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REVIEW

# Understanding the complexity of tumor-associated macrophages: Druggable and therapeutic insights

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**Abstract** Macrophages are immune cells capable of exerting both pro-tumor and anti-tumor effects. Tumor-associated macrophages (TAMs) comprise a heterogeneous group of macrophages originating from monocytes and resident tissue macrophages. Their phenotypes and functions vary depending on factors such as tumor type, location, and stage. TAMs can promote tumor growth, angiogenesis, metastasis, immunosuppression, and drug resistance, or they can facilitate antigen presentation and immune activation, thereby contributing to tumor elimination. As such, TAMs are potential targets for cancer therapy, and various pharmacological strategies and clinic-approved drugs have been suggested to modulate their activity, recruitment, and depletion. However, the complexity and diversity of TAMs present significant challenges to understanding their roles and designing effective drug interventions. This review summarizes the current knowledge of TAMs, and drug development for TAMs as anti-tumor therapy targets, emphasizing the importance of single-cell omics technologies for characterizing TAM heterogeneity and identifying therapeutic opportunities. Additionally, it presents the latest clinical trials focused on TAM-targeted therapies and drugs. Collectively, this review discusses the therapeutic opportunities and challenges of TAM-targeted drug therapies and offers future perspectives and directions for advancing our understanding and manipulation of TAMs in drug development.

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## 1. Introduction

Understanding the complexity of tumor microenvironment (TME) is crucial for advancing cancer therapy. Among the various cellular components within TME, tumor-associated macrophages (TAMs), a heterogeneous group of immune cells, play essential but diverse roles in cancer development and therapy resistance[1,2]. TAMs are derived from monocytes and tissue-resident macrophages and exert both pro-tumor and anti-tumor effects depending on their spatial distribution and interaction with other cells[3]. TAMs can promote tumor angiogenesis and cancer cell proliferation and metastasis, induce immunosuppressive TME, and confer resistance to anti-cancer therapy[4,5] (Fig. 1). Conversely, TAMs can directly mediate the phagocytosis of cancer cells, or interact with innate and adaptive immune cells to promote cytotoxic killing of tumor cells[6] (Fig. 1). Therefore, TAMs' dual roles in pro-tumor and anti-tumor activities underscore the importance of deciphering their functions within the TME.

Given their pivotal roles in modulating tumor behavior, targeting TAMs for cancer therapy has garnered significant attention[2,7−9]. Therapeutic strategies aimed at reprogramming TAMs to an anti-tumor phenotype, inhibiting their recruitment to tumor sites, or depleting them altogether are currently being explored[10−12]. However, TAMs are highly flexible, and their polarization is influenced by various cytokines, signaling pathways, and factors in the TME, which pose substantial challenges in studying their mechanisms and developing effective drugs[13,14]. The traditional model of macrophage polarization classifies macrophages into two broad categories: M1 and M2 macrophages[15]. M1 TAMs are induced by stimuli such as interferon-$\gamma$ (IFN-$\gamma$) or microbial products like lipopolysaccharide (LPS), and are characterized by their high expression of pro-inflammatory cytokines, including tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-6 (IL-6), and interleukin-1$\beta$ (IL-1$\beta$), and their ability to kill tumor cells[16,17]. M2 TAMs are typically induced by cytokines like interleukin-4 (IL-4) and interleukin-10 (IL-10). They are involved in tissue repair, wound healing, and immune suppression. M2 macrophages promote tumor progression[18].

However, this M1/M2 classification is overly simplistic and does not fully capture the complexity of TAMs, which exhibit significant heterogeneity[19]. Strategies for targeting specific subsets of TAMs are warranted. Recent advancements in single-cell omics, particularly single-cell RNA sequencing (scRNA-seq), have enabled the unbiased and comprehensive characterization of TME, including TAM populations[20,21]. Unlike traditional bulk sequencing methods, scRNA-seq allows the analysis of gene expression at the individual cell level, unveiling diverse subpopulations and dynamic states of TAMs that were previously obscured[21]. scRNA-seq also facilitates the integration of TAMs with other types of immune cells, uncovering their crosstalk with other cells[22−25].

Here, we will explore the latest advances in the understanding of TAMs, particularly through the lens of single-cell omics technologies, and summarize the clinical approaches to targeting TAMs in cancer treatment. We propose that a better understanding of TAM diversity and plasticity within cancer will enable the development of more effective and personalized anti-cancer therapies.

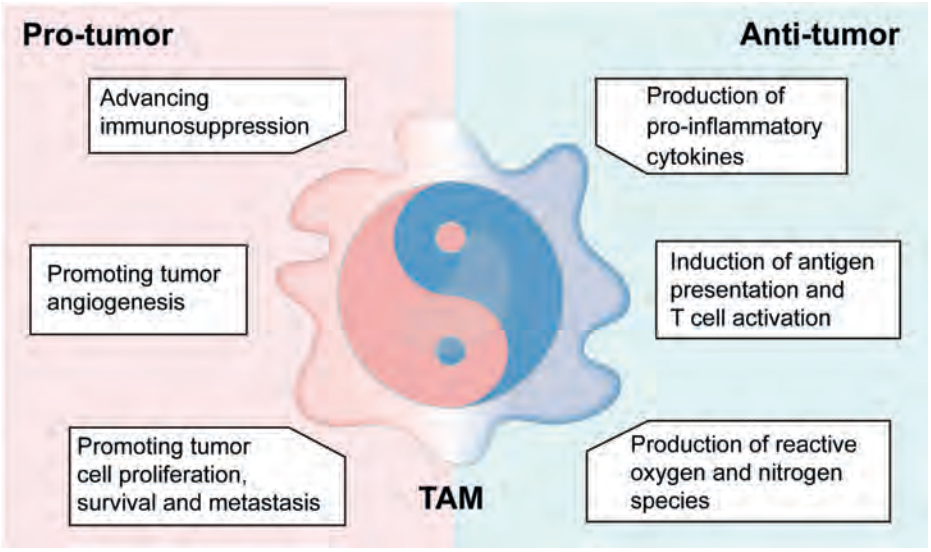


**Figure 1** The dual roles of tumor-associated macrophages (TAMs) in tumor development. TAMs play a dual role in tumor development. On one hand, TAMs can promote tumor progression by advancing immunosuppression, promoting tumor angiogenesis, and facilitating the proliferation, survival, and metastasis of tumor cells. On the other hand, TAMs can also suppress cancer progression through the production of pro-inflammatory cytokines, induction of antigen presentation and T-cell activation, and the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

## 2. The complex roles of TAMs in tumor development

TAMs play a dual role in cancer development and are a critical focus in cancer research. Developing strategies to modulate their function or deplete their populations within the TME is promising[26]. However, the dynamic and heterogeneous nature of TAMs presents significant challenges. In this section, we will provide an overview of the roles and contributions of TAMs to the tumor microenvironment, the challenges associated with targeting them in cancer therapy, and the rationale behind this approach.

### *2.1. Regulation of TAM polarization in the tumor microenvironment*

TAMs exhibit remarkable plasticity, with their polarization influenced by a variety of cytokines, signaling pathways, and factors within the TME.

A key regulator of TAM polarization is colony-stimulating factor 1 (CSF-1) and its receptor (CSF-1R)[27]. CSF-1, primarily secreted by malignant cells, binds to CSF-1R on TAMs, triggering receptor activation and initiating downstream pathways, such as the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/forkhead box protein O1 (FOXO1) axis, which promotes M1 to M2 polarization associated with tumor progression[28,29]. CSF-1R activation also activates other critical pathways, including extracellular signal-regulated kinase 1/2 (ERK1/2), signal transducer and activator of transcription 3 (STAT3), and phospholipase C gamma 2, which together drive M2 polarization[30]. In addition, the TME is rich in cytokines like IL-4 and IL-10, which also drive M2 polarization[31].

Furthermore, recent studies have revealed that metabolic reprogramming plays a pivotal role in TAM polarization and impacts their immune functions in the TME[32]. M1 macrophages primarily rely on glycolysis for rapid energy consumption, alongside the pentose phosphate pathway and fatty acid synthesis to support membrane integrity and pro-inflammatory functions[33]. In contrast, M2 macrophages switch to oxidative metabolism, characterized by fatty acid oxidation and oxidative phosphorylation, while decreasing glycolysis and pentose phosphate pathway activity[34,35]. This metabolic shift is intricately linked to the altered metabolic landscape of the TME, which often features conditions such as hypoxia and nutrient scarcity. Under these conditions, M2 macrophages adapt by switching from glycolysis to oxidative metabolism, allowing them to thrive in the low-oxygen, nutrient-poor TME. For example, lipid droplet-laden macrophages were enriched in hepatocellular carcinoma (HCC) tissues and were associated with disease progression in patients. Tumor-induced alterations in cellular lipids, along with the uptake of tumor-derived fatty acids, contribute to the synthesis of triglycerides and the formation of lipid droplets in macrophages. These lipid droplets enhance the survival and C−C motif chemokine ligand 20 (CCL20) secretion of macrophages, which in turn recruits C−C motif chemokine receptor 6-positive regulatory T cells (Tregs) to HCC tissue.

### *2.2. The cancer-promoting roles of TAMs*

#### *2.2.1. Advancing immunosuppression*

*2.2.1.1. Inhibition of CD8$^+$ T cell activity.* TAMs are generally believed to exhibit an M2-like phenotype, which plays a key role in the inhibition of cytotoxic T lymphocytes, also known as CD8$^+$ T cells (Fig. 2). CD8$^+$ T cells are end-effectors for cancer surveillance. The decreased infiltration of CD8$^+$ T cells into tumors is correlated with poor prognosis in cancer patients[36−38]. TAMs downregulate chemokines such as C−X−C motif chemokine ligand 9/10, which are essential for recruiting CD8$^+$ T cells into the tumor site[39]. Consequently, the diminished infiltration of cytotoxic CD8$^+$ T cells in the TME allows tumors to grow. Moreover, TAMs express various immune checkpoint ligands, including programmed death-ligand 1/2 (PD-L1/L2), B7-1 (CD80), and B7-2 (CD86). These ligands interact with their receptors on CD8$^+$ T cells, inhibiting CD8$^+$ T cell proliferation and activation, thus further impairing the anti-tumor response and contributing to the immune-evasive TME[40,41]. TAMs also express inhibitory receptors, such as human leukocyte antigen-E (HLA-E) and human leukocyte antigen-G (HLA-G), to induce immune suppression. HLA-E and HLA-G major histocompatibility complex (MHC) class I molecules negatively regulate the activation of CD8$^+$ T cells[42,43].

Another layer of TAM-mediated immunosuppression involves their interaction with Tregs. Tregs impair CD8$^+$ T cell activation and thus contribute to immune evasion[44]. Tregs and M2-like TAMs create a positive feedback loop that exacerbates the immunosuppressive state. M2-like TAMs promote the infiltration and activation of Tregs, which, in turn, facilitate the polarization of the M2-like phenotype of TAMs[7,45,46]. Mechanistically, TAMs secrete chemokines, such as CCL20, IL-10, C−C motif chemokine ligand 2−5 and transforming growth factor-beta (TGF-$\beta$), contributing to the recruitment of Tregs into the TME, while Tregs produce cytokines like IL-10 or repress CD8$^+$ T cell-derived IFN-$\gamma$, which promote the M2-like polarization of TAMs[40,45,47,48] (Fig. 3).

*2.2.1.2. Recruitment of myeloid-derived suppressor cells (MDSCs).* MDSCs represent a group of myeloid cells that have potent immunosuppressive activities. These cells inhibit various immune cells, including CD8$^+$ T cells and natural killer (NK) cells, thus contributing to the immune invasion[49,50]. TAMs secrete chemokines, including C−C motif chemokine ligand 2 (CCL2), C−C motif chemokine ligand 5, and C−X−C motif chemokine ligand 8, to attract MDSCs to the tumor site[51]. Additionally, TAMs also produce cytokines like IL-10, and growth factors such as granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, and vascular endothelial growth factor (VEGF), which promote the differentiation and survival of MDSCs[52,53] (Fig. 2).

*2.2.1.3. Induction of metabolic interference.* TAMs also affect the functional capacity of T cells through metabolic interference. They deplete essential amino acids such as L-arginine and tryptophan from the TME. L-Arginine is vital for cytotoxic CD8$^+$ T cells, and its depletion hinders cytotoxic T cell functionality[54,55]. Similarly, the consumption of tryptophan by TAMs also impairs the cytotoxic ability of T cells[55,56]. Additionally, TAMs adapt to the hypoxic conditions of the TME by relying on glycolysis, which produces lactic acid and contributes to the acidic tumor milieu. This environment supports the survival and function of Tregs while suppressing CD8$^+$ T cell proliferation, further inhibiting effective immune responses[34]. On the other hand, Tregs can alter the metabolic fitness of TAMs, thereby enhancing their ability to suppress immune responses[44].

