment of MDSCs to these sites. MDSCs expressing hepatocyte growth factor (HGF) and transforming growth factor-beta 1 (TGF-β1) play a crucial role in inducing EMT in cancer cells. **c**) Macrophages: Macrophages promote metastasis both from the primary tumor site and within metastatic sites. Tumor cell-derived colony-stimulating factor-1 (CSF-1) induces macrophages to produce epidermal growth factor (EGF), leading to the co-migration of macrophages and cancer cells. An increase in cathepsin activity in TAMs under IL-4 stimulation promotes cancer cell metastasis. Macrophages can also promote tumor cell invasion and migration within metastatic sites via the upregulation of pro-metastatic proteins in cancer cells. Metastasis-associated macrophages support metastasis through secreting granulin, a peptide that provides a fibrotic microenvironment. **d**) Dendritic cells: Dendritic cells can promote the development of metastasis by creating an immunosuppressive microenvironment at the metastatic site. Tumor-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) induces the development of immunosuppressive dendritic cells from monocytes. Infiltration of plasmacytoid dendritic cells in cancer tissue induces lymph node metastasis via the CXCR4/SDF-1 axis. This figure was created using www.BioRender.com. Abbreviations: MDSC, Myeloid-derived suppressor cell; TAM, Tumor-associated macrophage; TAN, Tumor-associated neutrophils; TADC, Tumor-associated dendritic cell; MAM, Metastasis-associated macrophage; TEM, Tie-2 expressing monocyte; PDC, Plasmacytoid dendritic cell; TME, Tumor microenvironment

This, in turn, recruits CXCR2-positive MDSCs to liver tissue [169]. Recruitment of MDSC cells to the pre-metastatic niche in distant organs is also facilitated by the expression of S100A8 and S100A9 by myeloid and tumor cells. These chemotactic proteins promote MDSC migration by activating TLR-4 or the receptor for advanced glycation end-products (RAGE) on MDSCs [108, 170]. VEGF-A, TGFβ, and TNFα released by the primary tumor induce the expression of S100A8 and S100A9 in premetastatic lungs [171]. In 4T1 tumor-bearing mice, Gr-1^{+}CD11b^{+} myeloid cells have been shown to infiltrate into the pre-metastatic lungs and promote aberrant vasculature formation and metastasis through

the upregulation of MMP-9 [172]. Intravenous injection of primary ovarian cancer cells conditioned with MDSCs in an NSG mouse model induced the formation of more metastatic foci in the liver and lungs of mice compared to control animals injected with non-conditioned cancer cells. MDSCs were found to enhance tumor cell stemness and their metastatic potential through the upregulation of miRNA101 in cancer cells, which subsequently suppresses the corepressor C-terminal binding protein-2 (CtBP2) [173]. Tumor-infiltrating MDSCs induce EMT in cancer cells through TGF-β1, epidermal growth factor (EGF), and hepatocyte growth factor (HGF) signaling pathways [174].

TAMs are another type of myeloid cell population that actively participate in the metastatic process (Fig. 2c). In experimental models of pancreatic cancer, liver-resident macrophages, known as Kupffer cells, facilitate the establishment of a pre-metastatic niche using tumor-derived exosomes that are rich in macrophage migration inhibitory factor (MIF). Upon MIF stimulation, these Kupffer cells secrete TGF-β, which in turn enhances the production of fibronectin production by hepatic stellate cells. This fibronectin-rich environment recruits pro-tumor bone marrow-derived macrophages to the premetastatic niche in the liver. Blocking these tumor-derived exosomes has been shown to prevent liver pre-metastatic niche formation and the subsequent development of metastasis [175].

Macrophages not only promote metastasis at the tumor site but also cause tumor cells to invade and migrate to the metastatic site. It has been shown that colony-stimulating factor-1 (CSF-1), which is secreted by cancer cells, promotes TAMs mobility and their secretion of EGF, leading to the simultaneous migration of both macrophages and cancer cells toward the tumor's blood vessels. TAM-derived EGF further activates the EGF receptors on cancer cells, thereby increasing tumor growth, invasion and intravasation. Furthermore, TAM-derived VEGF-A promotes cancer cell invasion into the blood vessels [176–178]. Moreover, TAMs have been demonstrated to promote the invasion and metastasis of breast cancer cells through integrin clustering and enhancing tumor cell adhesion to ECM [179]. IL-4 produced by cancer cells and/or stromal cells in the TME has been shown to stimulate cathepsin activity in the TAMs, which, in turn, enhances the invasiveness of cancer cells [180]. The elevated levels of cathepsin S in tumor samples patients with breast cancer have been associated with reduction in brain metastasis-free survival. Cathepsin S, synthesized by both tumor cells and TAMs, promotes blood-brain barrier (BBB) transmigration via proteolytic cleavage of junctional adhesion molecule (JAM)-B [181]. In the context of metastatic liver, monocytes and macrophages enhance the migration and invasion of tumor cells by upregulation of S100A8 and S100A9 in cancer cells, which subsequently stimulate tumor cell expression of MMP2 and MMP-9 [182]. Moreover, these inflammatory chemoattractants recruit more macrophages and tumor cells to pre-metastatic lungs via the upregulation of serum amyloid A3 in a TLR4-dependent manner [132, 183]. CCL2 produced by tumor cells in the metastatic site also induces the recruitment of inflammatory monocytes from the blood to the metastatic site where they promote cancer cell extravasation through VEGF-A secretion [184]. Macrophages also promote metastatic colonization through a variety of mechanisms. They enhance tumor cell survival via counter-receptor α4-integrins that bind to VCAM-1 on the surface of cancer cells in the metastatic site [185]. Metastasis-associated macrophages also promote colony formation abilities of cancer cells through the secretion of granulin that provides a fibrotic microenvironment favoring metastasis [186].

While many studies have described the mechanisms employed by various myeloid cell populations to promote metastasis, few have specifically investigated the pro-metastatic role of DCs in cancer [187]. Infiltration of DCs in metastatic sites has been shown in several studies. DCs promote metastasis by generating an immunosuppressive microenvironment at the metastatic site (Fig. 2d). In a model of pancreatic ductal adenocarcinoma in mice, a discrete $CD11b^+$ DC subset expressing the C-type lectin MGL2 (CD301b) and PD-L2 has been detected in the metastatic microenvironment. These immunosuppressive DCs are developed by monocytes, respond to granulocyte-macrophage colony-stimulating factor (GM-CSF) released by the tumor, and promote metastasis through the expansion of Treg cells and suppression of $CD8^+$ T cells at the metastatic sites [188]. In mouse models of breast cancer, infiltration of macrophages into bone has been shown to induce accumulation of pDCs, which in turn skews the immune response towards Th2 and upregulates Treg and MDSC populations in the metastatic bone. Moreover, osteolytic cytokines secreted by pDCs and $CD4^+$ T cells induce severe bone damage. Depletion of pDCs reduces tumor growth and abolishes bone metastasis and osteolysis by activating $CD8^+$ T cells and decreasing Treg and MDSC populations [189]. In addition to inducing suppressor cells, pDCs promote tumor metastasis through their secretions. Soluble factors secreted by pDCs isolated from the primary tumor of breast cancer patients have been reported to induce lymph node metastasis by stimulating CXCR4 expression in carcinoma cells. The CXCR4/SDF-1 axis has been shown to play a role in tumor metastasis in many types of cancer [140, 190] (Fig. 3).

6 TIMs and cancer therapeutic strategies, pre-clinical studies and clinical trials

The development of many therapeutic programs has been enabled by understanding the role and functions of TIMs in numerous pro-tumor processes, including immunosuppression, angiogenesis, metastasis, and resistance to anti-cancer therapies [191]. Various therapeutic approaches have recently been applied in preclinical cancer models to abrogate the tumor-promoting effects of TIMs. Clinical trials are currently underway to test some of the most successful methods used in clinical practice [192]. In this article, we review TIM-targeting treatments that may be beneficial for treating a variety of malignant cancers and enhancing patient outcomes.

6.1 Therapeutic strategies targeting TAMs

TAMs are a major part in the biological activity of cancer cells, making them promising targets for cancer therapy [193]. Two main therapeutic strategies are focused on TAMs: inhibiting their pro-cancer functions by blocking TAM recruitment or depleting them, and reprogramming them to activate their anti-cancer effects [194].

