



# The pleiotropic mode and molecular mechanism of macrophages in promoting tumor progression and metastasis

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## Abstract

Macrophages are the most abundant immune cells in primary and metastatic tumor tissues. Studies have shown that macrophages mainly exhibit a tumor-promoting phenotype and play a key role in tumor progression and metastasis. Therefore, many macrophage-targeted drugs have entered clinical trials. However, compared to preclinical studies, some clinical trial results showed that macrophage-targeted therapy did not achieve the desired effect. This may be because most of what we know about macrophages comes from *in vitro* experiments and animal models, while macrophages in the more complex human microenvironment are still poorly understood. With the development of technologies such as single-cell RNA sequencing, we have gained a new understanding of the origin, classification and functional mechanism of tumor-associated macrophages. Therefore, this study reviewed the recent progress of macrophages in promoting tumor progression and metastasis, aiming to provide some help for the formulation of optimal strategies for macrophage-targeted therapy.

**Keywords** Macrophages · TAMs (tumor-associated macrophages) · M1 · M2 · Macrophage-targeting immunotherapy

## Introduction

Although advances in traditional treatment methods (such as surgery, radiotherapy, chemotherapy, and gene-targeted therapy) have improved the prognosis of patients to a certain extent, local recurrence and distant metastasis are still the leading causes of death in cancer patients. In recent years, to solve this problem, researchers have gradually turned their attention from the study of tumor cells themselves to the study of tumor microenvironment (TME). With the in-depth study of TME, a new treatment method-immunotherapy has been successfully developed and applied in patients with refractory or metastatic cancer. Among them, immune checkpoint blockade (ICB) therapy targeting CD8<sup>+</sup>T cells has achieved particularly significant clinical effects in some cancer patients. Accordingly, many people believe that

immunotherapy (including ICB, tumor vaccines, and adoptive immune cell therapy, etc.) will become the new pillar of cancer treatment. However, a substantial proportion of patients experience limited clinical benefit after ICB therapy, and almost all cancer patients eventually develop drug resistance. The reasons are analyzed as follows: on the one hand, tumor intrinsic factors such as tumor mutation burden limit the therapeutic effect of ICB therapy, on the other hand, TME produces ICB resistance by limiting the infiltration and activation of effector *T* cells. Fortunately, studies have found that the immunosuppressive network established by tumor-associated macrophages (TAMs) is one of the main mechanisms affecting the therapeutic effect of ICB therapy, and macrophage-targeted therapy can greatly improve the therapeutic effect of ICB therapy.

Macrophages (M $\phi$ ) exist in almost all tissues and organs and play a crucial role in tissue homeostasis. As a pivotal component of the innate immune system, macrophages can recruit other immune cells to the site of infection, phagocytose and obliterate foreign pathogens, and activate the complement system and adaptive immunity [1]. In addition, macrophages play critical roles in development, disease (including cancer, infection, and inflammation), and tissue regeneration and remodeling. Actually, macrophages are the most pro-tumor immune cells in the TME. It has

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been demonstrated that tumors are significantly associated with the recruitment and polarization of macrophages. For example, tumor-secreted cytokines CSF-1 and CCL2 are the most important factors that promote the recruitment of macrophages. M1 exhibits pro-inflammatory, pro-immune and anti-tumor features, while M2 has anti-inflammatory, immunosuppressive and pro-tumor functions. In the TME, macrophages dynamically and continuously differentiate according to the changes in the current microenvironment. For example, IFN- $\gamma$ , TNF- $\alpha$ , IL-12, GM-CSF, etc. induce the polarization of macrophages to M1, and IL-4, IL5, IL-10, IL-13, etc. induce their polarization to M2. Although the M1/M2 polarization dichotomy limits an accurate description of macrophage function, it is currently the most widely used classification of macrophages.

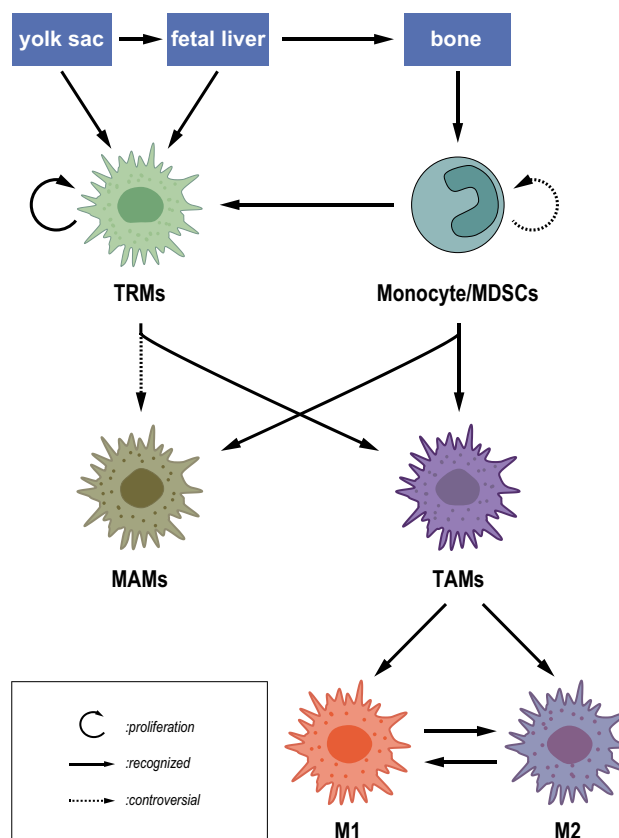
In addition to powerful immunosuppressive effects, macrophages have extensive tumor-promoting functions. For example, they can promote tumor progression and metastasis by participating in cancer stem cell activation, epithelial-mesenchymal transition (EMT), tumor angiogenesis, transendothelial migration, extracellular matrix (ECM) remodeling, and formation of pre-metastatic niches (PMN). Thus, therapies targeting macrophages may exert or improve anticancer therapeutic effects through broad and pleiotropic mechanisms. In conclusion, macrophages have emerged as one of the most promising therapeutic targets for controlling tumor recurrence and metastasis due to their powerful tumor-promoting characteristics.