#### *2.2.2. Promoting tumor angiogenesis*

*2.2.2.1. Secreting pro-angiogenic factors.* TAMs secrete several pro-angiogenic factors, including VEGF, IL-1$\beta$, IL-6,

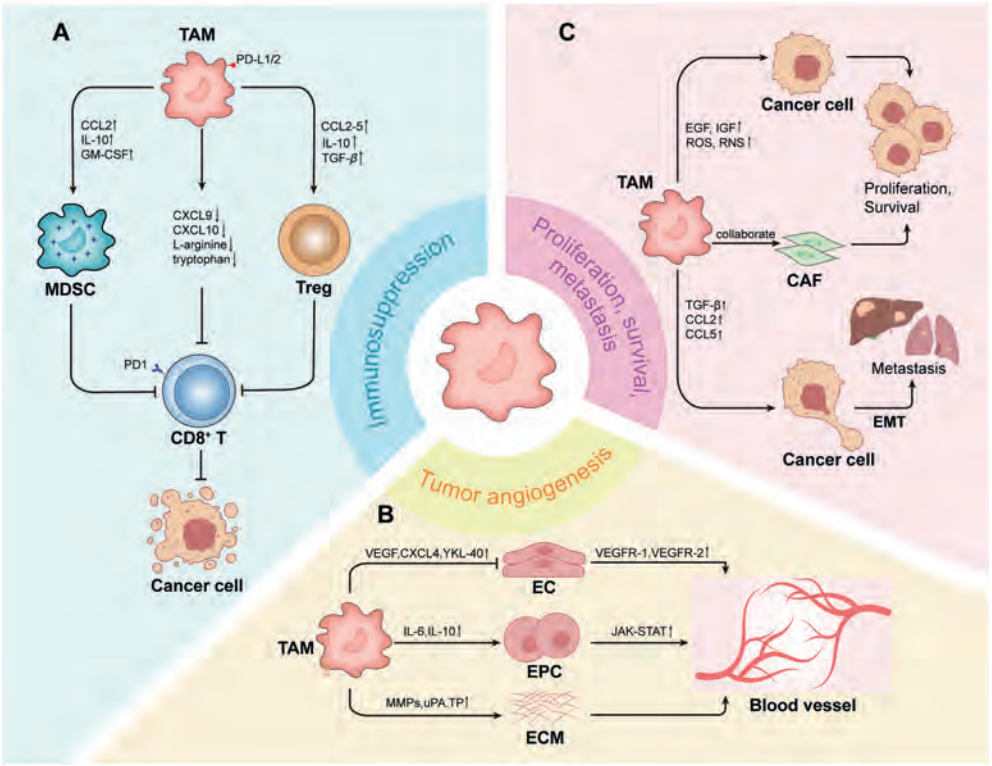


**Figure 2** The roles of TAMs in promoting cancer progression. (A) Advancing immunosuppression. TAMs can directly inhibit $CD8^+$ T cell activity or interact with Tregs and MDSCs to indirectly inhibit $CD8^+$ T cell activity through multiple mechanisms. (B) Promoting tumor angiogenesis. TAMs promote angiogenesis by secreting pro-angiogenic factors that stimulate endothelial cells to form new vessels, induce the differentiation of endothelial progenitor cells into mature endothelial cells, and remodel the extracellular matrix (ECM). (C) Promoting proliferation, survival, and metastasis of tumor cells. TAMs directly enhance the malignant phenotypes of tumor cells, via secretion of growth factors, interaction with cancer-associated fibroblasts (CAFs), and induction of tumor cell epithelial-to-mesenchymal transition (EMT).

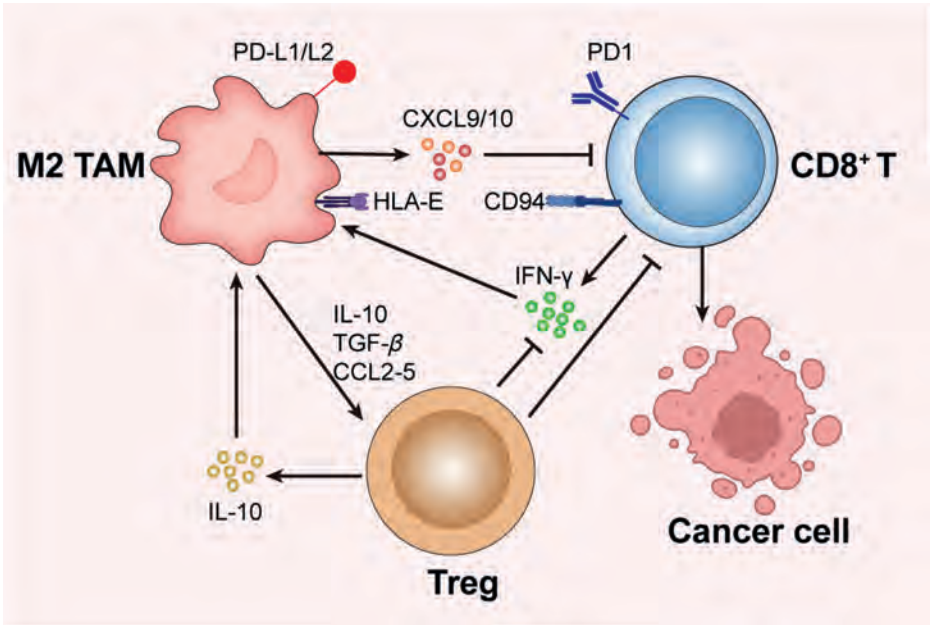


**Figure 3** Regulatory loops between M2 TAMs, Tregs and $CD8^+$ T cells. Illustration of the complex interactions within M2 TAMs, Tregs, and $CD8^+$ T cells, as well as the related cytokines and receptors, that contribute to immune modulation.

interleukin-8, and chemokines such as C−X−C motif chemokine ligand 4, C−X−C motif chemokine ligand 8, C−X−C motif chemokine ligand 10 (CXCL10), and CCL2, all of which promote the formation of tumor blood vessels[57]. Of these, VEGF is the most potent inducer of angiogenesis, binding to its receptors: VEGFR1−3. In particular, VEGFR2 activates the ERK1/2 and PI3K−Akt signaling pathways in endothelial cells, inducing tumor angiogenesis[58]. Evidence shows that depleting TAMs or knocking down *VEGF* expression in macrophages significantly impairs angiogenesis, whereas restoring *VEGF* expression rescues tumor angiogenesis[59]. TAMs also promote angiogenesis by secreting chitinase-3-like protein 1 (YKL-40), which activates ERK1/2 signaling in endothelial cells, enhancing the expression of VEGFR-1 and VEGFR-2, which in turn fosters vessel sprouting[60,61] (Fig. 2).

Notably, a specific subset of TAMs, TEK receptor tyrosine kinase-expressing monocytes (TEMs), plays a crucial role in tumor angiogenesis. TEMs are recruited into tumors by angiopoietin-2 (Ang-2), a ligand for TEK receptor tyrosine kinase (Tie2) in endothelial cells, and are instrumental in the formation of tumor blood vessels[62]. A higher number of TEMs in tumor tissues is positively correlated with decreased survival in cancer patients[63,64]. The accumulation of TEMs in tumors following chemotherapy, radiotherapy, and anti-angiogenic therapies also suggests that they may play a crucial role in vascular reconstruction[65,66]. However, the specific mechanism underlying TEM-induced tumor angiogenesis remains largely unknown.

*2.2.2.2. Inducing differentiation of endothelial progenitor cells.* TAMs also promote the differentiation of endothelial progenitor cells into mature endothelial cells, which are crucial for the formation of new blood vessels. IL-6 and IL-10, secreted by TAMs, activate the JAK−STAT3 signaling pathway in these progenitor cells, promoting VEGF release and tumor angiogenesis[67].

*2.2.2.3. Remodeling of the extracellular matrix (ECM).* TAMs further promote tumor angiogenesis by secreting matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA). These molecules facilitate the degradation of basement membranes and the ECM, which are essential for remodeling the pre-existing vasculature and enabling the formation of new tumor vessels[68,69] (Fig. 2).

### 2.2.3. Promoting proliferation, survival, and metastasis of tumor cells

TAMs directly promote tumor cell malignant phenotypes through multiple mechanisms. First, TAMs secrete high levels of growth factors, like epidermal growth factor and insulin-like growth factor, which bind with the respective receptors on cancer cells, promoting cell proliferation[70,71]. Second, TAMs produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), which induce oxidative and nitrosative stress in tumor cells. These stresses typically lead to DNA damage and are traditionally associated with cell death[72]. However, in malignant cells, ROS and RNS promote genomic instability, driving the emergence of more aggressive tumor clones[73]. Additionally, ROS and RNS activate pro-survival PI3K/Akt and mitogen-activated protein kinase (MAPK) pathways, which mediate the resistance of tumor cells to apoptosis[74]. Low levels of ROS also function as mitogens, stimulating cell cycle progression[75], while ROS-derived peroxynitrite promotes metastasis by activating MMPs to degrade the extracellular matrix[76]. Moreover, ROS upregulates hypoxia-inducible factor 1$\alpha$ (HIF-1$\alpha$), inducing VEGF-driven angiogenesis, which supports tumor growth and metastasis[77,78]. What's more, TAMs could collaborate with cancer-associated fibroblasts to create a supportive microenvironment for tumor growth[79,80].

In terms of metastasis, TAMs promote the epithelial-to-mesenchymal transition of tumor cells *via* factors such as TGF-$\beta$, which enhance the motility and invasiveness of tumor cells[81]. TAMs also secrete chemokines, including CCL2 and CCL5, which act as chemoattractants, guiding tumor cells toward blood and lymphatic vessels, thereby facilitating their dissemination to distant sites[82−84]. Furthermore, as mentioned earlier, TAMs degrade ECM and thus create a path for tumor cell invasion and migration[69,85].

## 2.3. The cancer-suppressing roles of TAMs

TAMs can also contribute to cancer suppression under certain conditions. This anti-tumor role is primarily exhibited when TAMs adopt an M1-like phenotype.

### 2.3.1. Production of pro-inflammatory cytokines

M1-like TAMs secrete pro-inflammatory cytokines, including IFN-$\gamma$, TNF-$\alpha$, and interleukin-12, which exert multiple anti-tumor effects. These cytokines activate $CD8^+$ T cells and NK cells, enhancing their capacity to recognize and destroy tumor cells[86]. Additionally, M1-like TAMs modulate the expression of adhesion molecules and chemokine receptors on tumor cells, impairing their migration and invasion[87,88]. In contrast, M2 macrophages contribute to tumor progression and immune evasion due to their immunosuppressive characteristics[10]. Studies have shown that reprogramming M2 macrophages into M1 macrophages can significantly enhance anti-tumor immune responses[89−92]. For example, D-lactate (DL), a metabolite produced by the gut microbiome, has been shown to reprogram the M2 macrophages to an M1 phenotype. Research indicates that D,L-loaded nanoparticles (DL@NP-M-M2pep) can specifically target M2 macrophages within the TME and boost the secretion of pro-inflammatory cytokines, IFN-$\gamma$, TNF-$\alpha$, and interleukin-12, thereby significantly improving anti-tumor immunity[93].

### 2.3.2. Induction of antigen presentation and T-cell activation

M1-like TAMs can act as antigen-presenting cells by processing and presenting tumor antigens, thereby priming T cells to recognize and target tumor cells[94]. Additionally, M1-like TAMs express high levels of co-stimulatory molecules, such as CD80 and CD86, which are critical for robust T cell activation and proliferation[95]. Moreover, they secrete chemokines like C−X−C motif chemokine ligand 9 and CXCL10, recruiting T cells to the tumor site and enhancing the overall anti-tumor immune response[96].

### 2.3.3. Production of ROS and RNS

ROS and RNS have dual and opposite roles in tumor progression. As mentioned before, TAMs generate ROS or RNS, contribute to DNA damage and genomic instability of tumor cells, which induces tumor clone selection, but also have cytotoxic effects on tumor cells[97,98]. ROS and RNS can directly induce tumor cell apoptosis and necrosis through oxidative and nitrosative stress[99]. In ovarian cancer, TAMs produce NO and ROS, which enhance chemotherapy sensitivity and promote tumor cell apoptosis[100].

Moreover, ROS and RNS can modulate the signaling pathways and gene expression of tumor cells, affecting their growth, differentiation, and survival[101]. Collectively, the effects of ROS and RNS mediated by TAMs remain controversial.