6.1.1 Inhibiting pro-tumor TAMs

One potential therapeutic approach is to prevent the macrophage recruitment to cancer tissues to reduce their tumorigenesis [195]. Recruitment of monocyte-derived macrophages to the tumor microenvironment is mediated by the chemokines CCL2 and CXCL12. Inhibition of CCL2/CCR2 or CXCL12/CXCR4 axis reduces macrophage recruitment and accumulation [196–199]. Additionally, studies have shown that the interaction between the chemokine CX3CL1 and its receptor CX3CR1 causes the recruitment of TAMs to soft tissues and promotes skin cancer [200]. Therefore, treatments that prevent TAM recruitment to the tumor microenvironment may be novel targets of CX3CL1/CX3CR1-mediated signaling [194]. In mouse models of pancreatic cancer and glioma, the use of macrophage colony-stimulating factor (M-CSF) inhibitors has been shown to effectively reduce TAMs and hinder tumor growth and development [201–204].

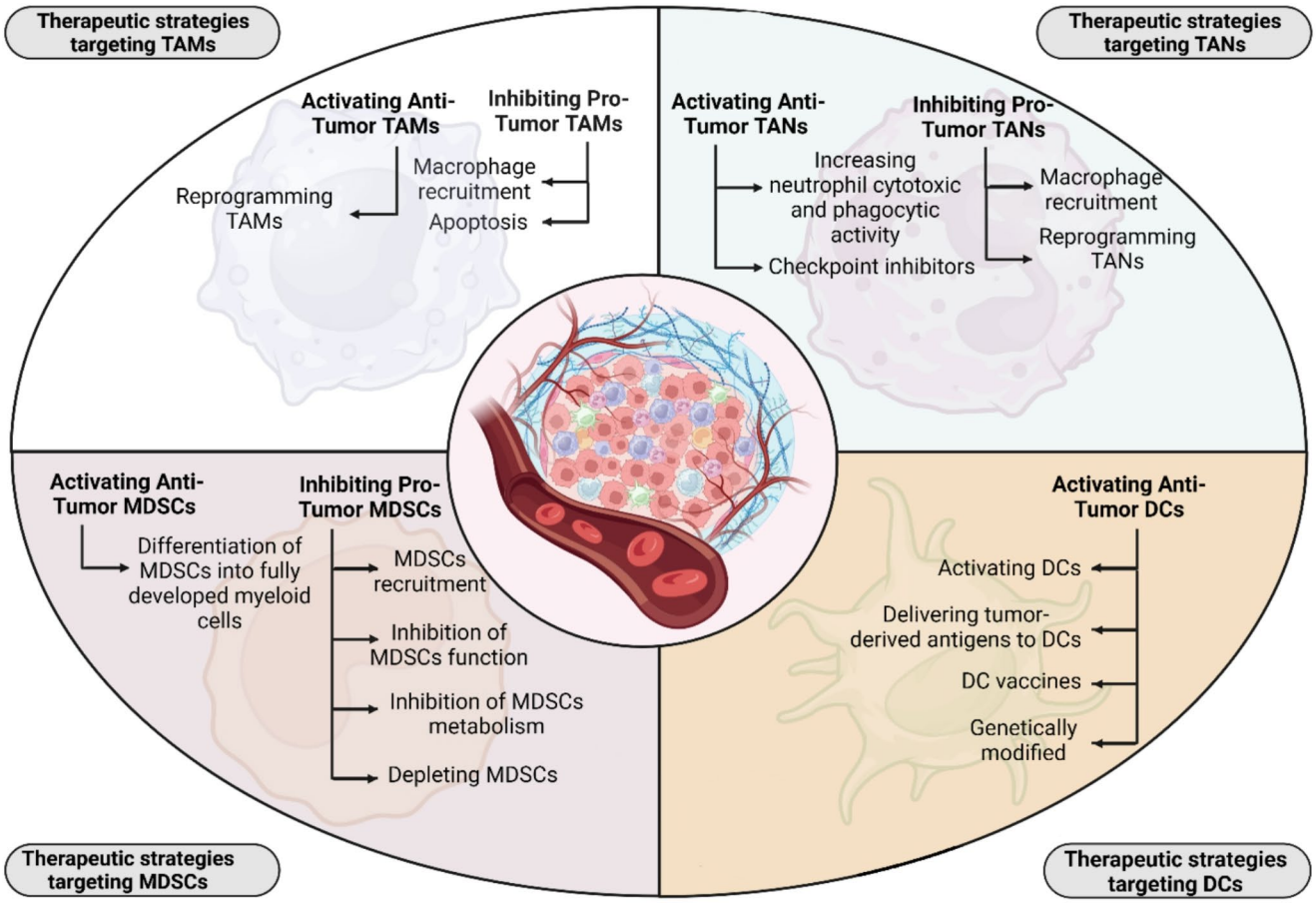

Fig. 3 Therapeutic strategies aimed into TIMs. This figure provides an overview of current strategies for targeting tumor-infiltrating myeloid cells in cancer therapy. This figure was created using www.BioRender.com

Two classes of drugs that block the CCL2/CCR2 axis are currently being used in clinical trials: CCL2 blocking antibodies (carlumab, CNTO888) and CCR2 small molecule inhibitors (PF-04136309) [205, 206]. There is significant evidence that blocking this axis in combination with other cancer treatments can improve the immune response. For instance, a study of pancreatic cancer demonstrated that the CCR2 inhibitor PF-04136309 combined with FOLFIRINOX chemotherapy increased target tumor response and was effective and safe [207]. Another study found that the CXCR4 antagonist BL-8040 inhibits neuroblastoma tumors and has the potential to treat childhood cancer [208]. In a transgenic breast cancer mouse model, the CXCL12 peptide antagonist CTCE-99,088 has been shown to significantly limit tumor development and metastasis [209].

In addition to eliminating TAM by preventing macrophage recruitment, depletion of TAMs (such as induction of apoptosis) is also highly preferable. Clearance of macrophages from the tumor microenvironment is accomplished by inhibiting the CSF-1 and its receptor (CSF-1R) axis [194] or by using substances including bisphosphonates, trabectedin [210, 211], and clodronate-loaded liposomes [212]. Several small molecules targeting CSF-1/CSF-1R, such as PLX3397/Pexidartinib, DCC-3014, BLZ945, FPA008/Cabiralizumab, and MCS110 [213]. The CSF-1R antagonist, PLX3397, can inhibit glioma cell growth in a mouse model of proneural glioma and induce tumor regression by depleting TAM [214]. Another study's findings showed that treatment with PLX3397 greatly decreased tumor growth and the number of macrophages in tumor tissues in breast cancer-bearing mice. The proportion of $CD8^+/CD4^+$ T cells is also increased [215]. In a phase III study in tenosynovial giant cell tumors (TGCTs) patients treated with pexidartinib showed significant improvement in symptoms and functional outcomes; this demonstrates the potential effectiveness of pexidartinib as a therapeutic option for individuals diagnosed with TGCT [216]. According to other clinical data, CSF-1R inhibitors fail to effectively inhibit relapsed glioblastoma (187) and refractory classical Hodgkin lymphoma [217]. Blocked of the CSF-1/CSF-1R axis may be a promising strategy in cancer treatment, particularly for TGCTs. However, it has been revealed that selecting the right patients according to tumor type and providing the right treatment may lead to better outcomes [194].

6.1.2 Activating anti-tumor TAMs

Many clinical studies suggest that removing TAMs may be an effective method. Nevertheless, it is crucial to keep pro-inflammatory and tumoricidal macrophages in the TME [218, 219]. Removing all macrophages could leave the body vulnerable to infectious diseases. Furthermore, macrophages are known for their plasticity, allowing them to develop diverse phenotypes in different microenvironments, including pro-inflammatory and anti-inflammatory. Therefore, reprogramming TAMs to have pro-inflammatory and anti-tumor characteristics may lead to better cancer treatment [194, 220].

Signal-regulated protein alpha (SIRPα) is a protein that interacts with CD47 molecules and is expressed by myeloid cells, including dendritic cells and macrophages [221]. The immune system has two types of checkpoints - adaptive and innate. While PD-1/PD-L1 are examples of adaptive immune checkpoints, cancer cells also use innate immune checkpoints such as SIRPα/CD47 to evade detection by the immune system. As a transmembrane protein, CD47 causes phagocytosis resistance and immunological escape in cancer cells when it binds to the SIRPα ligand on phagocytes. On the other hand, inhibiting the CD47-SIRPα interaction increases the removal of cancer cells by phagocytes, which triggers an innate immune response. This may also lead to the enhancement of the presentation of antigens by antigen-presenting cells (APCs), thereby facilitating the activation of T cells and the subsequent adaptive immune response against tumors [222]. Therefore, the SIRPα/CD47 pathway inhibitors have the ability to activate immune responses against cancer. This approach has been applied in the study of glioblastoma, where a monoclonal antibody (mAb) targeting CD47 was found to convert tumor-promoting TAMs into anti-tumor cells that could more effectively phagocytose cancer cells [223]. Another study using a tumor xenograft model showed that blocking CD47 with an antibody significantly increased the phagocytosis and the infiltration of inflammatory macrophages into tumor tissue of hepatocellular carcinoma, resulting in tumor cells elimination [224]. Additionally, the humanized anti-CD47 antibody Hu5F9-G4 has disrupted CD47-SIRPα recognition and interaction, while exhibiting a slight inhibitory effect on the function of normal human neuronal cells [225].