Although preclinical studies have confirmed the good therapeutic effect of targeting macrophages, and many targeted drugs have entered clinical trials. We still lack a thorough understanding of macrophages due to their high heterogeneity and plasticity. Inaccurate targeted therapy will greatly reduce the effect of anti-tumor therapy, and even some serious complications will occur. Therefore, this review details the current status of research on the tumor-promoting mechanisms of macrophages, as detailed below.

## Origin of macrophages

Macrophages is not only widely distributed in various healthy tissues, but also exists in most solid tumor tissues. Moreover, it is one of the most abundant immune cells in tumor tissue, and even accounts for up to 50% of immune cells [2]. So, where do these macrophages originate and how are they enriched in tumors? For more than half a century, the mainstream view has been that macrophages are derived from bone marrow hematopoietic stem cells. However, with the development of modern lineage tracing techniques and single-cell RNA sequencing (scRNA-seq), a large body of evidence has shown that they have different pathways of origin. First, in addition to myeloid-derived macrophages,

the researchers identified embryonic-derived macrophages in adult mouse tissues [3]. Subsequently, further studies confirmed that embryonic-derived macrophages also exist in human organs and tissues [4]. Therefore, it is currently recognized that there are three origins of macrophages, which are: yolk sac-derived erythromyeloid progenitors (EMPs) produced embryonic macrophages, embryonic monocytes generated by EMPs colonization in the fetal liver and monocyte-macrophages differentiated from bone marrow hematopoietic stem cells. (Fig. 1) Actually, macrophages in most normal tissues, namely tissue-resident macrophages (TRMs), are dominated by embryonic macrophages with self-renewal and proliferation capacity, supplemented by the recruitment of myeloid-derived macrophages. However, not all TRMs have multiple origins. For example, TRMs in



**Fig. 1** Macrophage Origin and Polarization. **a** Macrophages have three origins (yolk sac, fetal liver, and bone marrow) and two forms (TRMs and myeloid-derived macrophages). **b** Unlike TRMs, which have a well-defined self-proliferation ability, the self-proliferation ability of bone marrow-derived TAMs in tumor tissues remains controversial. **c** TAMs mainly consisted of myeloid-derived macrophages, followed by TRMs. However, unlike TAMs, whether MAMs are partially derived from TRMs remains controversial. **d** TAMs can be further polarized into M1 and M2, while M1 and M2 can be converted into each other. *TRMs* tissue-resident macrophages, *MAMs* metastasis-associated macrophages, *TAMs* tumor-associated macrophages

adult gastrointestinal and dermal tissues are almost exclusively derived from bone marrow, whereas TRMs in brain tissues are almost exclusively derived from embryos (yolk sac origin) [5].

Besides, there is currently controversy over the origin of TAMs. Lineage tracing studies in mouse models have shown that, in contrast to TRMs that are predominantly derived from embryonic precursors, the vast majority of TAMs are derived from myeloid-derived monocytes/monocyte-myeloid-derived suppressor cells (M-MDSCs) [6]. Therefore, it has been suggested that the “reservoir” of TAMs is mainly composed of circulating monocytes and M-MDSCs. However, recent studies have shown that TAMs have both embryonic and myeloid origins, at least in tumors such as lung cancer, pancreatic cancer, and glioblastoma [7]. These studies also found that TAMs of different origins have different phenotypic and functional characteristics. Among them, bone marrow-derived TAMs highly expressed genes related to immunosuppression and antigen presentation, while embryo-derived TAMs highly expressed genes related to tissue remodeling and wound healing [8]. Chow et al. found that Tim-4<sup>+</sup> luminal resident macrophages sequestered and inhibited the proliferation of CD8<sup>+</sup>T cells, and blocking Tim-4 enhanced the efficacy of ICB therapy and adoptive T cell therapy in mice [9]. Ramos and colleagues found that FOLR2<sup>+</sup>TRMs are positively associated with good prognosis by interacting with CD8<sup>+</sup>T cells in breast cancer tissue [10]. In addition, the proportion of TAMs of different origins varied with tumor progression. Through scRNA-seq technology, it was found that TAMs in the early stage of tumors were mainly embryonic-derived TRMs. And they promote tumor growth and proliferation by establishing a pro-tumor niche by promoting tumor cell EMT, invasion, and protecting tumor cells from adaptive immunity [11]. Similarly, Huggins et al. identified a novel lipid-associated macrophage derived from alveolar macrophages (AMs) in an animal model of breast cancer lung metastasis. Interestingly, their study showed that the aggregation of these cells occurred before the formation of tumor metastases [12]. Therefore, we speculate that TRMs may be more inclined to proliferate and function in the early stage of tumors compared with myeloid-derived macrophages.

Moreover, Antunes et al. found that myeloid-derived TAMs also have the ability to self-renew and proliferate, and inhibiting the recruitment of myeloid-derived macrophages only activates the proliferation compensatory mechanism of TAMs, but does not reduce the total number of TAMs [13]. Wang and colleagues found that granulocyte-macrophage colony-stimulating factor (GM-CSF) enhanced A2A receptor expression on TAMs and synergized with adenosine to induce proliferation of TAMs in liver cancer tissues [14]. These may be one of the reasons for the poor efficacy of pan-macrophage-targeted therapies, such as anti-CSF-1 antibody.