### *2.4. The identification of distinct TAM subpopulations and functional roles via single-cell sequencing*

While the dual roles of TAMs in promoting and suppressing tumor progression are well recognized, emerging evidence suggests that TAMs encompass a wider diversity of subpopulations with distinct functions and characteristics beyond the traditional M1/M2 polarization model[19]. This recognition highlights the importance of developing targeted strategies to identify and address specific TAM subsets. Such strategies have recently become feasible, thanks to advancements in scRNA-seq technology.

scRNA-seq, an innovative technique, allows the analysis of gene profiles at the resolution of individual cells[102]. Unlike conventional bulk RNA-seq measuring the gene average level of a population of cells, scRNA-seq can reveal the cellular heterogeneity and diversity within a tissue or organ, as well as the dynamic changes of gene expression over time and space[103,104]. scRNA-seq is now widely used for studying various biological systems, such as development, immunity, and cancer[105]. As for TAMs, scRNA-seq can directly identify multiple TAM clusters, analyze cellular developmental trajectories, and reveal the molecular mechanisms of TAM resistance[106,107]. However, it is important to note that scRNA-seq focuses primarily on mRNA expression and may not capture the full spectrum of protein-level characteristics, which are crucial for understanding TAM function and behavior. Cytometry by time-of-fligh (CyTOF), which complements scRNA-seq, addresses this limitation by enabling high-dimensional protein marker analysis at the single-cell level. CyTOF can measure over 70 markers simultaneously, providing detailed and comprehensive protein expression profiles[108,109]. When used in conjunction with scRNA-seq, CyTOF enhances the accuracy of TAM subset classification by validating the gene expression profiles identified in scRNA-seq, offering a more complete picture of TAM heterogeneity and functional diversity. For instance, in the study of 3-hydroxyanthranilic acid (3-HAA) in HCC, scRNA-seq and CyTOF analyses identified distinct macrophage subsets that were modulated by 3-HAA treatment. CyTOF revealed a significant increase in the percentage of F4/80$^{hi}$CX3CR1$^{lo}$Ki67$^{lo}$MHC-II$^{hi}$ macrophages and a decrease in F4/80$^{lo}$CD64$^{+}$PD-L1$^{lo}$ macrophages, complementing scRNA-seq data that showed 3-HAA's influence on the function of M1, M2, and proliferating macrophages[110]. Besides, recent studies have integrated scRNA-seq and spatial transcriptomics technologies to identify TAM subpopulations, with a particular focus on vimentin$^{high}$ macrophages. These vimentin$^{high}$ macrophages were found to interact with regulatory T cells and play a crucial role in tumor progression and response to immunotherapy[111].

Through the combined use of scRNA-seq, CyTOF and other single-cell omics, several major categories of TAMs have been identified, including immunoregulatory TAMs, inflammatory cytokine-enriched TAMs, interferon-primed TAMs, pro-angiogenic TAMs, and lipid-associated TAMs[21]. It is important to note that these classifications are not mutually exclusive; some TAM subpopulations exhibit overlapping characteristics (Fig. 4). For example, lipid-associated TAMs in breast cancer can be either immunosuppressive or inflammatory, as revealed by scRNA-seq analyses of both human and mouse tissues[112]. *SPP1*-positive TAMs contribute to an immunosuppressive TME while also displaying pro-angiogenic functions[21,113]. Therefore, to provide a

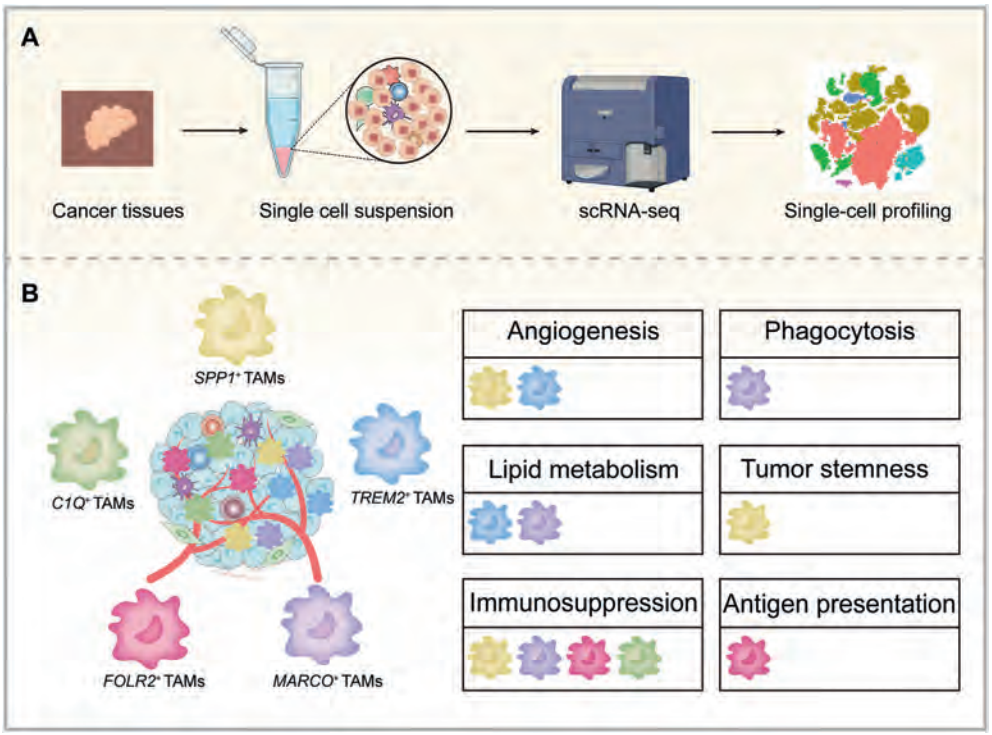


**Figure 4** Single-cell sequencing (scRNA-seq) reveals TAM heterogeneity. (A) A detailed procedure for scRNA-seq, enabling the analysis of gene profiles at the resolution of individual cells. (B) Identification of novel TAM subpopulations and their functional roles within the tumor microenvironment.

complementary perspective to existing reviews, this summary categorizes TAM subsets based on their core gene expression profiles.

#### 2.4.1. *SPP1-positive (SPP1$^+$) TAMs*

Secreted phosphoprotein 1 (*SPP1*/Osteopontin)$^+$ TAMs are characterized by high expression of *SPP1*[114]. SPP1 is a secreted phosphoprotein. It can function as a cytokine that interacts with integrins and cluster of differentiation 44 (CD44), mediating macrophage adhesion, migration, and activation[115−117]. It also contributes to macrophage-mediated tissue remodeling by modulating extracellular matrix components and regulating MMPs during immune responses and wound healing[118,119].

*SPP1*$^+$ TAMs highly secrete VEGF, a vital pro-angiogenesis factor. Thus, *SPP1*$^+$ TAMs are initially recognized as pro-angiogenic TAMs. A recent study generated a comprehensive atlas of tumor vasculature at single-cell resolution. This study identified *SPP1*$^+$ TAMs as a primary source of VEGF for neovascularization, highlighting their significant interactions with vascular cells and their co-occurrence with tip cells, which are essential for vessel sprouting, as demonstrated by spatial transcriptomics data[120]. Additionally, higher *SPP1* expression was observed in hypoxia-responsive macrophages located in the tumor's hypoxic core[120,121].

*SPP1*$^+$ TAMs have been linked to the stemness of cancer cells. Inhibition of SPP1 has been shown to decrease the levels of N-cadherin and $\beta$-catenin, as well as the activation of the AKT and STAT3 pathways, which are associated with tumor cell stemness[122]. Consistently, in gastric cancer, cancer stem cells express high levels of CD44, a functional receptor of SPP1. The SPP1/CD44 axis is likely linked to tumor stemness and contributes to resistance to anticancer therapies[123]. The significance of SPP1/CD44 signaling has also been implicated in glioma and HCC, further underscoring its role in therapy resistance and tumor progression[124,125].

*SPP1*$^+$ TAMs also exhibit an immunosuppressive function. *SPP1*$^+$ TAMs are primarily presented in the invasive front of colorectal cancers and are linked to the expression of HLA-G, a marker associated with immune evasion[126]. In liver cancer, a higher number of *SPP1*$^+$ TAMs correlate with immunotherapy resistance[124]. SPP1 secreted from TAMs also plays a role in promoting cancer-associated fibroblast infiltration while suppressing CD8$^+$ T cell infiltration into tumor tissues[127]. Additionally, SPP1 expression in certain TAM subpopulations decreases the efficacy of anti-PD-1 therapy in melanoma. Mechanistically, SPP1 can directly or indirectly promote the recruitment and expansion of Treg cells in the TME, reducing T cell activation and proliferation by modulating PD-L1 expression on TAMs[122].

#### 2.4.2. *TREM2-positive (TREM2$^+$) TAMs*

*TREM2*$^+$ TAMs are defined by the high expression of *TREM2* (Triggering Receptor Expressed on Myeloid Cells 2), primarily expressed on macrophages. *TREM2*$^+$ TAMs are related to lipid metabolism, actively scavenging lipoproteins through cluster of differentiation 36 and macrophage receptor with collagenous structure (MARCO)[128], characterizing them as lipid-associated macrophages[129]. scRNA-seq analyses of human tumors have identified *TREM2*$^+$ macrophages in various cancers[130]. In hepatocellular carcinoma, *TREM2*$^+$ TAMs display elevated expression of *TREM2*, folate receptor $\beta$ (*FOLR2*), and *CD163*, resembling lipid-associated macrophages, and are enriched in tumor tissues. Their presence is associated with poor prognosis. Pseudotime analysis indicates that *TREM2*$^+$ TAMs express genes involved in angiogenesis and exhibit high M2 polarization scores[131]. In lung cancer, *TREM2*$^+$ TAMs show enrichment in lipid metabolism genes (*e.g.*, apolipoprotein C1, apolipoprotein C2, and apolipoprotein E) and immunomodulatory proteins, including SPP1, complement C1q C chain, CD206, arginase-1, and IL-10[132].

*TREM2*$^+$ TAMs also exert robust immunosuppressive effects. They inhibit both CD4$^+$ and CD8$^+$ T cell activity while promoting the expansion of regulatory T cells. Depletion of *Trem2*$^+$ TAMs has been shown to reverse this immunosuppressive environment and suppress tumor growth[128]. In breast cancer, *TREM2*$^+$ TAMs correlate with the presence of immunosuppressive, desmoplastic, and hypoxic tumor stroma[128]. In melanoma, *TREM2*$^+$ TAMs overexpress several immunosuppressive markers, including *SPP1*, complement C1q C chain, *CD206*, arginase-1, and *IL10*, which are associated with the complement system and the regulation of immune suppression[133]. Additionally, *TREM2*$^+$ TAMs are implicated in T cell exhaustion, with experimental models demonstrating that combination therapy with anti-TREM2 and anti-PD-1 antibodies reduces M2-like TAM populations and enhances the activation of CD8$^+$ T cells[134]. As a result, the presence of *TREM2*$^+$ TAMs is typically associated with poor prognosis.

However, recent studies have highlighted a potentially protective role for *TREM2* in certain contexts. *Trem2* deficiency has been shown to accelerate glioblastoma progression *in vivo*[135]. Spatial sequencing analyses in glioblastoma have revealed that *TREM2* expression is downregulated in TAMs within the tumor, which negatively correlates with the expression of immunosuppressive myeloid signatures and markers of T cell exhaustion[136]. Furthermore, adeno-associated virus-mediated overexpression of *Trem2* has been found to inhibit glioblastoma progression and enhance the therapeutic efficacy of anti-PD-1 treatments[136].

Moreover, *TREM2*$^+$ TAMs play a critical role in angiogenesis across several cancer types. In liver cancer, these macrophages express higher levels of angiogenesis-related genes, such as *VEGFA*, fibroblast growth factor 18, and fibroblast growth factor receptor 1[131]. Further single-cell analyses in lung cancer have shown that *TREM2*$^+$ TAMs are strongly associated with tumor progression[132]. Pseudotime analysis suggests that these macrophages not only upregulate angiogenesis-related genes but also exhibit a pronounced M2 polarization, which is characteristic of their immunosuppressive and tumor-promoting roles[131].

#### 2.4.3. *MARCO-positive (MARCO$^+$) macrophages*

*MARCO* + TAMs are characterized by the high expression of the scavenger receptor MARCO[128]. MARCO (Macrophage Receptor with Collagenous Structure) is a pattern recognition receptor primarily expressed on macrophages, and it plays an important role in the immune response by mediating the recognition and phagocytosis of a wide variety of pathogens and particulate matter, such as bacteria and dead cells[137]. *MARCO*$^+$ macrophages are also associated with the activation of lipid metabolism-related pathways, such as liver X receptor/retinoid X receptor and farnesoid X receptor/liver X receptor[128,138].