Recent evidence suggests that inhibitors of the leukocyte immunoglobulin-like receptor (LILRB1)/MHC-I pathway can activate TAMs anti-neoplastic function, providing a novel approach for therapy [226, 227]. However, additional clinical trials are required to confirm and validate these processes [194]. Additionally, there are other methods that enhance the anti-cancer activity of TAMs, including CD40 agonists, TLR agonists, Phosphoinositide 3-kinases (PI3K) inhibitors, and histone deacetylase inhibitors (HDACis) [205, 228]. Phase I clinical trials are being conducted with CD40 agonists such as RO7009789, SEA-CD40, and CP-870,893 [194]. TLR agonists are currently being investigated in cancer research and have some efficacy in promoting polarization of TAMs towards the anti-cancer phenotype. Examples of these agonists are TLR4 (GSK1795091),

TLR7/8 (IMO-2125), and TLR9 (CMP-001) [229]. When the TLR7/8 agonist MEDI9197 was combined with an anti-PD-1 antibody, increased efficacy was observed in multiple isogenic models. This combination may polarize TAMs towards anti-tumor phenotype and activate $CD8^+$ T cells and NK cells [230]. Inactivation of PI3K induces tumor regression by up-regulating inflammatory cytokines such as IL-12, and stimulating $CD8^+$ T cells [231]. Examples of PI3Kγ inhibitors include IPI-549 and YY-20,394 [194]. TMP195, an HDAC antagonist, decreased tumor growth and metastasis in autochthonous mouse breast cancer models by modifying TAMs to a tumoricidal phenotype. Furthermore, TMP195 improved the antitumor effects of PD-1 therapy and chemotherapy [232]. The Glutamine synthetase (GS) antagonist, glufosinate, reduces metastasis in various mouse tumor models. This effect is associated with inhibition of angiogenesis and immunosuppression, as well as the reprogramming of TAMs into an anti-neoplastic type [233]. In syngeneic mouse tumor models of melanoma and non-small cell lung cancer, tumor-derived lactate induces the M2 polarization of macrophages by activating the ERK/STAT3 signaling pathway or the sensor protein Gpr132 [234]. Consequently, selumetinib or stattic or the suppression of Gpr132, which inhibits the ERK/STAT3 axis, reduced lactate-induced M2 polarization and showed significant anti-neoplastic effects in preclinical mouse models [235, 236]. IDO inhibitors block the generation of regulatory T cells and inhibition of cytotoxic T cells via macrophage-mediated immunosuppression [192]. However, several IDO inhibitors, including BMS-986,205, epacadostat, GDC-0919 (navoximod), NLG802, DN1406131, KHK2455, LY3381916, and 1-methyl-D-tryptophan (indoximod), have shown conflicting findings [237]. Research has shown that the adoptive transfer of chimeric antigen receptor-macrophage (CAR-M) that continue to express the transgene effectively inhibits tumor growth in mice that lack a functional immune system and have HER2-positive human tumors [238]. The success of this technique creates opportunities for utilizing modified macrophages' potential anti-tumor cytotoxicity [237]. Additionally, TAMs can be reprogrammed to a pro-inflammatory phenotype by being exposed to stimulators of interferon genes (STING) and pro-inflammatory cytokines [239, 240].

The sialic acid-binding immunoglobulin-type lectin (Siglec) family consists of glycan-binding receptors primarily expressed on immune cells [241]. These receptors play crucial roles in immune regulation, particularly in the context of cancer, where they can influence tumor progression and immune evasion. 14 Siglec genes discovered in humans such as Sialoadhesin/Siglec-1, CD22/Siglec-2, CD33/Siglec-3, myelin-associated glycoprotein/Siglec-4 [242]. This gene serves as a marker for certain types of cancer, like B-cell lymphoma. For example, CD22 and CD33 are used in targeted therapies for hematological cancers [243]. Recent studies have shown that mutations and copy number variations in these genes can affect the behavior of the tumor and the patient [244]. The expression of specific Siglecs on TAMs has been linked to their functional phenotype. Notably, Siglec-9 is predominantly expressed on TAMs and is associated with an immunosuppressive environment, leading to poor patient outcomes in cancers such as high-grade serous carcinoma (HGSC) [245]. These macrophages are associated with a protumorigenic phenotype, characterized by the expression of immunosuppressive markers such as CD163 and PD-L1. They are associated with decreased cytotoxic activity of CD8+T cells, contributing to an overall immunosuppressive tumor microenvironment [246].

The presence of Siglec-9+TAMs has been identified as an independent prognostic factor for poor survival in patients receiving immunotherapy. High levels of these macrophages have been linked with reduced efficacy of therapies targeting immune checkpoints like PD-1. Thereby, Siglec-9 blocking has shown potential to repolarize these macrophages from a protumor to an antitumor phenotype, which enhancing the efficacy of existing immunotherapies [247].

Other members of the Siglec family, such as Siglec-15, also play roles in modulating TAM behavior and immune responses in tumors. Siglec-15 expressed on tumor cells and macrophages and implicated in suppressing antitumor immunity [248].

The interaction between Siglec family genes and TAMs is an important area of cancer immunology research. Understanding how these receptors influence macrophage polarization and tumor progression may lead to the development of novel therapeutic strategies aimed at enhancing anti-tumor immunity through targeted modulation of the immune microenvironment. Using Siglecs as biomarkers to predict response to immunotherapy also may help improve patient outcomes in various malignancies [249] (Table 1).

The relationship between SLAM family genes and tumor-associated macrophages (TAMs) in the context of cancer is an emerging area of research that highlights the complex interplay between immune cells and tumor biology [250]. The SLAM (Signaling Lymphocytic Activation Molecule) family consists of a large number of receptors that are expressed on hematopoietic cells, including T cells and macrophages. These receptors play critical roles in immune signaling and regulation. Particularly, SLAMF7 and SLAMF9 have been shown to play a role in the modulation of TAM functions in various cancers [251].

Studies have displayed that SLAMF7 is associated with to influence the behavior of TAMs significantly. Research indicates that high expression levels of SLAMF7 on TAMs correlate with T cell exhaustion, especially in clear cell