In conclusion, it is still unclear how TAMs of different origins regulate the TME and cancer progression. Further clarification of this issue is of great significance for elucidating the diversity of TAMs functional phenotypes and targeted therapy strategies.

## Recruitment and polarization of TAMs

Tumor promotes the recruitment and polarization of macrophage. Ali N and colleagues [2] summarized the five recruitment axes of monocyte-macrophages, including CCL2/CCR2, CXCL12/CXCR4, VEGF/VEGFR, complement components (especially C5a/C5a receptors) and CSF-1/CSF-1R. Studies have found that tumors can also recruit macrophages/M-MDSCs through CCL3, CCL5, CX3CL1, IL34, and periostin. In addition, recent studies on tumor metabolism have shown that the hypoxic environment in tumors plays a key role in promoting the recruitment and differentiation of TAMs [15]. Metabolites in the TME may also be important factors in tumor recruitment of TAMs. For example, Barrio et al. found that adenosine can promote the recruitment of monocytes through a self-amplifying mechanism that is further adenosine production by M2 or MDSCs recruited by adenosine [16].

Traditionally, TAMs have been classified into M1 (classically activated macrophages) and M2 (alternatively activated macrophages) polarized phenotypes based on their functional characteristics. M1 exhibits pro-inflammatory, pro-immune, and anti-tumor features, while M2 has anti-inflammatory, immunosuppressive, pro-angiogenic, and metastasis-promoting functions [17]. Recently, some scholars have further subdivided M2 cells into four subgroups: M2a, M2b, M2c and M2d [1, 18]. The present findings suggest that IFN- $\gamma$ , TNF- $\alpha$ , Toll-like receptor (TLR) agonists (such as bacterial lipopolysaccharide (LPS)), IL-12, GM-CSF can induce TAMs polarization to M1 [19–22], while IL-4, IL5, IL-10, IL-13, IL-33, CSF-1, TGF- $\beta$ , FGF2, PGE2, Sonic Hedgehog (SHH), BMP4 and Sema3A induce TAMs polarization to M2 [20, 23–28]. Besides, accumulating evidence suggests that TAMs can promote their polarization toward M1 or M2 by ingesting tumor cell-derived exosomes [29–34]. In addition, metabolic reprogramming of tumors [20], hypoxic state of the TME [35], and remodeling of the ECM [36, 37] can promote TAMs polarization toward M2. However, TAMs differentiate dynamically and continuously according to changes in the current microenvironment, resulting in their high degree of heterogeneity and plasticity. On the one hand, their functional phenotypes have the characteristics of spatiotemporal distribution [11, 38]. That is, TAMs show different phenotypic and functional characteristics between different patients, between different tumors in the same patient, and even in different sites or different

stages of the same tumor. For example, despite the overall predominance of an anti-tumor phenotype, TAMs mainly exhibit an anti-tumor M1 phenotype in early tumor stage and a pro-tumor M2 phenotype in tumor progression [18, 39–41]. Besides, unlike M1 that are predominantly enriched in normoxic tumor areas, M2 are predominantly enriched in hypoxic, necrotic and perivascular tumor areas [20]. On the other hand, continued dynamic differentiation also results in a large number of intermediate transition states in TAMs, or TAMs with both M1 and M2 phenotypes [42–45]. Moreover, the M1/M2 polarization dichotomy is a taxonomy to describe the activation state of TAMs in vitro, limiting an accurate description of the multifunctional complexity of TAMs in humans [46–48]. Therefore, some scholars have tried to use scRNA-seq technology to classify TAMs subsets. For example, Zhang L divided TAMs in colorectal cancer into subgroups of C1QC<sup>+</sup> and SPP1<sup>+</sup>TAMs. Among them, C1QC<sup>+</sup>TAMs highly expressed genes involved in phagocytosis and antigen presentation, while SPP1<sup>+</sup>TAMs preferentially expressed genes involved in angiogenesis. This study further found that anti-CSF-1R treatment preferentially reduced C1QC<sup>+</sup>TAMs with inflammatory features and did not affect SPP1<sup>+</sup>TAMs expressing pro-angiogenic/tumorigenic genes [49]. In a pan-cancer scRNA-seq study, TAMs were further divided into four subgroups: SPP1<sup>+</sup>TAMs, C1QC<sup>+</sup>TAMs, ISG15<sup>+</sup>TAMs and FN1<sup>+</sup>TAMs [43]. In addition, Obradovic found that TREM2<sup>+</sup>/APOE<sup>+</sup>/C1Q<sup>+</sup> TAMs were associated with postoperative recurrence of clear cell renal cell carcinoma [50]. We believe that scRNA-seq technology will become a new classification method of macrophages and influence the formulation of targeted therapy strategies for macrophages. Despite its obvious limitations, the M1/M2 polarization dichotomy is currently the most commonly used method for classifying TAMs in medical research.