*MARCO*$^+$ TAMs have been identified in various cancer types, and characterize a pro-tumor cluster of TAMs[139,140]. Clinical studies have highlighted that elevated MARCO expression correlates with poor survival outcomes in patients, indicating its role as a potential prognostic marker[139,140]. Interestingly, the abundance of *MARCO*$^+$ TAMs is significantly related to resistance to anti-PD-1 therapy, underscoring their potential as predictive biomarkers for immunotherapy response[141−144]. Drugs targeting

MARCO are currently undergoing preclinical validation, with the aim of reshaping the tumor microenvironment and enhancing the efficacy of existing immunotherapies. MARCO plays a role in the regulation of macrophage polarization, often driving TAMs toward the M2-like phenotype. This M2 polarization promotes the secretion of immunosuppressive cytokines such as IL-10 and TGF-$\beta$[31,94]. Thus, MARCO inhibition can repolarize TAMs toward a pro-inflammatory phenotype, activating the anti-tumor capacities of NK and T cells, inhibiting Treg activities, and reducing tumor growth. Targeting MARCO has been shown to reverse this pro-tumor phenotype by activating the anti-tumor functions of NK cells and cytotoxic T cells while suppressing Treg cell activity[143,145,146]. Moreover, MARCO plays a role in the phagocytosis of macrophages, facilitating tumor cell clearance. MARCO binds to $\beta$5 integrin on tumor cells and activates the phosphatidylinositol 3-kinase-Ras-related C3 botulinum toxin substrate signal, which is crucial for efficient phagocytosis and removal of tumor cells[147].

#### 2.4.4. *FOLR2-positive (FOLR2$^+$) TAMs*

*FOLR2*$^+$ TAMs represent a subpopulation of macrophages with high levels of folate receptor $\beta$ (*FOLR2*), as well as hyaluronan receptor and mannose receptor C-Type 1 (*MRC1/CD206*)[148]. The gene signature of *FOLR2*$^+$ TAMs also includes genes such as selenoprotein P (*SEPP1*), solute carrier family 40 member 1 (*SLC40A1*), and *LYVE1*, along with markers associated with both M1 (*e.g.*, CD80, cluster of differentiation 40, and IL-6) and M2 (*e.g.*, CD163, MRC1, and IL-10) polarization[128].

Therefore, *FOLR2*$^+$ macrophages exhibit diverse functions that vary by cancer type. In breast cancer, scRNA-seq studies in both mouse and human tissues have identified *FOLR2*$^+$ macrophages, which are initially classified as T-cell-priming subsets. They serve as potent antigen-presenting cells that can prime and activate CD8$^+$ T cells[112]. A *FOLR2* gene signature is significantly associated with improved survival.

Conversely, *FOLR2*$^+$ TAMs can also contribute to an immunosuppressive microenvironment in lung cancer by facilitating the infiltration and differentiation of CD4$^+$NR4A3$^+$ cells into Tregs[149]. Moreover, also in human breast cancer and colorectal cancer, spatial analyses reveal a subset of *FOLR2*$^+$ macrophages exhibiting tumor-promoting properties based on immunofluorescence (CODEX imaging) and scRNA-seq datasets[150].

#### 2.4.5. *C1q-positive (C1q$^+$) TAMs*

Complement component 1q (C1q) is the first component of the classical complement pathway. Emerging evidence underscores the critical roles of *C1q*$^+$ TAMs in cancer immune evasion. These macrophages are characterized by a distinct secretory profile, prominently featuring the chemokine CXCL10 and the interleukin-35 subunit Epstein-Barr virus-induced gene 3, both of which contribute to the establishment of dysfunctional T-cell responses. *C1q*$^+$ TAMs are known to promote immune dysfunction by interacting with exhausted T cells[151−153]. For instance, in renal cell carcinoma, *C1q*$^+$ TAMs drive the upregulation of *PD-1* and lymphocyte-activation gene 3 on CD8$^+$ T cells, thereby impairing their function[152,154]. Similarly, in cervical cancer, patients with high densities of *C1q*$^+$ TAMs exhibit elevated expression of immune checkpoint molecules such as CD40 ligand (CD40L), T cell immunoreceptor with Ig and ITIM domains (TIGIT), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), LAG3, and PD-L1[155]. In preclinical models of melanoma, colon cancer, and lung cancer, *C1q*$^+$ TAMs express Epstein-Barr virus-induced gene 3, a subunit of interleukin-35, which further exacerbates T cell exhaustion[156].

*C1q*$^+$ TAMs can directly interact with T cells through the CXCL10-C−X−C motif chemokine receptor 3 (CXCR3) axis. This interaction is crucial for the recruitment and activation of Th1 responses[157]. Specifically, in lung cancer, increased CXCL10 production by *C1q*$^+$ TAMs correlates with elevated levels of signal transducer and activator of transcription 1 (STAT1) and interferon regulatory factor 1/7 (IRF1/7), which are important for immune activation[158,159]. Furthermore, in renal cell carcinoma, the density of *C1q*$^+$ TAMs significantly correlates with the levels of PD-1 and LAG3 on CD8$^+$ T cells, suggesting a role in the modulation of T cell exhaustion[153]. Notably, studies have shown that *C1q*$^+$ TAMs are mutually exclusive from *SPP1*$^+$ TAMs[24,158]. Furthermore, TAMs, exhibiting higher *C1q* but lower *SPP1*, express higher levels of immune checkpoint molecules than those with lower *C1q* and higher *SPP1* in cervical cancer[155]. Additionally, *C1q*$^+$ TAMs express elevated levels of human leukocyte antigen—DR isotype, potentially enhancing their interactions with other immune cells[157].

Clinically, the increased number of *C1q*$^+$ TAMs is associated with poor survival of patients across various cancers[160], including renal cell carcinoma, hepatocellular carcinoma, and breast cancer, with increased postsurgical recurrence[112,153,154]. In osteosarcoma, *C1q*$^+$ TAMs are reversely correlated with the survival of patients[161]. In pancreatic ductal adenocarcinoma, C1q is elevated in both primary tumors and hepatic metastases, compared to non-tumoral tissue, with the presence of *C1q*$^+$ TAMs linked to a worse prognosis[162].

## 3. Drug development and therapeutic strategies targeting TAM

Given their pivotal functions within the tumor microenvironment, targeting TAMs presents promising targets for cancer treatments[163]. Here are the key points that form the rationale for this therapeutic approach.

### 3.1. *Drug development strategies through TAM deletion*

Clodronate encapsulated in liposomes can be phagocytosed by macrophages, leading to their apoptosis[164,165]. Recognized as foreign particles by macrophages, the liposome-encapsulated clodronate is ingested, allowing the clodronate to be released within the cells. Clodronate is then metabolized into a non-hydrolyzable ATP analog, which could be subsequently transported into the mitochondria and bind with ATP/ADP translocase. This binding obstructs the respiratory chain and initiates apoptosis in the macrophages[164]. Clodronate-liposome-mediated depletion of TAMs has shown inhibitory effects on tumor growth in various mouse models[166−168]. However, the intravenous injection of clodronate-liposome does not allow for the targeting of specific organs or tissues, resulting in systemic macrophage depletion[169].

Recently, a chimeric antigen receptor (CAR) T therapy targeting the macrophage marker F4/80, called F4.CAR-T, has been reported to eliminate TAMs. The findings demonstrated that F4.CAR-T effectively killed macrophages and produced IFN-$\gamma$, consequently enhancing T cell activity and inhibiting tumor progression in a mouse lung cancer model[170]. The F4.CAR-T therapy also exhibits anti-tumor effects in mouse ovarian and pancreatic cancer models[171].

However, translating these findings into human clinical trials involves addressing several challenges, including ensuring the safety and efficacy of the treatment, understanding the different macrophage populations in human tissues, and developing targeted delivery mechanisms to avoid off-target effects.

### 3.2. Therapeutic approaches for inhibiting TAM recruitment

Inhibition of TAM recruitment is also a promising strategy for targeting TAMs. Macrophages or monocytes are recruited into tumor tissues by CSF-1, CCL2, and CXCL12 and become TAMs under stimulation of tumor cells or TME[3,172−175].

Firstly, CSF1R drives the recruitment and polarization of TAMs[27,176]. Blocking the CSF1/CSF1R axis reduces TAM infiltration by inhibiting monocyte differentiation and eliminating existing TAMs[177,178]. For example, PLX3397 (pexidartinib), a tyrosine kinase inhibitor, effectively inhibits CSF1R activity[179]. Currently, PLX3397 is being investigated in clinical trials for its potential to treat various malignancies, including glioblastoma, breast cancer, melanoma, and others, by reducing the recruitment of M2 macrophages[180−182]. The clinical potential of PLX3397 was further validated with its FDA approval in 2019 for the treatment of tenosynovial giant cell tumor (TGCT), based on the results of the ENLIVEN phase 3 trial (NCT02371369). Three additional studies are currently underway: 1) Phase 3 (NCT04488822) targeting TGCT management in China, 2) Phase 2 (NCT04703322) examining the use of Pexidartinib in Japanese TGCT populations for regional validation, and 3) Phase 2 (NCT01042379) exploring its potential application in breast cancer. These ongoing trials aim to address key challenges, including geographic applicability, dose optimization, and expansion into solid tumors, demonstrating a structured approach to post-marketing development[32]. Another CSF1R inhibitor, LY3022855, is also being tested in a clinical trial[183]. Additionally, combination therapies utilizing anti-CSF1R and anti-CD40 have demonstrated significant efficacy in reducing TAMs and Tregs. Consequently, there is an increased infiltration of tumor-infiltrating $CD8^+$ T cells targeting tumor cells[184].

The CCL2/CCR2 signaling pathway also plays a critical role in the TAM chemotaxis[2,185]. Within the TME, tumor cells and stromal cells, like endothelial cells, are capable of producing CCL2, which leads to the recruitment of *CCR2*-positive monocytes into tumor sites[186]. Consequently, the inhibition of the CCL2/CCR2 signal reduces the infiltration of TAMs[185,187−189]. Carlumab, a CCL2-neutralizing antibody, has been tested in the clinical trials (NCT00537368 and NCT01204996). However, Carlumab has yet to demonstrate significant anti-tumor effects[190]. Even when combined with standard chemotherapy agents, Carlumab still did not show substantial clinical efficacy[191]. In another phase II clinical trial (NCT00992186) focused on prostate cancer, Carlumab resulted in stable disease (SD) in a subset of patients, but no complete response (CR) or partial response (PR) was observed[192]. The exact anti-tumor effects of Carlumab require further investigation.

On the other hand, CCR2 inhibitors are also under evaluation[86,193]. MLN1202, a CCR2-neutralizing antibody, was evaluated in a clinical trial (NCT01015560). While the treatment was well-tolerated, its anti-tumor activity remained unclear[194]. CCX872 B, another CCR2 inhibitor, was also tested in advanced, unresectable pancreatic cancer (NCT02345408). The trial combined CCX872 B with the chemotherapy regimen 5-fluorouracil + leucovorin + irinotecan + oxaliplatin (FOLFIRINOX), enrolling 50 patients, 76% of whom had metastatic disease. The study reported a disease control rate of 78% and an objective response rate of 30%−37% for the combination of CX872 B and FOLFIRINOX, with no notable safety concerns related to CCX872 B. These findings suggest that CCX872 B may have a positive therapeutic effect in this patient population[195]. More recently, a dual CCR2/CCR5 antagonist, BMS-813160, in combination with Nivolumab (anti-PD-1), is being tested as both neoadjuvant and adjuvant therapy for locally advanced pancreatic ductal adenocarcinoma (NCT03767582)[196].

The CXCL12/CXCR4 pathway also recruits macrophages to the tumor microenvironment. Tumor cells secrete CXCL12 (also known as stromal cell-derived factor 1, or SDF-1), which binds to CXCR4 on monocytes. This signaling promotes the recruitment of monocytes into the TME and facilitates their transformation into immunosuppressive TAMs[197,198]. So far, more than 20 CXCR4-targeted therapies are under development. Mozobil (Plerixafor), a small molecule, has been approved in China for the treatment of lymphoma and myeloma. Motixafortide (BL-8040), a synthetic peptide targeting CXCR4, is being evaluated in clinical trials for breast and pancreatic cancer[199].

### 3.3. Targeting and druggable strategies by TAM reprogramming

Stimulatory signals from tumor cells, immune cells, and stromal cells can shift TAMs from anti-tumor to pro-tumor[154,173,200]. This plasticity offers potential strategies for the reprogramming of TAMs in cancer therapy.

One common treatment strategy is to use chemotherapy drugs to selectively reprogram TAMs[201,202]. For example, Cyclophosphamide, a widely used chemotherapy drug, enhances the secretion of pro-inflammatory M1 cytokines, while decreasing M2-related cytokines[173,203]. Another strategy involves the combination of DNMT inhibitor 5-azacytidine and $\alpha$-difluoromethylornithine, which has been shown to improve patient survival and reduce tumor burden. This combination therapy reduces M2-like TAMs and increases M1 TAMs within the TME[204].