Table 1 Therapeutic strategies aimed into TIMs

TIMs Targeting for Cancer Therapy	Treatment strategies	Mechanisms	Targets	Drug	References
Therapeutic strategies targeting TAMs	Inhibiting Pro-Tumor TAMs	Macrophage recruitment	CCL2/CCR2 axis	Carlumab, PF-04136309	[205–207]
			CXCL12/CXCR4 axis	CTCE-99,088, BL-8040	[208, 209]
			CX3CL1/CX3CR1 axis		[200]
			M-CSF		[201, 202]
		Apoptosis	CSF-1/ CSF-1R axis	PLX3397/Pexidartinib, DCC-3014, BLZ945, FPA008/Cabiralizumab, and MCS110	[213, 216] [213] [213]
			Bisphosphonates		[210]
			Trabectedin		[211]
			Clodronate-loaded liposomes		[212]
	Activating Anti-Tumor TAMs	Reprogramming TAMs	CD47/SIRPα axis	Hu5F9-G4	[225]
			LILRB1/MHC-I axis		[226]
			CD40 agonists	RO7009789, SEA-CD40, and CP-870,893	[194]
			TLR agonists	TLR4 (GSK1795091), TLR7/8 (IMO-2125), TLR9 (CMP-001), TLR7/8 (MEDI9197)	[229, 230]
			PI3Kis	IPI-549, YY-20,394	[194]
			HDACis	TMP195	[232]
			GS antagonist	Glufosinate	[233]
			ERK/STAT3 axis	Selumetinib, Stattic	[235, 236]
			IDO inhibitors	BMS-986,205, epacadostat, GDC-0919 (navoximod), NLG802, DN1406131, KHK2455, LY3381916, and 1-methyl-D-tryptophan (indoximod)	[237, 364]
			Anti-HER2 CAR-TAMs		[393]
Therapeutic strategies targeting TANs	Inhibiting Pro-Tumor TANs	Neutrophil recruitment	CXCL8/CXCR1, CXCR2 axis	Reparixin, Paclitaxel, AZD5069	[262, 266]
	Activating Anti-Tumor TANs	Reprogramming TANs	Blocking TGFβ, AGTR1, ACE, FATP2, CXCR4, NAMPT		[53, 269–271]
		Increasing neutrophil cytotoxic and phagocytic activity	FcαRI (CD89)		[273]
			CD47/SIRPα axis		[275, 276]
		Checkpoint inhibitors	Blocking VISTA, PD-L1, CD200R, LILRB2, PILRα, SIRPα, ACKR2		[279, 280, 282–287]
Therapeutic strategies targeting MDSCs	Inhibiting Pro-Tumor MDSCs	MDSCs recruitment	GM-CSF/G-CSF signaling pathway		[295, 296]
			CSF-1/CSF-1R axis		[298, 299]
			VEGF/VEGFR signaling pathway	Bevacizumab	[300–302]
			Anti-S100A8/A9	Tasquinimod	[305, 306]
			Anti-IL-1β	Anakinra, Canakinumab	[308, 310]
			CCL-2 and CCR-2 axis	CNTO888, PF-04136309, CCX872, BMS-813,160	[292, 312–314]
			CXCLs/CXCR1/2 axis	Reparixin, Paclitaxel, ABX-IL8, HuMax-IL8	[292, 322, 323]

Table 1 (continued)

TIMs Targeting for Cancer Therapy	Treatment strategies	Mechanisms	Targets		Drug	References
		Inhibition of MDSCs function	COX-2/PGE2/EP axis		Celecoxib, NSAIDs	[331–333]
			PDE5 inhibitors		Sildenafil, Tadalafil, Vardenafil	[336, 337]
			HDAC inhibitors		Entinostat, Ricolinostat	[341, 342]
			Nrf2 activator		Omaveloxolone, Nitroaspirin, Oxidized glutathione (NOV-002)	[346–349]
		Inhibition of MDSCs metabolism	Fatty acid metabolism	Inhibiting CPT1, LXR agonists	Etomoxir, GW3965, RGX-104	[353–355]
			Glycolysis metabolism	Inhibiting mTOR, activation of AMPK	Rapamycin, Metformin	[358–360]
			Tryptophan catabolism	Inhibiting IDO, Inhibiting IDO-TDO, Inhibiting Trp-Kyn-AhR pathway	Epacadostat, Navoximod, EOS200271, BMS-986,205	[364, 365]
			Adenosine metabolism	CD39-CD73-A2AR pathway, CD73/A2AR pathway	MEDI9447, AZD4635	[366, 367]
		Depleting MDSCs	Chemotherapy		Gemcitabine, Cyclophosphamide, Docetaxel, Doxorubicin	[292, 368]
			Inhibiting tyrosine kinase		Sunitinib	[369, 370]
			TRAIL-R agonists		DS-8273a	[371, 372]
			anti-CD33		BI 836,858, Gemtuzumab ozogamicin	[373, 374]
	Activating Anti-Tumor MDSCs	Differentiation of MDSCs into fully developed myeloid cells	STAT3 inhibitors		AZD9150	[324, 325]
			TLR agonists		ATRA, Vitamin D3, curcumin, icariin, β-glucans	[326–329]
Therapeutic strategies targeting DCs	Activating Anti-Tumor DCs	Activating DCs	Cytokine and TLR signaling, cGAS/STING pathway		FLT3-LG, GM-CSF, poly I: C variants	[378, 383]
		Delivering tumor-derived antigens to DCs				[378]
		DC vaccines			CMV pp65 mRNA-DCs, hTERT-DCs, WT1 mRNA-DCs, HER2-DCs, AKT-DC	[388–391, 393]
		Genetically modified			Ad-CCL21-DC	[399]

renal carcinoma (ccRCC). These SLAMF7 high CD38 high TAMs were associated with exhausted T cells and served as independent prognostic factors for patient outcomes [252]. The interaction between SLAMF7 on TAMs and T cells promotes the expression of inhibitory receptors on T cells, thereby leading to an immunosuppressive tumor microenvironment [253]. Additionally, studies have demonstrated that co-expression of SLAMF7 with macrophage markers like CD68 linked with better survival outcomes in high-risk neuroblastoma patients. This suggests that SLAMF7 may facilitate anti-tumor immunity through its interactions with TAMs [254].

SLAMF9 also has been identified as a receptor upregulated in TAMs in melanoma tumors. It participates in the recruitment of other immunosuppressive cells to tumor site, thereby enhancing the immunosuppressive capabilities of TAMs. Expression of this receptor is associated with the release of chemokines that recruit regulatory T cells and myeloid-derived suppressor cells (MDSCs), further supporting to a pro-tumor environment [255].

Hence, as discussed above, the relationship between SLAM family genes and TAMs is characterized by a complex interaction that affect tumor progression and immune evasion. SLAMF7 and SLAMF9 play pivotal roles in modulating the functions of TAMs and influence their ability to support or inhibit tumor growth. Understanding these interactions may provide a potential therapeutic path for target TAMs in cancer treatment to enhance anti-tumor immunity while mitigating immunosuppressive effects [254].

Nuclear factor ID3, also known as Inhibitor of DNA-binding 3 (ID3), is a transcriptional regulator that plays a significant role in various biological processes, including immune response and DNA repair mechanisms. It is encoded by the ID3 gene in humans. Activation of the nuclear factor ID3 plays a crucial role in transmitting the function of tumor suppressors to tumor-associated macrophages (TAMs). Recent research highlights that ID3 is required to modulating the balance between activating and inhibitory receptors on macrophages, which is essential for their antitumor activity [256].

Mechanism of ID3 action is through binding of transcription factors ELK1 and E2A at the SIRPA locus, and reducing SIRPA expression. This alteration allows macrophages to engage with tumor cells more effectively [257]. ID3 enhances the ability of macrophages, particularly Kupffer cells, to phagocytose live tumor cells and modulate immune responses. This is achieved by altering the macrophage inhibitory/activating receptor balance, which promotes phagocytic activity and the recruitment of lymphoid effector cells, such as NK and T CD8+cells, to the tumor site [258]. Studies have demonstrated that ID3 expression endow potent antitumor capabilities to macrophages. In particular, ectopic expression of ID3 in mouse bone-marrow-derived macrophages and human induced pluripotent stem cell-derived macrophages has been shown to enhance their ability to form an effective antitumor niche [259].

The findings suggest that targeting ID3 could be a promising strategy in cancer immunotherapy. By harnessing the antitumor properties of ID3-activated TAMs and enhancing their phagocytosis capacity, it may be possible to develop more effective cell therapies that enhance the immune system's ability to combat tumors. The potential for ID3 to reprogram TAMs from a tumor-promoting phenotype to an antitumor one represents a milestone in understanding macrophage biology in cancer contexts [256].

6.2 Therapeutic strategies targeting tans

Blocking TAN recruitment, reprogramming and polarizing these cells to active their anti-tumor properties, augmenting antibody-dependent cellular cytotoxicity (ADCC) activity, and utilizing checkpoint inhibitors represent key strategies in neutrophil-targeting cancer therapies [192, 260, 261].

Ongoing clinical trials are evaluating methods to prevent neutrophil recruitment into the tumor microenvironment by inhibiting CXCL8 or the chemokine receptors CXCR1 and CXCR2 [262, 263]. Reparixin, an inhibitor of CXCR1 and CXCR2, has demonstrated improved efficacy of 5-fluorouracil in vitro and in a mouse model of gastric cancer xenograft [264]. In xenograft mouse models of human pancreatic cancer, the inhibition of CXCR2 prevented the buildup of neutrophils, which in turn triggered the T cell response [265]. This led to the inhibition of metastatic progression and an augmented response to anti-PD-1 therapy [263]. In response to these promising preclinical findings, a phase II clinical trial is currently underway to assess the CXCR2 inhibitor AZD5069 in patients with pancreatic cancer [262]. Furthermore, the combination of Reparixin and Paclitaxel has been evaluated for safety [266], and a double-blind study is ongoing to explore the efficacy of this combination in treating metastatic triple-negative breast cancer [262].