## TAMs and tumor growth

To the body, the tumor is like an endless wound that keeps on starting to heal, but never completely heals [51]. In the process of tumorigenesis, precancerous lesions or oncogenic inflammation should eliminate abnormal cells by recruiting pro-inflammatory immune cells such as macrophages and dendritic cells, thereby inhibiting tumorigenesis. At this point, the recruited macrophages (M1) exert anti-tumor functions. The specific manifestations are: (1) phagocytosing and killing tumor cells; (2) presenting neoantigens to CD8<sup>+</sup>T cells to remove tumor cells and start the "immune editing" program; (3) producing cytotoxic factors (such as NO and ROS) to directly kill tumor cells; (4) release of pro-inflammatory factors (such as IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-2, IL-6, IL-12, IL-18, IL-23 and CXCL9) to further activate

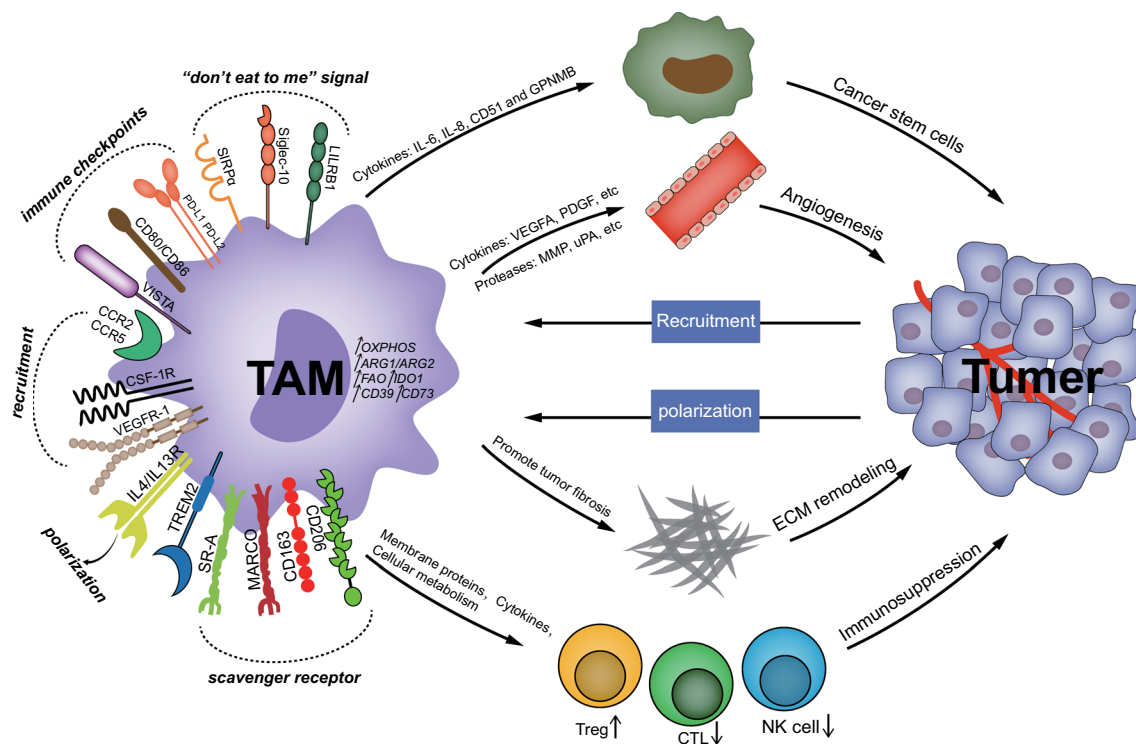
the anti-tumor immune response [52, 53]. In addition, M1 increases the expression of major histocompatibility complex class II (MHC II) molecules, resulting in a higher degree of activation of tumor-associated antigen-presenting cells (APCs) such as monocytes, macrophages, and dendritic cells (DCs) [54]. However, while exerting pro-inflammatory and anti-tumor functions, M1 also increases the gene mutation burden of precancerous cells by releasing IFN- $\gamma$ , TNF- $\alpha$ , TGF- $\beta$ , IL-1 $\beta$ , and reactive oxygen species/reactive nitrogen (ROS/NOS) [55, 56]. An increased gene mutation load is required for tumorigenesis. Gradually, the accumulation of gene mutational burden in precancerous cells leads to tumorigenesis, and tumor cells further promote macrophage recruitment and polarization toward a pro-tumor phenotype by regulating the TME. Importantly, M2 plays a multifaceted tumor-promoting role during tumor progression, as detailed below (Fig. 2).

## Promote cancer stem cells activation

Cancer stem cells (CSCs) are tumor cell subsets with stem cell-like properties that play a key role in tumorigenesis, immune evasion, metastasis and therapy resistance. Several studies have demonstrated that the acquisition and maintenance of CSCs activity can be regulated by TAMs through the secretion of cytokines such as IL-6, IL-8, CD51 and GPNMB [57–60]. Sharma et al. found that TAMs could activate the Notch1-Jagged1/2 signaling pathway through direct contact with tumor cells, thereby inducing stemness in cancer cells [61]. Additionally, TAMs can promote tumor growth and proliferation by secreting collagen [62] and insulin-like growth factor-1 (IGF-1) [63]. In addition, M2 increases the iron absorption rate of tumor cells by up-regulating the expression of ferroportin, which in turn promotes their growth and proliferation [64].