Additionally, Toll-like receptor (TLR) agonists have shown potential for reprogramming TAMs by activating the TLR signaling pathway. This activation upregulates the expression of M1-related genes, like *CD86*, *CD80*, and *CD40*. Several TLR agonists, including imiquimod and 852A (TLR7 agonists)[205], IMO-2055 (a TLR9 agonist)[206], and Rsiquimod (R848, a TLR7/TLR8 agonist)[207], are being tested for their effectiveness against solid tumors. Imiquimod is the only FDA-approved topical treatment for squamous and basal cell carcinomas[208,209], while IMO-2055 has demonstrated preclinical activity in various studies[210]. These findings suggest that TLR agonists could be combined with other anti-tumor agents for further clinical evaluation.

Tie2 inhibitors may also have the potential to target TAMs[211]. As mentioned before, TEMs play a crucial role in tumor angiogenesis, cancer cell invasion, and metastasis[212,213]. Inhibitors of Tie2, such as Rebastinib and Regorafenib, have demonstrated anti-tumor activity. Rebastinib, for example, alters immune cell composition in ascites and, when combined with chemotherapy, significantly extends survival in ovarian cancer models[214]. Regorafenib, a multi-kinase inhibitor with anti-angiogenic properties, targets both VEGFR2 and Tie2 tyrosine kinase activity, potentially inhibiting TEMs in addition to its effects on endothelial cells[215,216].

Chimeric Antigen Receptor Macrophage (CAR-M) therapy is another innovative strategy. CAR-M therapy involves genetically modifying macrophages to recognize and attack cancer cells.

Preclinical studies have shown the superior efficacy of CAR-M in solid tumors, and two CAR-M therapies have been approved for clinical trials[217,218]. CT-0508, an anti-HER2 CAR-M therapy, is currently being tested in a phase I clinical trial for patients with relapsed/refractory HER2-overexpressing tumors (NCT04660929)[217,219]. Another trial is evaluating MCY-M11, which expresses CAR targeting mesothelin for the treatment of recurrent/refractory ovarian cancer and peritoneal mesothelioma (NCT03608618)[220]. Recent studies have demonstrated that Vinblastine, a chemotherapeutic agent, has been shown to promote the conversion of M2-like TAMs into M1 macrophages, which in turn activate $CD8^+$ T cells[221]. Additionally, the use of second-generation chimeric antigen receptor (CAR) macrophages represents another promising strategy to enhance M1 polarization. By integrating the intracellular TIR domain of TLR4 with the CD3$\zeta$ signaling domain to construct the CD3$\zeta$−TIR−CAR, macrophages can be selectively reprogrammed to an M1 phenotype, not only enhancing M1-mediated antigen presentation but also promoting T cell activation[222].

These findings suggest that TAM reprogramming, through various therapeutic strategies, holds great promise for enhancing anti-tumor immunity and improving clinical outcomes for cancer patients.

### *3.4. Therapeutic strategies for modulating TAM-driven phagocytosis*

Cluster of differentiation 47 (CD47), a protein overexpressed on tumor cells, binds with SIRP$\alpha$ on macrophages and sends the "don't eat me" signal to macropahges[223−225]. Blocking the CD47−SIRP$\alpha$ axis will enhance macrophage phagocytosis[226]. This approach is particularly effective when combined with other treatments like transarterial chemoembolization or immune therapy targeting PD-L1. Combining anti-CD47 therapy with PD-L1 inhibitors or using bispecific antibodies targeting both PD-L1 and SIRP$\alpha$ significantly improves anti-tumor effects[227,228].

Another study showed that the MHC I component $\beta$2M expressed by cancer cells bound the inhibitory receptor leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1) on macrophages, similar to the CD47 pathway, preventing macrophage phagocytosis of tumor cells[229]. Inhibiting LILRB1 or its absence increased macrophage phagocytosis and prolonged survival by 70% in mice with tumors[230]. Combining this inhibition with anti-CD47 antibodies enhanced the macrophage's tumor-killing ability without harming normal tissues[229].

Moreover, CD24 is highly expressed in tumors and binds to Siglec10 in macrophages, also inhibiting phagocytosis[231,232]. Blocking Siglec10 in hepatocellular carcinoma reduces the levels of immunosuppressive molecules, enhances $CD8^+$ T cell cytotoxicity, and improves the efficacy of the anti-PD-1[233]. Consequently, upregulation of Siglec10 is linked to poor patient prognosis, and its inhibition, CD24 blockade, or genetic ablation reduces tumor growth and prolongs survival *in vivo*[231].

### *3.5. Advancing TAM-targeted therapies via single-cell sequencing*

scRNA-seq provides valuable insights into TAM subpopulations, revealing their dynamic changes and heterogeneity. Therefore, this technology can guide the development of drugs targeting specific TAM subgroups, potentially altering their behavior or abundance to enhance the anti-tumor response.

A key pro-tumoral role of TAMs is to suppress the immune system and promote tumor immune evasion[173,234,235]. As discussed previously, *TREM2* has been considered as an essential gene for the immunosuppressive function of TAMs[129,130]. In a mouse model, targeting *Trem2*$^+$ macrophages with an anti-TREM2 antibody has shown promise in enhancing the efficacy of ICIs, increasing T cell anti-tumor activity, and suppressing tumor growth [130]. Moreover, in humans, anti-TREM2 antibody PY314, without or with the combination of Pembrolizumab (anti-PD-1), is being assessed under an ongoing clinical trial (NCT 04691375)[134]. MARCO is another potential target. *MARCO*$^+$ TAMs have been linked to immunosuppression and poor patient outcomes[236,237]. In mouse breast cancer, colon carcinoma, and melanoma models, anti-MARCO immunoglobulin G exhibits an anti-tumor effect through inducing a pro-inflammatory role of TAMs and increasing tumor immunogenicity and also enhances the effectiveness of immune checkpoint blokadge[141]. Similarly, studies in other cancer models showed that targeting MARCO inhibited tumor growth and metastasis effectively, and increased tumor microenvironment immunogenicity[143,238], thus sensitizing tumors to immune treatments like anti-CTLA-4 or anti-PD-L1[141,144,239]. Nonetheless, further clinical applications are required to test the effectiveness of anti-MARCO therapy.

Additionally, pro-angiogenic TAMs are prevalent in most solid tumors and play a critical role in stimulating angiogenesis, making them potential therapeutic targets. To date, anti-angiogenic therapies in cancer focus on the inhibition of the VEGF−VEGFR signal[240]. However, these drugs will lead to tumor hypoxia and drug resistance[88,241]. One of the mechanisms is that hypoxia promotes TEM recruitment *via* Ang-2[60,242]. Combining VEGF inhibitors with Ang-2 inhibitors has shown promise for improving outcomes. For example, in mouse models of glioblastoma, a bispecific Ang-2/VEGF antibody improved survival and delayed tumor growth more effectively than either therapy alone[243]. Similarly, a humanized bispecific nanobody, BI836880, could target VEGF and Ang-2 simultaneously and also showed a significant effect on suppressing nasopharyngeal cancer[244]. Another target for pro-angiogenic TAMs would be SPP1. As we have summarized, SPP1 is crucial for TAM pro-angiogenic functions. Bromodomain and extraterminal inhibitors were identified as potential drugs that suppressed SPP1 expression in TAMs. In multiple tumor models, bromodomain and extraterminal inhibitors could reduce tumor growth by inhibiting SPP1 expression and blocking the CD44−SPP1 axis [123,245−248].

There are also other novel strategies for targeting TAMs based on the utility of scRNA-seq. TREM1, a proinflammatory molecular expressed on monocytes and macrophages, is another potential anti-tumor target[249,250]. A TREM1 agonist, PY159, has been developed to promote a proinflammatory TME, enhancing T cell activation and showing anti-tumor efficacy in mouse models[249]. Similarly, nonapeptide GF9, a TREM1 inhibitor[251,252], reduced tumor burden[252] and sensitized the tumor cells to anti-PDL1 treatment[46].

Collectively, advancements in understanding TAM biology, particularly through scRNA-seq, have opened new avenues for targeting TAM-mediated immunosuppression, angiogenesis, etc. These insights have led to the development of novel therapeutic agents that are being tested in preclinical and clinical settings (summarized in Table 1).

**Table 1** Preclinical agents and clinical trials for targeting TAMs.

| Target | Cancer type | Drug | Combinational therapy | Phases | Result[a] | Clinical trial ID[b] |
|---|---|---|---|---|---|---|
| Inhibition of TAM recruitment | | | | | | |
| CCL2/CCR2 | Prostate cancer | Carlumab | N\A | II | Stable disease: 1 patient (>6 months), 14 patients (34%, ≥3 months) mOS: 10.2 months | NTC00992186 |
| | Advanced or metastatic pancreatic cancer | CCX872B+ FOLFIRINOX | N\A | Ib | ORR: 30%−37%<br>Tumor control rate: 78% | NCT02345408 |
| CCR5 | Triple-negative breast cancer | Leronlimab | Carboplatin | Ib/II | Confirmed partial response: 20% (2/10 patients)<br>Stable disease: 40% (4/10 patients) | NCT03838367 |
| CXCL12 | Chronic lymphocytic leukemia | NOX-A12 | Bendamustine + Rituximab | IIa | ORR:86% (24/28 patients) mPFS: 15.4 months<br>mOS: Not reached (3-year survival rate >80%) | NCT01486797 |
| GM-CSF | Ovarian cancer | GM-CSF | GM-CSF+ TPIV200 | II | PFS: 11.3 *vs.*11 months (HR = 0.93, $P = 0.656$)<br>15.2-Mo OS: 94.8% *vs.* 93.4% (HR = 1.71, $P > 0.05$)<br>No patient experienced $a \geq$ grade 3 drug-related adverse event | NCT02978222 |
| | Breast cancer | GM-CSF+ Trastuzumab | GM-CSF+ Trastuzumab+ Nelipepimut-S | IIb | 25.7-Mo DFS: 83.8% *vs.* 89.8% ($P = 0.18$)<br>Triple-negative breast cancer<br>DFS: 70.2% *vs*.92.6% ($P = 0.01$) | NCT01570036 |
| CSF-1R | Metastatic breast cancer (mBC) or metastatic castration-resistant prostate cancer (mCRPC) | LY3022855 | N\A | I | Stable disease: 5 mBC patients (23%, lasting 82−302 days) and 3 mCRPC patients (25%, lasting 50−124 days)<br>Durable stable disease: 2 mBC patients (9%, >9 months)<br>Non-target neck mass: 1 mBC patient (4.5%, palpable reduction) | NCT02265536 |
| | Tenosynovial giant cell tumor | Vimseltinib | N\A | III | ORR: 40% (33/83 patients) *vs.* 0% (0/40 patients) (difference 40%; $P < 0.0001$) | NCT05059262 |
| | Tenosynovial giant cell tumor | Vimseltinib | N\A | II | ORR: 72%<br>Median treatment duration: 25.1 months | NCT03069469 |
| | Tenosynovial giant cell tumor | Pexidartinib | N\A | II | ORR: 39% (24/61 patients) *vs.* 0% (0/59 patients) (difference 39%; $P < 0.0001$) | NCT02371369 |
| | Advanced solid tumors | Surufatinib | N\A | I | ORR: 11.7% (9/77 patients)<br>DCR: 41.6% (32/77 patients)<br>In advanced neuroendocrine tumors: ORR (38.1%, 8/21), DCR (85.7%, 18/21), PFS (16.9 months) | NCT02133157 |
| Reprogramming of TAMs | | | | | | |
| TLR7 | Advanced liver cancers | RO7119929 | N\A | I | Complete response: 1 patient (6%)<br>Stable disease: 10 patients (63%)<br>Progressive disease: 5 patients (31%) mOS: 6.5 months<br>mPFS: 1.4 months | NCT04338685 |
| TLR8 | Squamous cell cancer of the head and neck | Motolimod (VTX-2337) | Cetuximab | Ib | ORR: 15% (2/13 patients)<br>Partial response: 2 patients<br>Stable disease: 5 patients<br>Progressive disease: 2 patients<br>DCR: 54% (7/13 patients) | NCT01334177 |
| TLR3 | PD-1-resistant advanced melanoma | BO-112 | Pembrolizumab | II | ORR: 25%<br>CRR: 10%<br>Partial response rate: 15%<br>Stable disease: 40%<br>DCR: 65% | NCT04570332 |