Neutrophils can be reprogrammed to become activated and fight against tumors through various strategies such as reduction of tumor hypoxia [267] and blocking certain molecules like TGFβ [53], angiotensin II type 1 receptor (AGTR1) [268], angiotensin converting enzyme [268], fatty acid transport protein 2 (FATP2) [269], CXCR4 [270], and nicotinamide phosphoribosyl transferase [271]. Additionally, IFNβ or GM-CSF + IFNγ therapy causes neutrophils to polarize into an active anti-tumor state [192].

Another treatment method includes increasing neutrophil cytotoxic and phagocytic activity [192]. Neutrophils express FcγRs, which enable them to eliminate tumor cells through ADCC [272]. Human neutrophils not only express

FcγRs but also have FcαRI (also called CD89), which is a potent inducer of ADCC and a high-affinity receptor for IgA [273]. Interestingly, anti-CD20 IgA therapy prevented lymphoma in mice genetically engineered to express human FcαRI through the action of cytotoxic neutrophils (mice do not express FcαRI) [274]. Additionally, by inhibiting the CD47-SIRPα axis, neutrophils' IgA-mediated cytotoxic activity can be enhanced [275]. The trogoptosis mechanism can maintain the ADCC activity of neutrophils against cancer cells both in vitro and in vivo [276]. It is noteworthy that inhibiting the CD47-SIRPα axis can increase neutrophils' ability to kill tumor cells through trogocytosis [276]. Targeting the CD47-SIRPα axis has been considered an effective approach to enhance neutrophil anti-tumor activity, either alone or in combination with therapeutic antibodies [192].

Utilizing checkpoint inhibitors to target neutrophils represents another approach to counteract their immunosuppressive activities. Ligands of immune checkpoint molecules, such as PD-L1 [277, 278] and V-domain immunoglobulin suppressor of T-cell activation (VISTA) [279, 280], are expressed by neutrophils. In preclinical tumor models, VISTA has been demonstrated to inhibit TLR-mediated downstream signaling activation in myeloid cells. The blockade of VISTA leads to the conversion of monocytes and DCs into proinflammatory cells, thereby promoting T cell infiltration and bolstering T cell-mediated antitumor immunity responses [280]. A poor prognosis has been related to the presence of PD-L1^{+} neutrophils in individuals with hepatocellular carcinoma or gastric cancer. In vitro studies have shown that neutrophils expressing PD-L1 can inhibit T cell function; however, PD-L1 blockade can reverse this effect [281, 282]. In addition to triggering adaptive immune responses, blocking PD-L1 on neutrophils has been shown to increase their cytotoxicity against PD-1-expressing cancer cells [283]. Other myeloid checkpoint molecules, such as CD200R [284], LILRB2 [285], paired immunoglobulin-like type 2 receptor alpha (PILRα) [286] and SIRPα [287], are possible targets to reduce neutrophils' immunosuppressive functions and enhance their effector functions [192]. The importance of CD200R and PILRα expression on neutrophils is not fully understood. On the other hand, studies conducted on mouse tumor models suggest that neutrophils can contribute to the effectiveness of agents that block the CD47-SIRPα signaling axis or the receptor LILRB2, which function as inhibitors of neutrophil activation [285, 288]. Neutrophil precursors have been found to express PD-1 [289] and atypical chemokine receptor 2 (ACKR2) in recent investigations [290]. ACKR2 is crucial for regulating the differentiation of myeloid cells, and its deletion in mice results in increased neutrophil recruitment, which exhibits enhanced cytotoxic activity against cancer cells [290].

6.3 Therapeutic strategies targeting MDSCs

The recognition of the important role played by MDSCs in tumor growth and metastasis has stimulated the search for therapeutic plan to eradicate these cells and abrogate their tumorigenic effects [66, 291]. These strategies can be divided into five different groups: (1) inhibiting the proliferation and recruitment of MDSCs; (2) promoting the differentiation of MDSCs into fully developed myeloid cells; (3) prevention of MDSCs activity; (4) hindering the metabolic processes of MDSCs; and (5) direct depletion of MDSCs [292–294].

There are various methods that can prevent the expansion and recruitment of MDSCs in the TME. In this context, we will discuss some of the latest studies.

6.3.1 Anti-colony-stimulating factors

Many preclinical researches indicated that inhibition of GM-CSF/G-CSF signaling reduces MDSC retention and improves the immune response in tumor cells [295, 296]. The differentiation of myeloid cells from M-MDSCs to TAMs occurs constantly in tumor sites, mainly through CSF-1 and HIF-1α [297]. Polarization of M2 macrophages in the TME can be limited by effective strategies that inhibit CSF-1R [203]. Previous investigations have noted that CSF-1/CSF-1R inhibition in preclinical tumors is more effective when combined with radiation, paclitaxel, an anti-VEGFR antibodies, and immune checkpoint inhibitors [298, 299]. Finally, combination therapy based on CSF blockade should be further investigated as a potential way to prevent MDSC development in cancer patients [292].

6.3.2 Anti-VEGF/VEGFR therapy

Targeting the VEGF/VEGFR signaling pathway, may be hindered MDSC recruitment and its ability to promote angiogenesis [292]. Thus, Anti-VEGF/VEGFR therapy could be effective against MDSCs in cancer patients. Bevacizumab-based treatment resulted in a significant reduction in the percentage of PMN-MDSCs in the peripheral blood of non-small-cell lung carcinoma (NSCLC) patients [300]. Nevertheless, treatment with bevacizumab alone did not result in a reduction of MDSC accumulation in the peripheral blood of renal cell carcinoma (RCC) patients [301]. These differences may be due to changes in the dosage, timing, or interval drug administrations. In fact, anti-VEGF/VEGFR agents have been shown to eliminate MDSCs from tumors, spleen, and blood circulation dose-dependently [302].

6.3.3 Anti-S100A8/A9

In various mouse tumor models, inhibition of S100A8 and S100A9 has been shown to inhibit tumor growth by preventing the accumulation of MDSCs [303, 304]. Tasquinimod is an oral compound that binds to S100A9 and prevents its interaction with sensors such as RAGE and TLR4 [305]. Treatment of cancer with tasquinimod reduced the number of circulating monocytes and infiltration of MDSCs into tumor sites, and induce M1 polarization in TAMs [306]. The results suggest that targeting S100A8/A9 could be beneficial in improving the immunosuppressive role of MDSCs in cancer. However, the effectiveness of S100A8/A9-targeting techniques needs further investigation [292].

6.3.4 Anti-IL-1β

The role of IL-1β in tumorigenesis and development is primarily attributed to its ability to induce persistent and unresolved inflammation, stimulate angiogenesis, and facilitate the expansion and migration of MDSCs [307]. Currently, there are various agents that can restrain IL-1, such as IL-1Ra (anakinra), antibodies that are specific to IL-1β (canakinumab), and inflammasome inhibitors [308–310]. Combining IL-1β blockade with other cancer treatments, such as chemotherapy, may result in additional benefits [311].

6.3.5 Anti-CCL2/CCR2

Combining CCL2/CCR2 blockade with radiation therapy, immunotherapy, and targeted therapy can improve cancer prevention. This combination has also led to a reduction in the number of tumor-associated MDSCs and an increment in tumor-infiltrating lymphocytes in mice [292, 312]. Clinical trials have evaluated the efficacy of CNTO888 (a humanized mAb targeting CCL2) [313], PF-04136309 (a small molecule inhibitor of CCR2) [207], CCX872 (CCR2 inhibitor) [314], and BMS-813,160 (CCR2 inhibitor), in combination with immunotherapy or chemotherapy to treat cancer [292]. A possible explanation for the unsatisfactory results of current studies is that CCL2 neutralizing antibodies and CCR2 inhibitors may not adequately block the CCL2-CCR2 axis for a long time [313, 315]. Various alternative factors, including CCR5 ligands, regulate MDSC infiltration into tumors. Therefore, inhibiting a single chemokine may not have significant therapeutic effects [316]. Albeit, targeting chemokine receptors may be beneficial because a single receptor can interact with multiple chemokines, it is worth noting that many CC chemokines can attract both APCs and TILs simultaneously [317]. However, the CC chemokine/receptor axis has great ability in cancer treatment, especially when combined with immunotherapy agents [292].