## Promote angiogenesis

The unlimited proliferation of tumor cells requires continuous consumption of a large amount of oxygen and nutrients. When the TME fails to meet the metabolic demands of the tumor, solid tumors turn on a program called an "angiogenesis" switch. This procedure replenishes the tumor with nutrients and removes waste by triggering the formation of a dense network of blood vessels. Importantly, TAMs play a key role in turning on the "angiogenic switch". It can secrete various cytokines (such as VEGFA, platelet-derived growth factor (PDGF), angiopoietin, placental growth factor (PIGF), adrenomedullin (AMD), VEGFC, TNF, IL-1 $\beta$ , IL-6, CCL18, CXCL8, CXCL12, FGF2, WNT7B and signaling protein 4D (Sema4D)) to promote angiogenesis [65–67]. Among them, VEGFA mainly comes from TAMs and promotes the recruitment, proliferation and maturation of endothelial cells by



**Fig. 2** TAMs promote the growth of tumor cells

binding to VEGF receptor 2. In addition, TAMs degrade ECM by expressing membrane-bound or soluble proteases such as matrix metalloproteinases, urokinase-type plasminogen activator (uPA), thymidine phosphorylase, and cathepsin, assisting endothelial cell migration and formation of new vascular buds, and mobilizing free VEGFA in ECM [68]. TAMs also degrade collagen in the ECM by endocytosis in a mannose receptor-dependent manner [69]. Interestingly, TIE2<sup>+</sup>TAMs aggregated around tumor blood vessels, where they supported vascular sprouting or anastomosis in a paracrine fashion [70].

TAMs are also associated with high permeability of neo-vascularization within tumors. On the one hand, TAMs promote the transendothelial migration of tumor cells by secreting inflammatory factors (such as VEGFA and TGF-β) that cause endothelial cells to lose adherent junctions, expand the vascular endothelial cell space and increase permeability. On the other hand, overexpression of these angiogenic growth factors produces immature new blood vessels that appear to be barely covered by pericytes and loosely bound to the basement membrane [71]. When tumor cells migrate around blood vessels, TIE2<sup>+</sup>TAMs open a door for tumor cells to enter the vasculature by assisting their transendothelial migration [72]. Ginter and colleagues found that the tumor metastasis microenvironment (TMEM), involving tumor cells, TAMs, and endothelial cells, is the gateway for hematogenous dissemination of the primary tumor and

lymph nodes of breast cancer [73]. Additionally, preclinical studies have demonstrated that targeted killing or depletion of TAMs can reduce the number of circulating tumor cells [74].

In addition to participating in angiogenesis, TAMs may be associated with increased infiltration and density of lymphatic vessels. It has been found that TAMs can promote lymphangiogenesis and lymph node metastasis by secreting VEGF-C/D [75] and expressing S1PR1 [76] and PDPN [77]. Furthermore, TAMs can differentiate into lymphatic endothelial progenitors and integrate with existing lymphatic vessels to induce new lymphatic sprouting [60].

**Suppress immune response**

We conclude that TAMs mainly exert their immunosuppressive abilities in the following four ways.

**Membrane proteins**

TAMs highly express T cell immune checkpoint ligands on the membrane surface, including PD-L1 (also known as B7H1 or CD274), PDL2 (also known as B7-DC or CD273), CD80 (also known as B7-1), and CD86 (also known as B7-2) [78]. PD-L1 and PD-L2 expression of TAMs is up-regulated by stimulation of cytokines and hypoxia, and they induce effector T cell exhaustion by binding to the

inhibitory receptor PD-1 on the membrane surface of effector *T* cells. However, CD80 and CD86 inhibit the activity of effector *T* cells by binding to CTLA-4 on effector *T* cells. Indeed, TAMs themselves also express high levels of PD-1, which has the ability to reduce their antigen presentation and increase the expression of immunosuppressive factors such as ARG1, IL-10, and TGF- $\beta$  [2, 79]. Kryczek et al. found that another member of the B7 superfamily (B7-H4) expressed by TAMs is also involved in suppressing the immune activity of effector *T* cells [80]. In addition, the V-type immunoglobulin domain-containing suppressor of *T* cell activation (VISTA) expressed on the membrane of TAMs is a novel immunosuppressive checkpoint and is often considered to be an indicator of poor prognosis in various cancers [81]. Furthermore, SIRP $\alpha$  [82], LILRB1 [83], Siglec-10 [84] expressed by TAMs transmit the signal of “don’t eat me” by binding to CD47,  $\beta$ 2M and CD24 on the surface of tumor cell membranes, respectively, thereby protecting cancer cells from being phagocytosed by TAMs.

Scavenger receptors are composed of a structurally diverse group of membrane proteins (including A-H classes) that have important effects on inflammatory responses, tissue repair and remodeling, and innate immune responses by recognizing a broad range of ligands [79]. Among the various scavenger receptors expressed by macrophages, CD206, SR-A (also known as CD204) and CD163 have been widely used as biomarkers for M2. Many scavenger receptors, including SR-A [85], MARCO [86], and Clever-1 (also known as stabilin-1 or FEEL1) [87], contribute to the expression of tumor-promoting activity in macrophages through ligand binding. Fleur et al. found that MARCO<sup>+</sup>TAMs in non-small cell lung cancer promoted Treg cell proliferation and IL10 production, and decreased CD8<sup>+</sup>T cell activity [88]. Masetti et al. found that MARCO<sup>+</sup>TAMs can maintain the growth and invasion of prostate cancer by promoting lipid metabolism and lipid accumulation [89]. Recent studies have found that TREM2<sup>+</sup>TAMs are associated with exhaustion of effector *T* cells and resistance to anti-PD-1 therapy. Targeted TREM2 therapy inhibits tumor growth and improves ICB efficacy while remodeling TAMs [90]. However, TREM2 plays different roles in the occurrence and development of different malignant tumors, and its specific biological function needs to be further confirmed by a large number of studies [91].