| | | | | | | |
|---|---|---|---|---|---|---|
| TLR7/8 | Advanced solid tumors | Resiquimod | Pembrolizumab+ Resiquimod | I/II | 22 treatment-related adverse events were grade 1 or 2<br>No interaction with pembrolizumab<br>One partial response (melanoma, 0.3 mg monotherapy) | NCT04799054 |
| TLR9 | Advanced melanoma | CMP-001 | Pembrolizumab | Ib | ORR: 23.5% (23/98 patients) *vs.* 11.5% (7/61 patients)<br>Median duration of response: >1 year<br>Delayed response after initial PD: 7 patients | NCT02680184 |
| CAR | Ovarian cancer or malignant peritoneal mesothelioma | MCY-M11 | N\A | I | Treated in dose level (DL) escalating cohorts<br>Stable disease:3 patients in DL2<br>One remaining in stable disease for 6 months | NCT03608618 |
| STAT3 | Advanced solid tumors | OPB-31121 | N\A | I | Stable disease: 8 patients<br>Progressive disease:10 patients<br>Tumor shrinkage: 2 patients (1 colon cancer, 1 rectal cancer) | NCT00657176 |
| | Advanced hepatocellular carcinoma | OPB-31121 | N\A | I | Recommended dose for OPB-31121: 200 mg<br>DCR of 25.0%−42.9%<br>A median time to progression of 61.0 days | NCT01406574 |
| | Hematologic malignancies | OPB-51602 | N\A | I | Recommended dose for OPB-51602: 4 mg<br>No clear therapeutic response | NCT01423903 |
| | Glioma or melanoma | WP1066 | N\A | I | PFS:2.3 months (95% CI: 1.7 months-NA months)<br>OS: 25 months (95% CI: 22.5 months-NA months) | NCT01904123 |
| Restoration of the phagocytosis in TAMs | | | | | | |
| CD47 | Untreated higher-risk myelodysplastic syndromes | Magrolimab | Azacitidine | Ib | ORR:75%, CRR: 33%<br>Median response time: 1.9 months<br>Median complete response duration: 11.1 months<br>Median overall response duration: 9.8 months<br>PFS: 11.6 months<br>In TP53-mutant patients, CRR: 40%, OS:16.3 months, 40% achieved complete response with mOS of 16.3 months. | NCT03248479 |
| | Advanced gastric/gastroesophageal junction adenocarcinoma | AK117 | Cadonilimab + XELOX | II | ORR: 75% (6 patients)<br>Tumor shrinkage exceeding 50%: 5 patients | NCT05235542 |
| | Higher-risk myelodysplastic syndrome | IMM01 | Azacitidine | II | ORR: 64.7%<br>CRR: 29.4%<br>The median time to response: 1.9 months (95%CI: 1.8−2.8) | NCT05140811 |
| | Anti-PD-1 failed classical Hodgkin lymphoma | IMM01 | Tislelizumab | II | ORR: 65.6% (21/32 patients)<br>Complete response: 18.8% (6/32 patients)<br>DCR was 93.8% (30/32 patients) | NCT05833984 |
| | Refractory microsatellite stable metastatic colorectal cancer | Evorpacept (ALX-148) | Pembrolizumab + Cetuximab | II | ORR: 6.3% (1 patient)<br>PSF: 2.6 months<br>OS: 10.9 months<br>DCR:12.5% | NCT05167409 |
| | Acute myeloid leukemia | AK117 | Azacitidine | Ib/II | Clinical trial for acute myeloid leukemia patients (ongoing) | NCT04980885 |
| | Advanced solid tumors | STI-6643 | N\A | I | Clinical trial for advanced solid tumors patients (ongoing) | NCT04900519 |

[a]mOS, median overall survival; ORR, objective response rate; mPFS, median progression-free survival; PFS, progression-free survival; HR, hazard ratio; 15.2-Mo OS, 15.2-month overall survival rate; 25.7-Mo DFS, 25.7-month disease-free survival; DFS, disease-free survival; DCR, disease control rate; CRR, complete response rate; OS, overall survival.

[b]Data from ClinicalTrials.gov.

### *3.6. Current challenges and obstacles in the application of TAM-targeted strategies*

Despite the promising potential of targeting TAMs in cancer immunotherapy, several clinical trials have revealed significant challenges that warrant further investigation. For example, Pexidartinib, as we mentioned before, has been approved for treating TGCT, and is being tested in breast cancer and other malignancies. However, in a Phase 2 trial for glioblastoma, Pexidartinib was discontinued due to limited efficacy[253]. Similarly, the combination of Cabiralizumab, an anti-CSF1R antibody, and nivolumab in pancreatic cancer failed to meet its primary endpoint. Carlumab, targeting CCL2 to inhibit TAM recruitment in prostate cancer, also showed no significant impact on disease progression[192]. These examples highlight the complexity and heterogenicity of cancers, underscoring the need for further efforts to assess the efficacy of anti-TAM treatments. In addition to the efficacy, several challenges must be addressed for TAM-targeted therapies to succeed:

1) Safety concerns. As demonstrated in the Carlumab trial for prostate cancer, targeting CCL2 may lead to off-target effects, highlighting the risks associated with modulating the immune system. This suggests that precision targeting of specific TAM subpopulations, such as *SPP1*$^{+}$ or *C1q*$^{+}$ TAMs, could minimize the risk of unwanted immune suppression or enhancement, which could otherwise result in adverse effects.
2) Therapeutic resistance. Like other immunotherapies, TAM-targeting strategies are susceptible to resistance mechanisms. Tumor plasticity, as evidenced by the failure of the Cabiralizumab/nivolumab combination, presents a significant challenge. Tumors can adapt by recruiting compensatory myeloid cells, thereby limiting the efficacy of TAM-targeted therapies.
3) Delivery methods: The experience with Pexidartinib underscores the difficulty in effectively delivering TAM-targeting agents to the tumor microenvironment. Despite success in treating other cancers, its failure in glioblastoma highlights the significant biological barriers that must be overcome to ensure efficient drug delivery.

These challenges illustrate the need for continued research to optimize TAM-targeted therapies and address key issues related to safety, resistance, and drug delivery.

## 4. Conclusion and perspectives

The field of TAM-targeted therapies is rapidly evolving, with the integration of emerging technologies and innovative strategies. Here, we summarize the latest knowledge regarding TAM heterogeneity and functions, introduce the advantage of scRNA-seq in uncovering TAM heterogeneity, and discuss the implications for developing effective anti-cancer drugs targeting TAMs.

TAMs are not a homogeneous population, exhibiting variations in phenotype and function based on their tumor location and cancer stage. This heterogeneity complicates the development of universal TAM-targeting therapies[14,254]. Moreover, TAMs' plasticity, induced by the tumor microenvironment, may undermine the therapeutic effects, as TAMs may revert to a pro-tumor phenotype after treatment[254]. Rather than adhering to a binary classification of M1 or M2, TAMs display a spectrum of functional states, further complicating targeting efforts[255,256]. Moreover, systemic macrophage targeting may also result in unintended consequences, such as impaired wound healing and increased susceptibility to infections[257,258]. Consequently, studying TAM heterogeneity is crucial for understanding tumor progression mechanisms and anti-cancer drug development.

As scRNA-seq technology advances, we will gain a deeper insight into the diversity and functionality of TAMs. TAMs are progressively emerging as potential targets for cancer therapy, promising significant breakthroughs in cancer treatment. However, we must also recognize the dual roles that TAMs play in tumor development, as they both promote tumor angiogenesis and modulate immune responses, suppressing tumor growth. scRNA-seq technology enables us to comprehensively grasp the molecular characteristics and functions of different TAM subpopulations and to design various drugs targeting TAMs. This translational journey from scRNA sequencing to drug discovery not only enhances the precision and effectiveness of targeted therapy but also contributes to the advancement of personalized medicine, providing more suitable treatment strategies for specific patient groups. Additionally, emerging technologies such as scATAC-seq, scChIP-seq, CyTOF, and spatial transcriptomics are also poised to find extensive applications in TAM research[259,260]. The combined use of these techniques will provide us with a more comprehensive perspective, aiding in the understanding of both biological and spatial characteristics of TAMs.

In the future, there will be a growing focus on the combination of therapeutic strategies targeting TAMs to enhance the efficacy of cancer treatment. Ongoing clinical trials and preliminary research have already demonstrated the potential application prospects of therapies targeting TAMs in cancer treatment. With further research and clinical experiments, we can anticipate the entry of more anti-cancer drugs targeting TAMs into clinical practice, offering new treatment options for cancer patients.

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## Author contributions

An-Qi Li, Huichang Bi, and Jian-Hong Fang proposed the conception; An-Qi Li, Fang Huang, Sulaiya Talaiti, and Jian-Hong Fang drafted the manuscript; An-Qi Li, Huichang Bi, and Jian-Hong Fang edited the manuscript; An-Qi Li, Fang Huang, Sulaiya Talaiti, and Xiao Yang prepared figures and table. All of the authors have read and approved the final manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

## Declaration of generative AI in scientific writing

The authors confirm that no generative AI or AI-assisted technologies were used in the writing, data analysis, figure generation, or any other part of the preparation of this manuscript.