6.3.6 Anti-CXCLs/CXCR1/2

Inhibition of the CXCLs/CXCR1/2 axis and combination of chemotherapy drugs has been demonstrated to be synergistic effects in antitumor activities [264, 318]. Studies have shown that therapies targeting CXCLs/CXCR1/2 can ameliorate the effectiveness of immune checkpoint inhibitors (ICIs), as well as genetically modified and transferred T cells and NK cells by preventing the migration of PMN-MDSCs to the tumor site [319–321]. So far, various clinical trials have evaluated CXCR1/2 inhibitors, including Reparixin and Paclitaxel, for the metastatic breast cancer treatment [292]. Moreover, two humanized monoclonal antibodies, ABX-IL8 and HuMax-IL8, which target IL-8, have been extensively researched [322]. Notably, HuMax-IL8 has demonstrated safety and tolerability in patients with advanced tumors, and it is currently being investigated in a phase Ia/II clinical trial in combination with nivolumab (NCT03400332) [323].

Approaches to enhance MDSC differentiation into non-suppressive myeloid cells include the use of STAT3 inhibitors (such as AZD9150, an antisense oligonucleotide inhibitor of STAT3) [324, 325], and agonists targeting TLRs [292]. ATRA, also known as all-trans retinoic acid, is a vitamin A derivative that exhibits agonistic behavior on retinoid-activated transcriptional regulators (RARα and RARβ). Successive activation of downstream signals by these regulators results in maturation of the original myeloid cells into less immunosuppressive and fully differentiated variants [326]. Vitamin D3 can induce MDSCs differentiation to enhance the immune responses against tumors, similar to ATRA [327]. Preclinical tumor models have shown that curcumin [326], icariin (ICA) [328], and β-glucans [329] could potentially be used as therapies to promote the differentiation of MDSCs and decrease associated immunosuppression [292].

Another therapeutic approach involves the inhibition of MDSCs function. In this context, we will provide a brief overview of recent advances in the inhibition of MDSC activity.

6.3.7 COX-2/PGE2/EP axis inhibitors

This pathway stimulate the recruitment of MDSCs, preserve their suppressive activity, and modulate PD-L1 expression of MDSCs [292]. Studies have investigated the impact of blocking the COX-2/PGE2/EP axis on MDSC proliferation in cancer [330, 331]. An example of this is using celecoxib (both a COX-2 inhibitor and a nonsteroidal antiinflammatory drug)

in dietary treatment. This resulted in reduced localization and accumulation of all subtypes of MDSCs, either locally or systemically, in tumor-bearing mice. Also, it reduced ROS and nitric oxide (NO) levels [332]. Furthermore, when an anti-CD40 agonist and celecoxib were used together, expression of ARG-1 in MDSCs was reduced and the survival rate of GL261 glioma mice was increased compared to either treatment alone [333]. The current treatments that aim at COX-2 with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors result in harsh side effects due to the suppression of prostanoids throughout the body. Consequently, there is a possibility of targeting the molecules downstream of the PGE2 pathway as an alternative approach [334].

6.3.8 Phosphodiesterase 5 (PDE5) inhibitors

Sildenafil, tadalafil, and vardenafil classified as PDE5 inhibitors [335]. These inhibitors may mitigate the immunosuppressive properties of MDSCs by boodting the intracellular cyclic guanosine monophosphate (cGMP) levels, thereby reducing the expression of ARG-1, iNOS, and IL-4Ra in MDSCs [336, 337]. A trial was conducted to assess the safety and tolerance of tadalafil in patients diagnosed with metastatic melanoma. The results revealed that the treatment was both effective and safe for stable patients, who exhibited an increase in CD8+T cells alongside a reduction in MDSCs associated with metastatic disease. This trial was open-label and incorporated a dose de-escalation [338]. According to a clinical trial with the registration number NCT00843635, the use of tadalafil in patients with HNSCC resulted in decreased levels of MDSCs and Tregs in both the peripheral blood and tumor sites [339].

6.3.9 Epigenetic regulators

HDAC serve a significant function as epigenetic regulators [340]. Recent research have shown that HDAC can strengthen the effectiveness of immunotherapeutic agents in mouse tumor models by lowering the expression level of ARG-1, iNOS, and COX-2 in MDSCs [341, 342]. A study conducted on mouse models with EL4 lymphoma and LLC (Lewis lung carcinoma) found that entinostat, a selective class I HDACi, reduced the immunosuppressive capabilities of PMN-MDSCs. In contrast, M-MDSCs express elevated levels of class II HDAC6, and the immunosuppressive activity of M-MDSCs was diminished by inhibiting HDAC6 using ricolinostat [343].

6.3.10 Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway activator

In tumor-bearing mice with systemic Nrf2-deletion or myeloid lineage Nrf2-deficiency, ROS are abnormally increased in MDSCs, resulting in greater susceptibility to cancer metastasis [344, 345]. Phase I trials for NSCLC and melanoma have been completed for Omaveloxolone, which is an Nrf2 activator [292]. Other therapies such as nitroaspirin or NO-releasing aspirin [346, 347] and oxidized glutathione (NOV-002) [348, 349] have the potential to inhibit the function of MDSCs [292].

Another therapeutic approach for targeting MDSC metabolism involves the inhibition of various metabolic pathways, such as fatty acid metabolism, glycolysis, tryptophan catabolism, and adenosine metabolism [292].

6.3.11 Targeting fatty acid metabolism

MDSCs are characterized by increased uptake of free fatty acids (FFAs) and elevated expression of key enzymes involved in fatty acid oxidation (FAO) [350, 351]. Targeting the fatty acid metabolism of MDSCs may inhibit their immune suppression. Inhibition of carnitine palmitoyltransferase 1 (CPT1), the first rate-limiting enzyme of the FAO pathway, using etomoxir has been shown to slow down tumor progression in a T-cell-dependent manner in various mouse tumor models. Furthermore, the immunosuppressive effect of tumor-infiltrating MDSCs was completely abolished when etomoxir was combined with low-dose chemotherapy [352]. MDSCs have other targets involved in lipid metabolism, including the transcription factor liver-X receptors (LXRα and LXRβ). The use of LXR agonists inhibits tumor growth and stimulates anti-tumor immunity [353]. A recent study has shown that two LXRβ agonists, GW3965 and RGX-104, can reduce MDSC levels in various tumor models [354]. This is achieved through increasing the transcriptional target of apolipoprotein E (ApoE) through agonism of LXR binding to low-density lipoprotein receptor-related protein 8 (LRP8) on MDSCs, resulting in decreased survival of MDSCs. In addition, RGX-104 has been shown to be effective against cancer in mouse models when combined with various immune-based agents such as chimeric antigen receptor (CAR)-T cells and anti-PD-1 antibodies [355].

6.3.12 Targeting glycolysis

Glycolytic enzymes are increased in MDSCs, leading to a high rate of glycolysis. This protects them from apoptosis and causes their accumulation in cancer patients [356]. Research has demonstrated that the mTOR inhibitor rapamycin reduces glycolysis, immunosuppressive function, and the amount of tumor-infiltrating M-MDSC in mice with tumors [357]. Furthermore, HIF-1α regulates the glycolytic pathway of MDSCs, and its activity can be suppressed through the activation of AMP-activated

protein kinase (AMPK). Studies have shown that treatment of AMPK with metformin inhibits the proliferation and immune response of MDSCs in mouse tumors [358, 359]. Additionally, metformin therapy has been shown to suppress MDSC activity by reducing the expression and activity of extracellular CD39 and CD73 enzymes in MDSC in ovarian cancer patients [360].

6.3.13 Targeting tryptophan catabolism

The tryptophan-kynurenine-aryl hydrocarbon receptor (Trp-Kyn-AhR) pathway is widely recognized as a mediator of cancer resistance [361]. IDO and tryptophan 2,3-dioxygenase (TDO) play a crucial role in the initial rate-limiting step of converting L-tryptophan to N-formyl L-kynurenine [292]. IDO exhibits high expression in tumor-infiltrating cells such as fibroblasts, endothelial cells, and MDSCs [362]. IDO activation exerts multiple effects, including the inhibition of T and NK cells, recruitment and activation of Tregs and MDSCs, and the promotion of angiogenesis and tumor metastasis [363]. Several IDO inhibitors, such as epacadostat, navoximod, EOS200271, and BMS-986,205, have been shown to be safe and effective in patients with advanced malignancies [364]. currently, researchers are investigating dual IDO-TDO inhibitors and novel inhibitors of the Trp-Kyn-AhR pathway, like enzymes that degrade Kyn, direct AhR antagonists, and tryptophan mimetics [365].