Besides, Hu et al. found that DC-SIGN<sup>+</sup>TAMs were associated with inactivation of CD8<sup>+</sup>T cells, and anti-DC-SIGN treatment enhanced the therapeutic effect of PD-1 inhibitors [92]. Qi et al. found that Gal-9<sup>+</sup>TAMs are associated with effector *T* cell exhaustion [93]. Chow et al. found that Tim-4<sup>+</sup>luminal resident macrophages could sequester and inhibit the proliferation of CD8<sup>+</sup>T cells, and blocking Tim-4 enhanced the efficacy of ICB and adoptive *T* cell therapy in mice [9]. TAMs also negatively regulate NK and *T* cell

activity by expressing atypical major histocompatibility complex class I (MHC-I) molecules such as HLA-E and HLA-G, thereby exerting immunosuppressive effects [72]. TAMs also express ligands for the death receptors FAS and TRAIL, which bind to their related receptors on *T* cells and lead to *T* cell apoptosis by activating the caspase 3 and caspase 8 pathways [60, 72]. In conclusion, the specific membrane-expressed receptors of TAMs play an important role in promoting tumor immunosuppression, and blocking them can significantly improve the outcome of immunotherapy in patients. Compared with pan-macrophage-targeted therapy, we believe that targeting receptors on the surface of macrophage membranes is a precise, safe, and more effective therapeutic strategy.

### Cytokines

TAMs can suppress the function of effector *T* cells by secreting a series of cytokines to recruit natural regulatory *T* cells (nTreg) and induce the differentiation of adaptive regulatory *T* cells (iTreg) [72]. For example, TAMs-derived chemokines CCL2, CCL3, CCL4, CCL5, CCL20, and CCL22 promote the recruitment of immunosuppressive nTregs to tumors [19, 78, 94]. TGF $\beta$ , IL-10 and exosomes derived from TAMs can induce the differentiation and expansion of CD4<sup>+</sup>T cells to iTreg [72, 95]. Besides, TAMs can inhibit the cytotoxic activity of effector *T* cells and NK cells through the expression of IL-10 and TGF $\beta$ , thereby promoting tumor progression [78, 96]. Specifically, secreted TGF $\beta$  can directly inhibit CD8<sup>+</sup> *T* cell function through transcriptional repression of genes encoding functional cytokines such as perforin, granzymes, and cytotoxins [97]. Alternatively, secreted TGF $\beta$  indirectly inhibits effector *T* cells by upregulating the expression of indoleamine 2,3-dioxygenase (IDO) in plasma cell-like dendritic cells (pDC) and CCL22 in myeloid DC (mDC) [98]. Membrane-bound TGF- $\beta$  can also affect NK cell phenotype and cytotoxicity through direct cell-to-cell contact [99]. IL-10, which mainly comes from TAMs, can indirectly attenuate the activity of CD8<sup>+</sup>T cells by inhibiting DC secretion of IL-12 [100]. Finally, the lysosomes of TAMs inhibit the cross-presentation of antigens due to their highly active cysteine protease activity, thereby inhibiting the activity of CD8<sup>+</sup>T cells [101].

### Cellular metabolism

M2 participates in the metabolism of L-arginine through high expression of arginase. On the one hand, arginine depletion of M2 leads to "arginine starvation" of effector *T* cells, which in turn inhibits the proliferation and activation of effector *T* cells by blocking the cell cycle [102]. On the other hand, ornithine (M2-related arginine metabolite), as a precursor of proline and polyamines, can remodel the

ECM by promoting collagen synthesis, remodeling of damaged tissues, and formation of fibrosis. Moreover, TAMs can degrade tryptophan in TME through high expression of IDO, thereby inhibiting the cytotoxic activity of T cells and NK cells. A large amount of kynurenine (a metabolite of tryptophan mediated by IDO) can play an immunosuppressive function directly or by binding to AhR on the surface of Treg cells, NK cells and DC cell membranes [103]. In addition, TAMs indirectly exert pleiotropic immunosuppressive functions by promoting the hydrolysis of extracellular ATP to adenosine by expressing high levels of membrane-bound nucleotidase CD39 and CD73, or by initiating NAD<sup>+</sup> extracellular adenosine synthesis by CD38 [20, 104]. Recently, Hinshaw et al. found that TAMs can regulate metabolic processes through the Hedgehog (Hh) signaling pathway, thereby promoting their immunosuppressive activity [105].

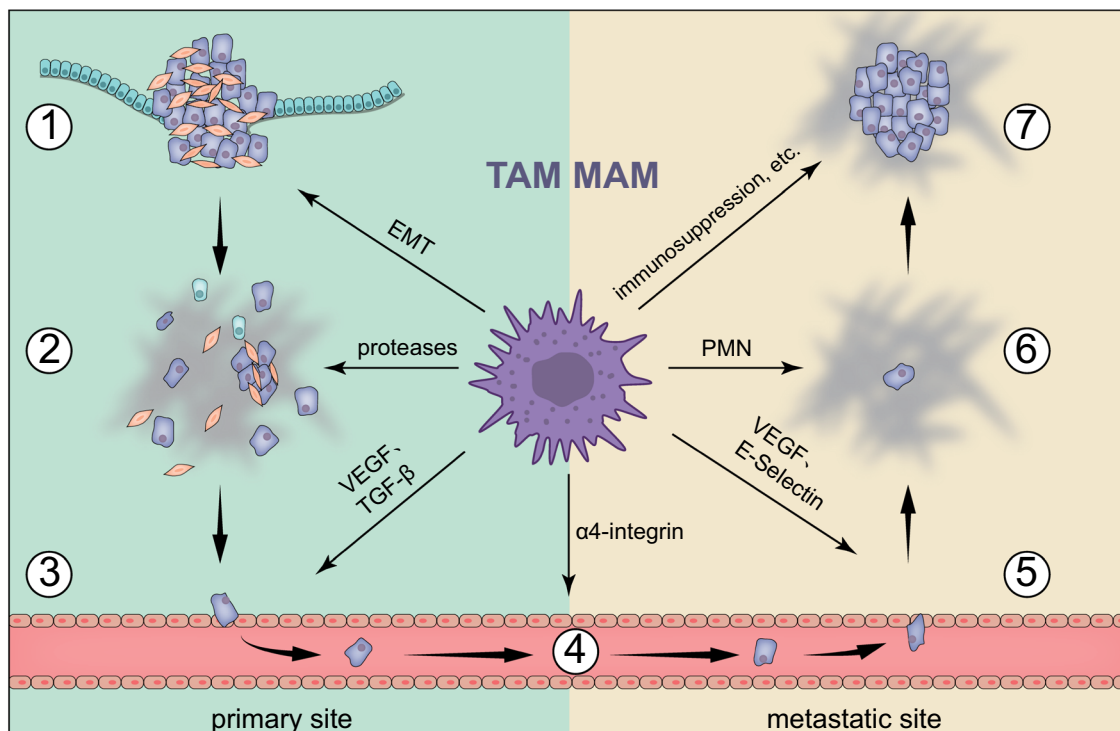
**ECM remodeling**

It is well known that one of the key factors in the failure of ICB therapy is T cell exclusion, that is, the dense fibrotic structure of the ECM hinders the physical contact of CD8<sup>+</sup>T cells with cancer cells, thereby rendering them unable to perform the function of killing cancer cells. Therefore, overcoming this physical barrier imposed by

the ECM is a necessary precondition to guarantee the success of ICB therapy. Increasing evidence has confirmed that TAMs play an important role in the formation of ECM fibrosis. The traditional view is that TAMs mainly activate tumor-associated fibroblasts by releasing inflammatory factors, and then indirectly induce ECM fibrosis [106]. However, studies have shown that TAMs can modulate tumor-associated fibrosis by directly participating in ECM remodeling [107]. Not only that, there is evidence that M2 cells have the potential to transform into tumor-associated fibroblasts [108].

**TAMs, MAMs and distant metastasis**

Tumors metastasize mainly through the following steps: (1) establishment of a pre-metastatic niche (PMN), (2) metastasis and seeding of primary tumor cells (including invasion, migration, vascular infiltration, circulation, vascular extravasation and seeding), (3) growth and proliferation of metastatic tumor cells (including micrometastases, dormancy and secondary growth). And TAMs play an important role in almost all processes. (Fig. 3).



**Fig. 3** Macrophages promote distant metastasis of tumors. **a** The formation process of distant metastasis of tumor includes: invasion, migration and vascular infiltration of primary tumor cells, survival and vascular extravasation of circulating tumor cells, and seeding and

proliferation of metastatic tumor cells. **b** During the whole process of tumor metastasis, macrophages play an important promoting role through different molecular mechanisms. *EMT* Epithelial-mesenchymal transition, *PMN* pre-metastatic niche

## Establishment of PMN

Tumor-secreted factors including EVs, cytokines and chemokines, and other molecular components contribute to tumor cell metastasis. Before the primary tumor cells spread into the blood circulation, the soluble factors (including CCL-2, TNF $\alpha$ , VEGF-A, TGF $\beta$  and CXCL1) [109] and EVs [110] released by the primary tumor cells are first released into the blood circulation and recruit macrophages/MDSCs to pre-metastatic organs [56]. Furthermore, tumor cell-derived tissue factor (TF) [111] and exosomes [112] can promote the recruitment of macrophages by promoting the formation of microthrombi in pre-metastatic organs. The recruited macrophages/MDSCs, together with neutrophils, establish a PMN by remodeling ECM, creating an immunosuppressive environment, stimulating neovascularization, and secreting inflammatory factors [56]. Blocking the recruitment of these myeloid cells to the PMN can significantly reduce the incidence of metastasis and improve disease-free survival [113]. It is worth mentioning that although it was initially thought that TRMs such as alveolar macrophages (AMs) were not involved in tumor metastasis, recent studies have found that AMs can function as metastasis-associated macrophages (MAMs) [12, 114, 115]. For example, Sharma et al. showed that AMs can promote the formation of pre-metastatic niches by inhibiting antitumor immunity [114]. Nosaka et al. found that monocyte-derived AMs promote the progression of lung metastases via leukotriene B4 (LTB4) [115]. In addition, Huggins et al. discovered a novel pro-metastatic lipid-associated macrophage subset (Lgals3, Trem2) in breast cancer lung metastases, and suggested that this cell population was derived from AMs [12].

## Tumor metastasis

Tumor cell reprogramming is a hallmark of tumor invasion initiation. In epithelial cell carcinoma, epithelial-mesenchymal transition (EMT) is the main manifestation of tumor cell reprogramming. EMT encompasses dynamic changes in cellular organization from epithelial to mesenchymal phenotypes, which leads to functional changes in cell migration and invasion [116]. EMT can enhance the metastatic ability of tumor cells, which is manifested by remodeling of the cytoskeleton, changes in cell polarity, loosening of intercellular and cell-matrix junctions, individualization of cells, acquisition of cell motility, and enhancement of cell invasive capacity [117]. In addition, EMT is associated with stem cell properties, cell viability, metabolic changes, and drug resistance [117, 118]. Importantly, TAMs can promote EMT of tumor cells by releasing various cytokines, such as TGF- $\beta$ , Wnt-1, EGF, IL-6, IL-8, IL-10, TNF- $\alpha$ , COX-2 and heme oxygenase-1

(HO-1). Mechanistically, these cytokines promote EMT by increasing the expression and activation of EMT-related transcription factors such as Zeb, Snail, Twist, and FoxQ1, which in turn downregulates the expression of E-cadherin and epithelial cell adhesion molecule (EPCAM).