6.3.14 Targeting adenosine metabolism

The metabolic pathway of adenosine, known for its immunosuppressive properties, is essential in tumor immunity modulation [366]. The CD39-CD73-A2AR pathway has emerged as a target of many pharmacological agents, in which CD39 and CD73 facilitate the conversion of extracellular ATP into adenosine and subsequently inhibit the T cell effector function through the adenosine receptor A2A (A2AR). Current investigations are underway in early-phase clinical trials to assess these agents, both as monotherapies and in conjunction with immunotherapeutic approaches. Primary results suggest that they are well-tolerated [367]. Clinical trials for patients with carcinoma and NSCLC are also underway for MEDI9447 and AZD4635, which target CD73/A2AR [292].

Clinical trials have investigated various therapeutic strategies to target MDSCs, including depleting their populations through low-dose chemotherapy [368], Sunitinib [369, 370], TNF-related apoptosis induced ligand-receptor (TRAIL-R) agonists [371, 372], and anti-CD33 [373, 374]. These methods have been explored as a means of combating MDSCs in order to improve patient outcomes [292].

Chemotherapy drugs not only directly eradicate cancer cells but also have the capability to adjust the immune system by targeting and eliminating MDSCs, which are responsible for suppressing the immune response [368]. Gemcitabine, cyclophosphamide, docetaxel, and doxorubicin are commonly used chemotherapy agents that effectively reduce the number of MDSCs in individuals with cancer [292].

Sunitinib is a type of tyrosine kinase inhibitor that targets multiple pathways and prevents angiogenesis while also modulating immune dysfunction. It has received approval for the treatment of individuals diagnosed with metastatic renal cell carcinoma (mRCC) [375]. Beyond its primary effects, sunitinib can also reduce levels of MDSCs, which contributes to its antitumor activity [369, 370]. An experiment was conducted on eight mRCC patients who received the combination of autologous tumor lysate-loaded DC vaccine and sunitinib. The findings indicated that there were no adverse events related to the vaccine, and five patients exhibited reactive T cell responses to tumor lysate, with four of them experiencing reduced frequencies of MDSCs [376].

TRAIL-Rs, classified as death receptors, consist of TRAIL-R1 (commonly referred to as DR4/CD261) and TRAIL-R2 (known as DR5/CD262) [292]. In a study (phase I) involving 16 patients with end stage of cancer, administration of the TRAIL-R2 agonistic antibody DS-8273a led to a reduction in peripheral blood levels of MDSC in the majority of patients, also a notable reduction in tumor-infiltrating MDSCs observed in half of the patients. This treatment did not influence on the neutrophils, monocytes, other myeloid cells and lymphocytes levels [377].

Targeting CD33 on MDSCs represent a promising therapeutic strategy for the treating a range of human cancers. Researches have exhibited the effectiveness of BI 836,858, a fully humanized and Fc-engineered monoclonal antibody directed against CD33, in inhibiting CD33-mediated signaling transduction in patients with myelodysplastic syndrome (MDS). This antibody has been found to deplete MDSC via ADCC [374]. It has also been reported that gemtuzumab ozogamicin, an immunotoxin that targets CD33 and is a humanized mAb, can reduce MDSCs levels. This subsequently leads to the reactivation of T cell and CAR-T cell responses against various types of cancer in vitro [373].

6.4 Therapeutic strategies targeting TADCs

DCs are vital antigen-presenting cells (APCs) that significantly influence the immune system's response to tumors. Therefore, an effective treatment strategy is to improve DCs function, proliferation, and tumor-derived antigen specificity [378]. It is now clear that different cancer treatments, including chemotherapy/radiotherapy, immunotherapy such as immune-checkpoint blockade and adoptive T-cell therapy,

affect the function of tumor DCs and thus determine the therapeutic effect [84]. Furthermore, several immunotherapeutic strategies centered on DCs have been developed, which involve the DCs activating, delivering tumor-derived antigens to DCs, and using DC vaccines [378–380].

6.4.1 DCs in cancer therapy

The death of tumor cells induced by radiotherapy and chemotherapy results in the release of several molecules, including high mobility group box 1 (HMGB1), ATP, and tumor-derived DNA. These molecules trigger the immune response of DCs located within the TME. Additionally, DCs may improve the efficacy of T-cell therapy [381]. They secrete the chemokines CXCL9 and CXCL10, which attract T cells to the location of tumor. CD40-CD40L interactions between DCs and T cells further enhance T cell activation [378].

The strategy of immune checkpoint blockade (ICB) aims to prevent interference with immune checkpoints, thereby inhibiting the immune system to effectively target the tumor. To enhance the effect of ICB treatment, DC-activating adjuvants like αCD40 antibody, polyinosinic: polycytidylic acid (poly I: C), fms-related tyrosine kinase 3 ligand (FLT3LG), and cGAMP are utilized in combination with ICB as they have the potential to improve DC functions [378].

6.4.2 DC-based immunotherapy

One approach to DC-based immunotherapy focuses on the direct stimulation of DCs through the application of various agents, including FLT3-LG, GM-CSF, and poly I: C variants. in addition to cytokines, TLR signaling is also a potent stimulator of DC activation. The cDC1 subset, which is vital for tumor suppression and primarily expresses TLR3, making the TLR3 agonist poly I: C a potential cancer treatment to activate cDC1s [378, 382]. However, clinical trials have revealed a high risk of toxic reactions associated with poly I: C [383], leading to the development of substitutes such as poly-ICLC, poly I: C12U, and nanoparticle-encapsulated poly I: C with lower toxicity [378]. Another strategy involves genetic engineering of tumor cells to GM-CSF production [378].

The pathways involving cyclic GMP-AMP synthase (cGAS) and STING are crucial for activating DCs-mediated immunity unto tumors. The DNA sensing processes in DCs are modulated by SIRPα signaling. Blocking the interaction between CD47 and SIRPα enhances cGAS-STING signaling by improving the detection of tumor mitochondrial DNA in a subset of SIRPα$^+$ cDC2. This induces type I interferons and fosters a robust anti-tumor immunity [384]. In melanoma mouse models, administration of STING agonists resulted in tumor rejection and heightened immune responses [385].

Beyond the activation of dendritic cells, the introduction of tumor-derived antigens can stimulate DCs to strengthen the immune system against tumor. These antigens could be administered as whole tumor lysates or as tumor-specific antigens, such as neoantigens identified by next-generation sequencing and bioinformatics tools [378, 386].

To make DC vaccines, immature DCs (such as conventional DCs or moDCs) are extracted from the blood of cancer patients and stimulated with tumor antigens (in the form of tumor lysates or specific antigens), to facilitate their maturation and activation. Genetic tools like clustered regulatory interspaced short palindromic repeats/CRISP-associated protein 9 (CRISPR-Cas9) system and viral vectors can be used to improve dendritic cell function. Once activated and loaded with tumor antigens, these dendritic cells are reintroduced into the patient causing antigen-specific immunity. Nonetheless, the efficacy of DC vaccines may be reduced due to the immunosuppressive nature of the TME and the immune evasion strategies employed by tumor cells. To overcome this challenge, ICB therapy has been integrated with DC vaccine to counteract the effects of the TME [378, 387].

6.4.3 Clinical trials of DC-based tumor immunotherapy

In clinical trials, DC-associated cancer immunotherapy can be divided into two groups: DC vaccines and other DC-related trials. several clinical trials have tested DC vaccines targeting various tumor-specific or tumor-associated antigens, including cytomegalovirus (CMV) pp65, telomerase, Her2, and Wilms' tumor 1 (WT1) [388]. In two phase I clinical studies, glioblastoma (GBM) patients were immunized with CMV pp65 mRNA-loaded DCs, resulting in increased frequencies of IFNγ$^+$, TNFα$^+$, CCL3$^+$ multifunctional, and CMV-specific CD8$^+$ T cells. Additionally, long-term disease-free survival and overall survival were also improved in patients receiving this vaccine [389, 390]. A phase II clinical trial demonstrated that immunization of adults against acute myeloid leukemia (AML) using hTERT-DCs (autologous DCs expressing human telomerase reverse transcriptase) was safe and effective, also may improve recurrence-free survival [391]. In another phase II clinical trial, WT1 mRNA-electroporated DCs were discovered to be a successful method in preventing or postponing AML relapse after standard chemotherapy by inducing WT1-specific CD8+T cell responses [392]. In an anti-HER2 studies, DC1 vaccination was a safe and immunogenic method to induce tumor-specific T cell responses in patients with HER2-positive breast cancer [393].

immunization of autologous lysate DC has been shown to stimulate T cells. In a phase III clinical trial, it enhanced tumor immunity and improved overall survival in advanced colorectal cancer patients [394]. DC immunotherapy for mesothelioma using allogeneic tumor cell lysates has been shown to be effective and safe in humans in a phase I clinical trial using autologous DC pulsed with allogeneic tumor cell lysates [395]. In a phase III study, adoptive transfer of autologous activated killer T cells and DCs (AKT-DC) increased the $CD8^+/CD4^+$ T cell ratio in NSCLC survivors [396].