In addition to promoting EMT, TAMs can participate in tumor invasion and metastasis by producing a variety of proteolytic enzymes that degrade basement membrane and ECM. These enzymes include metalloproteinases (MMP2, MMP7, MMP9), urokinase-type plasminogen activator (uPA), COX2, and cathepsins. TAMs also produce several other molecules to advance tumor cell invasion. One example is osteoadhesin (also known as SPARC), which promotes migration by increasing tumor cell-ECM interactions through integrins [119]. When migrating to the vicinity of blood vessels, tumor cells infiltrate into the vasculature with the assistance of TAMs (see above for details).

In the process of tumor metastasis, some paracrine circuits between TAMs and tumor cells play an important role. For example, preclinical studies have found that breast cancer cells can recruit TAMs by releasing CSF-1 and promote their secretion of EGF and Wnt-1, thereby further supporting tumor cell migration and infiltration into blood vessels [120]. In addition, neuregulin (NRG1) produced by breast cancer cells can promote the secretion of Jag-1 (ligand of Notch receptor) by TAMs, and Jag-1 further promotes the transendothelial migration and infiltration of tumor cells through the Notch signaling pathway [121]. In squamous cell carcinoma, tumor-initiating cells (TICs) induce Fc $\epsilon$ R1 $\alpha$ <sup>+</sup>TAMs to accumulate in their vicinity by overexpressing IL-33. In turn, Fc $\epsilon$ R1 $\alpha$ <sup>+</sup>TAMs promoted the low differentiation and invasiveness of TICs through the expression of TGF- $\beta$ , and further up-regulated the expression of IL-33 [122].

During hematogenous metastasis, tumor cells must overcome challenges such as immune monitoring, fluid shear stress, and oxidative stress. Although Bernabé et al. demonstrated that TAMs promote the survival of tumor cells in the blood circulation, the specific mechanism remains unclear [111]. In addition, previous studies have found that macrophages can activate the PI3K/Akt signaling pathway in tumor cells through the interaction of  $\alpha$ 4 integrin and vascular cell adhesion molecule-1 (VCAM-1), thereby supporting the survival of cancer cells in the circulation [123]. Afterwards, tumor cells reside in the capillary bed of the PMN and infiltrate into the parenchyma within hours of their entry into the blood. Intact lung imaging reveals that macrophages are required for tumor cell extravasation [124]. Qian et al. found that inflammatory monocytes can promote tumor cell extravasation at least by secreting VEGF [124]. Häuselmann et al. showed that monocytes can promote transendothelial extravasation of tumor cells by inducing E-selectin-dependent endothelial cell retraction and regulating tight junctions through dephosphorylation of VE-cadherin [125].



MAMs derived from inflammatory monocytes are one of the most abundant immune cell types in the metastatic tumor niche [126]. They are recruited by CCL2, which is highly expressed by tumor metastatic cells and endothelial cells [127], and adhere to cancer cells via autocrine CCL-3, thus leading to prolonged residence of many MAMs at metastatic sites [128]. That is, CCL2 is mainly responsible for the recruitment of macrophages, while CCL3 is mainly responsible for the retention of macrophages. MAMs play an important role in maintaining the immunosuppressive microenvironment and promoting the growth of metastatic tumors. For example, MAMs can inhibit the activity of effector *T* cells by secreting CCL20 and expressing CD80/86 and PDL-1/2 [56, 129], and inhibit the antitumor activity of NK cells by releasing HGF and expressing membrane-bound TGF- $\beta$  [130, 131]. In addition, MAMs can promote the growth of metastatic tumors through high expression of VEGFR-1 and IL-4R [126, 132]. In a model of pancreatic ductal adenocarcinoma liver metastases, granulins secreted by MAMs promotes the transformation of hepatic stellate cells into myofibroblasts, which secrete periostin, thereby creating a fibrotic microenvironment that sustains metastatic tumor growth [133]. Moreover, because the recruitment of inflammatory monocytes is faster than the rate of differentiation into MAMs, a large number of metastasis-associated macrophage precursors (MAMPCs) are also present at tumor metastatic sites. Ultimately, immunosuppressive MAMPCs can differentiate into MAMs within hours [56].

## Conclusion

In this review, we summarize the latest research progress of macrophages, including its origin, classification, functional roles and molecular mechanisms in different stages of tumors. Based on our research, we believe that macrophages are very potential anti-cancer therapeutic targets, and the development and application of macrophage-targeted drugs has important clinical significance for improving the prognosis of cancer patients. But our current understanding of TAMs is still relatively limited due to their high heterogeneity and plasticity, as well as the intricate interactions between cells within the TME. Therefore, we strongly recommend further research in macrophage-targeted therapy in the future. In this context, the application of new technologies (including scRNA-seq, mass cytometry, multiplex fluorescence immunohistochemistry, TAMs in vivo imaging, and spatial transcriptome sequencing) and the development of clinical trials will be very helpful for our comprehensive understanding of TAMs. In conclusion, TAMs-targeted therapy is a very promising antitumor immunotherapy strategy. However, to obtain the optimal-targeted macrophages therapy, that is, to deliver specific macrophage-targeted

drugs dynamically and efficiently in real time, we still need to conduct more in-depth research on TME and TAMs.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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