Additionally, a phase I/II clinical trial demonstrated that the efficacy of tumor antigen-specific DC and lymph node homing was significantly increased by treating the vaccination site with potent memory antigens such as tetanus/diphtheria (Td) toxoid [397].

In other DC-related studies, DCs were combined with the TLR-3 agonist, poly-ICLC, to treat metastatic pancreatic cancer. Results from this study revealed an increase in tumor-specific T cells [398]. Additionally, in a phase I clinical trial, DCs were genetically modified using an adenoviral (Ad) vector carrying the CCL21 gene (Ad-CCL21-DC). This stimulated tumor antigen-specific immunity and increased CD8+T cell infiltration and PD-L1 expression in the tumor [399].

7 Discussion

The role of tumor-infiltrating myeloid cells (TIMs) in the tumor microenvironment (TME) is increasingly recognized as a critical factor that affects cancer progression and treatment outcomes [400]. In this review, the complex interactions between various TIM subtypes, including TAMs, TANs, MDSCs, and TADCs has highlighted and exhibited both pro-tumor and anti-tumor functions that make therapeutic strategies complicated.

The tumor microenvironment is a complex and dynamic ecosystem where various immune cell subsets interact with tumor cells, which influence each other's differentiation and functional characteristics [401]. The phenotype heterogeneity and functional plasticity of the TIMs indicate important challenges in understanding their roles in cancer [402]. Innate immune cells, including macrophages, neutrophils, and dendritic cells, play critical roles in modulating the TME. They can produce a range of cytokines and chemokines, which affect TIM differentiation [403]. For instance, peripheral blood monocytes are recruited to the TME and can differentiate into TAMs, which can polarize into two main phenotypes: M1 (pro-inflammatory and anti-tumor) and M2 (anti-inflammatory and pro-tumor). The balance between these phenotypes is crucial; while M1 macrophages initially exhibit anti-tumor properties by the production of pro-inflammatory cytokines and help to remove tumor cells, M2 macrophages can facilitate immunosuppression and promote angiogenesis, thereby enhancing tumor survival and metastasis [404].

Adaptive immune cells, especially T cells, also have great effects on TIMs. TME consist of diverse T cell phenotypes, which influencing the behavior of TIMs through direct cell interactions and cytokine signaling [405]. For example, regulatory T cells (Tregs) release immunosuppressive cytokines that improve M2 polarization of macrophages, so providing an immunosuppressive environment that contributes to the progression of the tumor. Furthermore, exhausted T cells can express various immune checkpoints that may inhibit the activation of TIMs, making the immune landscape more complicated [406]. Cytokines are essential in mediating the interactions between different immune cell subsets. For example, transforming Growth Factor-beta (TGF-β) and Interleukin-4 (IL-4) are known to promote M2 macrophages polarization. Conversely, pro-inflammatory cytokines like Interferon-gamma (IFN-γ) can stimulate M1 polarization. The presence of these cytokines in the TME not only causes TIM differentiation but also affects their functional abilities in tumor immunity [407]. Thus, interaction between various immune cell subsets in TME is crucial for modulating the differentiation and phenotypic characteristics of TIMs. Understanding these interactions is vital for the development of effective immunotherapy that can reprogram TIMs to more anti-tumor phenotype [408].

Given their critical roles in mediating immune responses in the TME, TIMs represent promising targets for cancer therapy [409]. This review also explains several therapeutic strategies aimed at reprogramming or depleting immunosuppressive TIM populations while enhancing the presence or function of immunostimulatory myeloid cells. For example, a method that blocks specific signaling pathways involved in TAM polarization could convert the balance from a pro-tumor to an anti-tumor environment. Additionally, the combination of current approaches like checkpoint inhibitors or chemotherapy can increase overall treatment efficacy by reducing resistance mechanisms associated with TIMs [410, 411]. Recent studies emphasize the complexity and diversity of TIMs in various cancer types. For instance, a pan-cancer analysis from 192 tumor samples of 129 patients showed unique subtypes of TIMs and indicated significant changes in their abundance and functional states before and after immunotherapy. This variability emphasizes the importance of understanding TIM dynamics for developing effective cancer treatments [412, 413].

There are several challenges of targeting TIMs in cancer therapy. Functional diversity between the TIM subsets makes the development of targeted therapies complicated.

This is due to the fact that interventions that can be effective for one subset might unintentionally boost the activity of another [414]. Furthermore, the dynamic nature of TIM populations requires continuous monitoring and characterization during treatment to adjust the best strategies [415]. Future studies should focus on clarifying a specific mechanism that influence TIM behavior in the tumor microenvironment. Advanced techniques like single-cell RNA sequencing and mass cytometry offer valuable insights into the diversity of TIM populations and their interactions with other immune cells. Understanding these interactions is essential for creating more effective combination therapies that not only focus on TIMs but also utilize their potential to boost anti-tumor immunity [416, 417].

Recent advancements in single-cell sequencing and spatial transcriptomics have greatly improved our understanding of myeloid cell behavior in different cancer contexts. These technologies provide valuable information on the tumor microenvironment (TME) and the functions of myeloid cells, which are essential for developing targeted therapies and personalized medicine [418]. Single-cell RNA sequencing (scRNA-seq) has transformed our understanding of the tumor microenvironment (TME), especially in relation to the diversity of myeloid cells in cancer. Myeloid cells, including tumor-associated macrophages, dendritic cells, and myeloid-derived suppressor cells, play critical roles in tumor progression, immune evasion, and response to therapeutic agents [419]. Spatial transcriptomics (ST) has become an essential method for mapping how myeloid cells are organized within tumors. This technology allows researchers to precisely examine gene expression patterns and provide insight into cellular interactions [420]. ST has been used to distinguish between tumor and non-tumor tissues, as well as to identify unique spatial regions like tumor interfaces and tertiary lymphoid structures (TLSs). These areas are critical for understanding the immune landscape and potential prognostic factors. For instance, studies have shown that specific myeloid cell populations can be found in specific tumor regions, affecting T-cell activity and overall immune responses [421]. The combination of ST with single-cell analysis has made it easier to identify important cellular interactions that are linked to treatment responses. This combined approach is leading to precision medicine strategies that customize therapies based on the specific spatial and cellular characteristics of each tumor [422, 423].

Studies using single-cell RNA sequencing (scRNA-seq) have revealed the complexity of myeloid cell populations within Pancreatic Ductal Adenocarcinoma (PDAC). This type of cancer is featured by its highly immunosuppressive environment, due to myeloid cell infiltration [424]. A study examining HPV-positive tonsillar cancer demonstrated the expansion of myeloid cells and their diverse roles in managing immune responses. Through single-cell analysis, researchers identified different dendritic cell lineages and the processes of macrophage polarization, emphasizing the importance of these cells in patient prognosis. The results suggest that specific myeloid biomarkers may be utilized for targeted therapies and enhancing survival rates [425]. A comprehensive study involving nearly 900,000 cells from lung cancer patients used both scRNA-seq and spatial transcriptomics. This research identified significant changes in myeloid cell phenotypes associated with tumor progression and treatment response, highlighting an inverse relationship between anti-inflammatory macrophages and cytotoxic immune cells. These findings are crucial for understanding the role of myeloid cells in immune evasion in lung cancer [15]. Recent research using single-cell sequencing and spatial transcriptomics is unraveling the intricate behaviors of myeloid cells in cancer. These technologies are not only enhancing our understanding of tumor biology but also set the stage for developing more effective therapeutic strategies based on individual patient profiles [426, 427].

8 Conclusion

Given the heterogeneity and plasticity of myeloid cells and their capacity to support various aspects of tumor biology, the effective management of TIMs has been the target of different therapeutic strategies. All of these tactics are intended to reduce or modulate immunosuppressive cell populations while increasing populations of immunostimulatory cells. Moreover, some important issues, such as the difference in myeloid cell abundance between patients with different tumor types or within the same tumor type, should be taken into account in future treatment to ensure specific and long-lasting immunity.

Acknowledgements Not applicable.

Author contributions All authors contributed to the study conception and design. Literature Search, Writing - Original Draft, were performed by M.S.H, F.S.T. and M.B. The review and editing of the manuscript were done by A.R, M.B. and M.S.H. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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