## References


1. Bied M, Ho WW, Ginhoux F, Bleriot C. Roles of macrophages in tumor development: a spatiotemporal perspective. *Cell Mol Immunol* 2023;**20**:983−92.
2. Xiang X, Wang J, Lu D, Xu X. Targeting tumor-associated macrophages to synergize tumor immunotherapy. *Signal Transduct Target Ther* 2021;**6**:75.
3. Christofides A, Strauss L, Yeo A, Cao C, Charest A, Boussiotis VA. The complex role of tumor-infiltrating macrophages. *Nat Immunol* 2022;**23**:1148−56.
4. Komohara Y, Fujiwara Y, Ohnishi K, Takeya M. Tumor-associated macrophages: potential therapeutic targets for anti-cancer therapy. *Adv Drug Deliv Rev* 2016;**99**:180−5.
5. Zhang S, Xie F, Li K, Zhang H, Yin Y, Yu Y, et al. Gold nanoparticle-directed autophagy intervention for antitumor immunotherapy *via* inhibiting tumor-associated macrophage M2 polarization. *Acta Pharm Sin B* 2022;**12**:3124−38.
6. Lecoultre M, Dutoit V, Walker PR. Phagocytic function of tumor-associated macrophages as a key determinant of tumor progression control: a review. *J Immunother Cancer* 2020;**8**:e001408.
7. Cheng K, Cai N, Zhu J, Yang X, Liang H, Zhang W. Tumor-associated macrophages in liver cancer: from mechanisms to therapy. *Cancer Commun* 2022;**42**:1112−40.
8. Yang Q, Guo N, Zhou Y, Chen J, Wei Q, Han M. The role of tumor-associated macrophages (TAMs) in tumor progression and relevant advance in targeted therapy. *Acta Pharm Sin B* 2020;**10**:2156−70.
9. Wang YC, Wang X, Yu J, Ma F, Li Z, Zhou Y, et al. Targeting monoamine oxidase A-regulated tumor-associated macrophage polarization for cancer immunotherapy. *Nat Commun* 2021;**12**:3530.
10. Ngambenjawong C, Gustafson HH, Pun SH. Progress in tumor-associated macrophage (TAM)-targeted therapeutics. *Adv Drug Deliv Rev* 2017;**114**:206−21.
11. Andon FT, Digifico E, Maeda A, Erreni M, Mantovani A, Alonso MJ, et al. Targeting tumor associated macrophages: the new challenge for nanomedicine. *Semin Immunol* 2017;**34**:103−13.
12. Singh Y, Pawar VK, Meher JG, Raval K, Kumar A, Shrivastava R, et al. Targeting tumor associated macrophages (TAMs) *via* nanocarriers. *J Control Release* 2017;**254**:92−106.
13. Etzerodt A, Tsalkitzi K, Maniecki M, Damsky W, Delfini M, Baudoin E, et al. Specific targeting of $CD163^+$ TAMs mobilizes inflammatory monocytes and promotes T cell-mediated tumor regression. *J Exp Med* 2019;**216**:2394−411.
14. Li S, Yu J, Huber A, Kryczek I, Wang Z, Jiang L, et al. Metabolism drives macrophage heterogeneity in the tumor microenvironment. *Cell Rep* 2022;**39**:110609.
15. Yunna C, Mengru H, Lei W, Weidong C. Macrophage M1/M2 polarization. *Eur J Pharmacol* 2020;**877**:173090.
16. Bashir S, Sharma Y, Elahi A, Khan F. Macrophage polarization: the link between inflammation and related diseases. *Inflamm Res* 2016; **65**:1−11.
17. Belgiovine C, D'Incalci M, Allavena P, Frapolli R. Tumor-associated macrophages and anti-tumor therapies: complex links. *Cell Mol Life Sci* 2016;**73**:2411−24.
18. Kadomoto S, Izumi K, Mizokami A. Macrophage polarity and disease control. *Int J Mol Sci* 2021;**23**:144.
19. Chavez-Galan L, Olleros ML, Vesin D, Garcia I. Much more than M1 and M2 macrophages, there are also $CD169^+$ and $TCR^+$ macrophages. *Front Immunol* 2015;**6**:263.
20. Li PH, Kong XY, He YZ, Liu Y, Peng X, Li ZH, et al. Recent developments in application of single-cell RNA sequencing in the tumour immune microenvironment and cancer therapy. *Mil Med Res* 2022;**9**:52.
21. Ma RY, Black A, Qian BZ. Macrophage diversity in cancer revisited in the era of single-cell omics. *Trends Immunol* 2022;**43**: 546−63.
22. Hara T, Chanoch-Myers R, Mathewson ND, Myskiw C, Atta L, Bussema L, et al. Interactions between cancer cells and immune cells drive transitions to mesenchymal-like states in glioblastoma. *Cancer Cell* 2021;**39**:779−92.
23. Zhang C, Liu Y, Jiang J, Chen C, Duan Z, Su H, et al. Targeting tumor cell-to-macrophage communication by blocking Vtn−C1qbp interaction inhibits tumor progression *via* enhancing macrophage phagocytosis. *Theranostics* 2024;**14**:2757−76.
24. Cheng S, Li Z, Gao R, Xing B, Gao Y, Yang Y, et al. A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. *Cell* 2021;**184**:792−809.
25. Mulder K, Patel AA, Kong WT, Piot C, Halitzki E, Dunsmore G, et al. Cross-tissue single-cell landscape of human monocytes and macrophages in health and disease. *Immunity* 2021;**54**:1883−900.
26. Kloosterman DJ, Akkari L. Macrophages at the interface of the co-evolving cancer ecosystem. *Cell* 2023;**186**:1627−51.
27. Stanley ER, Chitu V. CSF-1 receptor signaling in myeloid cells. *Cold Spring Harb Perspect Biol* 2014;**6**:a021857.
28. Zhou Y, Zeng J, Tu Y, Li L, Du S, Zhu L, et al. CSF1/CSF1R-mediated crosstalk between choroidal vascular endothelial cells and macrophages promotes choroidal neovascularization. *Investig Ophthalmol Vis Sci* 2021;**62**:37.
29. Vergadi E, Ieronymaki E, Lyroni K, Vaporidi K, Tsatsanis C. Akt signaling pathway in macrophage activation and M1/M2 polarization. *J Immunol* 2017;**198**:1006−14.
30. Harrington M, Konicek BW, Xia XL, Song A. Transcriptional regulation of the mouse CSF-1 gene. *Mol Reprod Dev* 1997;**46**:39−44.
31. Gao J, Liang Y, Wang L. Shaping polarization of tumor-associated macrophages in cancer immunotherapy. *Front Immunol* 2022;**13**: 888713.
32. Kzhyshkowska J, Shen J, Larionova I. Targeting of TAMs: can we be more clever than cancer cells?. *Cell Mol Immunol* 2024;**21**: 1376−409.
33. Pavlou S, Lindsay J, Ingram R, Xu H, Chen M. Sustained high glucose exposure sensitizes macrophage responses to cytokine stimuli but reduces their phagocytic activity. *BMC Immunol* 2018;**19**:24.
34. Andrejeva G, Rathmell JC. Similarities and distinctions of cancer and immune metabolism in inflammation and tumors. *Cell Metab* 2017; **26**:49−70.
35. Batista-Gonzalez A, Vidal R, Criollo A, Carreno LJ. New insights on the role of lipid metabolism in the metabolic reprogramming of macrophages. *Front Immunol* 2019;**10**:2993.
36. Kersten K, Hu KH, Combes AJ, Samad B, Harwin T, Ray A, et al. Spatiotemporal co-dependency between macrophages and exhausted $CD8^+$ T cells in cancer. *Cancer Cell* 2022;**40**:624−38.
37. Lu Y, Sun Q, Guan Q, Zhang Z, He Q, He J, et al. The XOR−IDH3alpha axis controls macrophage polarization in hepatocellular carcinoma. *J Hepatol* 2023;**79**:1172−84.
38. St Paul M, Ohashi PS. The roles of $CD8^+$ T cell subsets in antitumor immunity. *Trends Cell Biol* 2020;**30**:695−704.
39. Petty AJ, Li A, Wang X, Dai R, Heyman B, Hsu D, et al. Hedgehog signaling promotes tumor-associated macrophage polarization to suppress intratumoral $CD8^+$ T cell recruitment. *J Clin Investig* 2019; **129**:5151−62.
40. Cassetta L, Pollard JW. Targeting macrophages: therapeutic approaches in cancer. *Nat Rev Drug Discov* 2018;**17**:887−904.
41. Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. *Nature* 2017; **545**:495−9.
42. Morandi F, Pistoia V. Interactions between HLA-G and HLA-E in physiological and pathological conditions. *Front Immunol* 2014; **5**:394.

43. Marchesi M, Andersson E, Villabona L, Seliger B, Lundqvist A, Kiessling R, et al. HLA-dependent tumour development: a role for tumour associate macrophages?. *J Transl Med* 2013;**11**:247.
44. Vilbois S, Xu Y, Ho PC. Metabolic interplay: tumor macrophages and regulatory T cells. *Trends Cancer* 2024;**10**:242−55.
45. Liu C, Chikina M, Deshpande R, Menk AV, Wang T, Tabib T, et al. Treg cells promote the SREBP1-dependent metabolic fitness of tumor-promoting macrophages *via* repression of $CD8^+$ T cell-derived interferon-gamma. *Immunity* 2019;**51**:381−97.
46. Wu Q, Zhou W, Yin S, Zhou Y, Chen T, Qian J, et al. Blocking triggering receptor expressed on myeloid cells-1-positive tumor-associated macrophages induced by hypoxia reverses immunosuppression and anti-programmed cell death ligand 1 resistance in liver cancer. *Hepatology* 2019;**70**:198−214.
47. Chen Y, Song Y, Du W, Gong L, Chang H, Zou Z. Tumor-associated macrophages: an accomplice in solid tumor progression. *J Biomed Sci* 2019;**26**:78.
48. Dees S, Ganesan R, Singh S, Grewal IS. Regulatory T cell targeting in cancer: emerging strategies in immunotherapy. *Eur J Immunol* 2021;**51**:280−91.
49. Li K, Shi H, Zhang B, Ou X, Ma Q, Chen Y, et al. Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. *Signal Transduct Target Ther* 2021;**6**:362.
50. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol* 2021;**21**:485−98.
51. Bule P, Aguiar SI, Aires-Da-Silva F, Dias JNR. Chemokine-directed tumor microenvironment modulation in cancer immunotherapy. *Int J Mol Sci* 2021;**22**:9804.
52. Huang R, Kang T, Chen S. The role of tumor-associated macrophages in tumor immune evasion. *J Cancer Res Clin Oncol* 2024; **150**:238.
53. Trikha P, Carson WE. Signaling pathways involved in MDSC regulation. *Biochim Biophys Acta* 2014;**1846**:55−65.
54. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, et al. L-Arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell* 2016;**167**:829−42.
55. Wang Y, Wang D, Yang L, Zhang Y. Metabolic reprogramming in the immunosuppression of tumor-associated macrophages. *Chin Med J (Engl)* 2022;**135**:2405−16.
56. Munn DH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL. Inhibition of T cell proliferation by macrophage tryptophan catabolism. *J Exp Med* 1999;**189**:1363−72.
57. Lee WS, Yang H, Chon HJ, Kim C. Combination of anti-angiogenic therapy and immune checkpoint blockade normalizes vascular-immune crosstalk to potentiate cancer immunity. *Exp Mol Med* 2020;**52**:1475−85.
58. Simons M, Gordon E, Claesson-Welsh L. Mechanisms and regulation of endothelial VEGF receptor signalling. *Nat Rev Mol Cell Biol* 2016;**17**:611−25.
59. Stockmann C, Doedens A, Weidemann A, Zhang N, Takeda N, Greenberg JI, et al. Deletion of vascular endothelial growth factor in myeloid cells accelerates tumorigenesis. *Nature* 2008;**456**:814−8.
60. Larionova I, Kazakova E, Gerashchenko T, Kzhyshkowska J. New angiogenic regulators produced by TAMs: perspective for targeting tumor angiogenesis. *Cancers (Basel)* 2021;**13**:3253.
61. Shao R, Hamel K, Petersen L, Cao QJ, Arenas RB, Bigelow C, et al. YKL-40, a secreted glycoprotein, promotes tumor angiogenesis. *Oncogene* 2009;**28**:4456−68.
62. De Palma M, Murdoch C, Venneri MA, Naldini L, Lewis CE. Tie2-expressing monocytes: regulation of tumor angiogenesis and therapeutic implications. *Trends Immunol* 2007;**28**:519−24.
63. Xue R, Sheng Y, Duan X, Yang Y, Ma S, Xu J, et al. Tie2-expressing monocytes as a novel angiogenesis-related cellular biomarker for non-small cell lung cancer. *Int J Cancer* 2021;**148**:1519−28.
64. He YF, Wang CQ, Yu Y, Qian J, Song K, Sun QM, et al. Tie2-expressing monocytes are associated with identification and prognoses of hepatitis B virus related hepatocellular carcinoma after resection. *PLoS One* 2015;**10**:e0143657.
65. Chen L, Li J, Wang F, Dai C, Wu F, Liu X, et al. Tie2 expression on macrophages is required for blood vessel reconstruction and tumor relapse after chemotherapy. *Cancer Res* 2016;**76**:6828−38.
66. Zhu C, Kros JM, Cheng C, Mustafa D. The contribution of tumor-associated macrophages in glioma neo-angiogenesis and implications for anti-angiogenic strategies. *Neuro Oncol* 2017;**19**: 1435−46.
67. Nakamura R, Sene A, Santeford A, Gdoura A, Kubota S, Zapata N, et al. IL10-driven STAT3 signalling in senescent macrophages promotes pathological eye angiogenesis. *Nat Commun* 2015;**6**:7847.
68. Bahr JC, Li XY, Feinberg TY, Jiang L, Weiss SJ. Divergent regulation of basement membrane trafficking by human macrophages and cancer cells. *Nat Commun* 2022;**13**:6409.
69. Afik R, Zigmond E, Vugman M, Klepfish M, Shimshoni E, Pasmanik-Chor M, et al. Tumor macrophages are pivotal constructors of tumor collagenous matrix. *J Exp Med* 2016;**213**:2315−31.
70. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity* 2014;**41**:49−61.
71. Ruffell B, Coussens LM. Macrophages and therapeutic resistance in cancer. *Cancer Cell* 2015;**27**:462−72.
72. Srinivas US, Tan BWQ, Vellayappan BA, Jeyasekharan AD. ROS and the DNA damage response in cancer. *Redox Biol* 2019;**25**: 101084.
73. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch Toxicol* 2023;**97**: 2499−574.
74. Wen C, Wang H, Wu X, He L, Zhou Q, Wang F, et al. ROS-mediated inactivation of the PI3K/AKT pathway is involved in the antigastric cancer effects of thioredoxin reductase-1 inhibitor chaetocin. *Cell Death Dis* 2019;**10**:809.
75. Hong Y, Boiti A, Vallone D, Foulkes NS. Reactive oxygen species signaling and oxidative stress: transcriptional regulation and evolution. *Antioxidants* 2024;**13**:312.
76. Mori K, Uchida T, Yoshie T, Mizote Y, Ishikawa F, Katsuyama M, et al. A mitochondrial ROS pathway controls matrix metalloproteinase 9 levels and invasive properties in RAS-activated cancer cells. *FEBS J* 2019;**286**:459−78.
77. Kobayashi Y, Oguro A, Imaoka S. Feedback of hypoxia-inducible factor-1alpha (HIF-1alpha) transcriptional activity *via* redox factor-1 (Ref-1) induction by reactive oxygen species (ROS). *Free Radic Res* 2021;**55**:154−64.
78. Shi Y, Gilkes DM. HIF-1 and HIF-2 in cancer: structure, regulation, and therapeutic prospects. *Cell Mol Life Sci* 2025;**82**:44.
79. Tajaldini M, Saeedi M, Amiriani T, Amiriani AH, Sedighi S, Mohammad Zadeh F, et al. Cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs); where do they stand in tumorigenesis and how they can change the face of cancer therapy?. *Eur J Pharmacol* 2022;**928**:175087.
80. Luo Y, Chen Y, Jin H, Hou B, Li H, Li X, et al. The suppression of cervical cancer ferroptosis by macrophages: the attenuation of ALOX15 in cancer cells by macrophages-derived exosomes. *Acta Pharm Sin B* 2023;**13**:2645−62.
81. Fan QM, Jing YY, Yu GF, Kou XR, Ye F, Gao L, et al. Tumor-associated macrophages promote cancer stem cell-like properties *via* transforming growth factor-beta1-induced epithelial-mesenchymal transition in hepatocellular carcinoma. *Cancer Lett* 2014;**352**:160−8.
82. Williams CB, Yeh ES, Soloff AC. Tumor-associated macrophages: unwitting accomplices in breast cancer malignancy. *NPJ Breast Cancer* 2016;**2**:15025.

83. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature* 2011;**475**:222−5.
84. Ma J, Shayiti F, Ma J, Wei M, Hua T, Zhang R, et al. Tumor-associated macrophage-derived CCL5 promotes chemotherapy resistance and metastasis in prostatic cancer. *Cell Biol Int* 2021;**45**:2054−62.
85. Vasiljeva O, Papazoglou A, Kruger A, Brodoefel H, Korovin M, Deussing J, et al. Tumor cell-derived and macrophage-derived cathepsin B promotes progression and lung metastasis of mammary cancer. *Cancer Res* 2006;**66**:5242−50.
86. Liu M, Liu L, Song Y, Li W, Xu L. Targeting macrophages: a novel treatment strategy in solid tumors. *J Transl Med* 2022;**20**:586.
87. Ozga AJ, Chow MT, Luster AD. Chemokines and the immune response to cancer. *Immunity* 2021;**54**:859−74.
88. De Palma M, Biziato D, Petrova TV. Microenvironmental regulation of tumour angiogenesis. *Nat Rev Cancer* 2017;**17**:457−74.
89. Rao L, Wu L, Liu Z, Tian R, Yu G, Zhou Z, et al. Hybrid cellular membrane nanovesicles amplify macrophage immune responses against cancer recurrence and metastasis. *Nat Commun* 2020;**11**: 4909.
90. Cao X, Li B, Chen J, Dang J, Chen S, Gunes EG, et al. Effect of cabazitaxel on macrophages improves CD47-targeted immunotherapy for triple-negative breast cancer. *J Immunother Cancer* 2021; **9**:e002022.
91. Gunassekaran GR, Poongkavithai Vadevoo SM, Baek MC, Lee B. M1 macrophage exosomes engineered to foster M1 polarization and target the IL-4 receptor inhibit tumor growth by reprogramming tumor-associated macrophages into M1-like macrophages. *Biomaterials* 2021;**278**:121137.
92. Yang K, Han W, Jiang X, Piffko A, Bugno J, Han C, et al. Zinc cyclic di-AMP nanoparticles target and suppress tumours *via* endothelial STING activation and tumour-associated macrophage reinvigoration. *Nat Nanotechnol* 2022;**17**:1322−31.
93. Han S, Bao X, Zou Y, Wang L, Li Y, Yang L, et al. D-Lactate modulates M2 tumor-associated macrophages and remodels immunosuppressive tumor microenvironment for hepatocellular carcinoma. *Sci Adv* 2023;**9**:eadg2697.
94. Basak U, Sarkar T, Mukherjee S, Chakraborty S, Dutta A, Dutta S, et al. Tumor-associated macrophages: an effective player of the tumor microenvironment. *Front Immunol* 2023;**14**:1295257.
95. Wang S, Wang J, Chen Z, Luo J, Guo W, Sun L, et al. Targeting M2-like tumor-associated macrophages is a potential therapeutic approach to overcome antitumor drug resistance. *NPJ Precis Oncol* 2024;**8**:31.
96. Reschke R, Gajewski TF. CXCL9 and CXCL10 bring the heat to tumors. *Sci Immunol* 2022;**7**:eabq6509.
97. Covarrubias A, Byles V, Horng T. ROS sets the stage for macrophage differentiation. *Cell Res* 2013;**23**:984−5.
98. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked?. *Free Radic Biol Med* 2010;**49**:1603−16.
99. Storz P. Reactive oxygen species in tumor progression. *Front Biosci* 2005;**10**:1881−96.
100. Asare-Werehene M, Tsuyoshi H, Zhang H, Salehi R, Chang CY, Carmona E, et al. Plasma gelsolin confers chemoresistance in ovarian cancer by resetting the relative abundance and function of macrophage subtypes. *Cancers (Basel)* 2022;**14**:1039.
101. Glorieux C, Liu S, Trachootham D, Huang P. Targeting ROS in cancer: rationale and strategies. *Nat Rev Drug Discov* 2024;**23**:583−606.
102. Zheng GX, Terry JM, Belgrader P, Ryvkin P, Bent ZW, Wilson R, et al. Massively parallel digital transcriptional profiling of single cells. *Nat Commun* 2017;**8**:14049.
103. Papalexi E, Satija R. Single-cell RNA sequencing to explore immune cell heterogeneity. *Nat Rev Immunol* 2018;**18**:35−45.
104. Zhang Y, Wang D, Peng M, Tang L, Ouyang J, Xiong F, et al. Single-cell RNA sequencing in cancer research. *J Exp Clin Cancer Res* 2021;**40**:81.
105. Stubbington MJT, Rozenblatt-Rosen O, Regev A, Teichmann SA. Single-cell transcriptomics to explore the immune system in health and disease. *Science* 2017;**358**:58−63.
106. Yang S, Wang M, Hua Y, Li J, Zheng H, Cui M, et al. Advanced insights on tumor-associated macrophages revealed by single-cell RNA sequencing: the intratumor heterogeneity, functional phenotypes, and cellular interactions. *Cancer Lett* 2024;**584**:216610.
107. Chu X, Tian Y, Lv C. Decoding the spatiotemporal heterogeneity of tumor-associated macrophages. *Mol Cancer* 2024;**23**:150.
108. Artyomov MN, Van den Bossche J. Immunometabolism in the single-cell era. *Cell Metab* 2020;**32**:710−25.
109. Wagner J, Rapsomaniki MA, Chevrier S, Anzeneder T, Langwieder C, Dykgers A, et al. A single-cell atlas of the tumor and immune ecosystem of human breast cancer. *Cell* 2019;**177**:1330−45.
110. Xue C, Gu X, Zheng Q, Shi Q, Yuan X, Chu Q, et al. Effects of 3-HAA on HCC by regulating the heterogeneous macrophages-A scRNA-Seq analysis. *Adv Sci (Weinh)* 2023;**10**:e2207074.
111. Qiu X, Zhou T, Li S, Wu J, Tang J, Ma G, et al. Spatial single-cell protein landscape reveals vimentin(high) macrophages as immune-suppressive in the microenvironment of hepatocellular carcinoma. *Nat Cancer* 2024;**5**:1557−78.
112. Nalio Ramos R, Missolo-Koussou Y, Gerber-Ferder Y, Bromley CP, Bugatti M, Nunez NG, et al. Tissue-resident FOLR2$^+$ macrophages associate with CD8$^+$ T cell infiltration in human breast cancer. *Cell* 2022;**185**:1189−207.
113. Meng X, Zheng Y, Zhang L, Liu P, Liu Z, He Y. Single-cell analyses reveal the metabolic heterogeneity and plasticity of the tumor microenvironment during head and neck squamous cell carcinoma progression. *Cancer Res* 2024;**84**:2468−83.
114. Qi J, Sun H, Zhang Y, Wang Z, Xun Z, Li Z, et al. Single-cell and spatial analysis reveal interaction of FAP$^+$ fibroblasts and SPP1$^+$ macrophages in colorectal cancer. *Nat Commun* 2022;**13**:1742.
115. Yi X, Luo L, Zhu Y, Deng H, Liao H, Shen Y, et al. SPP1 facilitates cell migration and invasion by targeting COL11A1 in lung adenocarcinoma. *Cancer Cell Int* 2022;**22**:324.
116. He C, Sheng L, Pan D, Jiang S, Ding L, Ma X, et al. Single-cell transcriptomic analysis revealed a critical role of SPP1/CD44-mediated crosstalk between macrophages and cancer cells in glioma. *Front Cell Dev Biol* 2021;**9**:779319.
117. Liu F, Zhang J, Gu X, Guo Q, Guo W. Single-cell transcriptome sequencing reveals SPP1-CD44-mediated macrophage-tumor cell interactions drive chemoresistance in TNBC. *J Cell Mol Med* 2024; **28**:e18525.
118. Coulis G, Jaime D, Guerrero-Juarez C, Kastenschmidt JM, Farahat PK, Nguyen Q, et al. Single-cell and spatial transcriptomics identify a macrophage population associated with skeletal muscle fibrosis. *Sci Adv* 2023;**9**:eadd9984.
119. Cheng Y, Chen X, Feng L, Yang Z, Xiao L, Xiang B, et al. Stromal architecture and fibroblast subpopulations with opposing effects on outcomes in hepatocellular carcinoma. *Cell Discov* 2025;**11**:1.
120. Pan X, Li X, Dong L, Liu T, Zhang M, Zhang L, et al. Tumour vasculature at single-cell resolution. *Nature* 2024;**632**:429−36.
121. Wei J, Chen Z, Hu M, He Z, Jiang D, Long J, et al. Characterizing intercellular communication of pan-cancer reveals SPP1+ tumor-associated macrophage expanded in hypoxia and promoting cancer malignancy through single-cell RNA-Seq data. *Front Cell Dev Biol* 2021;**9**:749210.
122. Xu L, Chen Y, Liu L, Hu X, He C, Zhou Y, et al. Tumor-associated macrophage subtypes on cancer immunity along with prognostic analysis and SPP1-mediated interactions between tumor cells and macrophages. *PLoS Genet* 2024;**20**:e1011235.
123. Xie W, Cheng J, Hong Z, Cai W, Zhuo H, Hou J, et al. Multi-transcriptomic analysis reveals the heterogeneity and tumor-promoting role of SPP1/CD44-mediated intratumoral crosstalk in gastric cancer. *Cancers (Basel)* 2022;**15**:164.
124. Fan G, Xie T, Li L, Tang L, Han X, Shi Y. Single-cell and spatial analyses revealed the co-location of cancer stem cells and SPP1$^+$

macrophage in hypoxic region that determines the poor prognosis in hepatocellular carcinoma. *NPJ Precis Oncol* 2024;**8**:75.
125. You G, Zheng Z, Huang Y, Liu G, Luo W, Huang J, et al. scRNA-seq and proteomics reveal the distinction of M2-like macrophages between primary and recurrent malignant glioma and its critical role in the recurrence. *CNS Neurosci Ther* 2023;**29**:3391−405.
126. Ozato Y, Kojima Y, Kobayashi Y, Hisamatsu Y, Toshima T, Yonemura Y, et al. Spatial and single-cell transcriptomics decipher the cellular environment containing HLA-G$^+$ cancer cells and SPP1+ macrophages in colorectal cancer. *Cell Rep* 2023;**42**:111929.
127. Liu Y, Xun Z, Ma K, Liang S, Li X, Zhou S, et al. Identification of a tumour immune barrier in the HCC microenvironment that determines the efficacy of immunotherapy. *J Hepatol* 2023;**78**:770−82.
128. Rakina M, Larionova I, Kzhyshkowska J. Macrophage diversity in human cancers: new insight provided by single-cell resolution and spatial context. *Heliyon* 2024;**10**:e28332.
129. Khantakova D, Brioschi S, Molgora M. Exploring the impact of TREM2 in tumor-associated macrophages. *Vaccines (Basel)* 2022;**10**:943.
130. Molgora M, Esaulova E, Vermi W, Hou J, Chen Y, Luo J, et al. TREM2 modulation remodels the tumor myeloid landscape enhancing anti-PD-1 immunotherapy. *Cell* 2020;**182**:886−900.
131. Zhou L, Wang M, Guo H, Hou J, Zhang Y, Li M, et al. Integrated analysis highlights the immunosuppressive role of TREM2$^+$ macrophages in hepatocellular carcinoma. *Front Immunol* 2022;**13**:848367.
132. Zhang H, Liu Z, Wen H, Guo Y, Xu F, Zhu Q, et al. Immunosuppressive TREM2$^+$ macrophages are associated with undesirable prognosis and responses to anti-PD-1 immunotherapy in non-small cell lung cancer. *Cancer Immunol Immunother* 2022;**71**:2511−22.
133. Xiong D, Wang Y, You M. A gene expression signature of TREM2$^{hi}$ macrophages and gammadelta T cells predicts immunotherapy response. *Nat Commun* 2020;**11**:5084.
134. Binnewies M, Pollack JL, Rudolph J, Dash S, Abushawish M, Lee T, et al. Targeting TREM2 on tumor-associated macrophages enhances immunotherapy. *Cell Rep* 2021;**37**:109844.
135. Sun R, Han R, McCornack C, Khan S, Tabor GT, Chen Y, et al. TREM2 inhibition triggers antitumor cell activity of myeloid cells in glioblastoma. *Sci Adv* 2023;**9**:eade3559.
136. Zhong J, Xing X, Gao Y, Pei L, Lu C, Sun H, et al. Distinct roles of TREM2 in central nervous system cancers and peripheral cancers. *Cancer Cell* 2024;**42**:968−84.
137. Kanno S, Hirano S, Sakamoto T, Furuyama A, Takase H, Kato H, et al. Scavenger receptor MARCO contributes to cellular internalization of exosomes by dynamin-dependent endocytosis and macropinocytosis. *Sci Rep* 2020;**10**:21795.
138. Donadon M, Torzilli G, Cortese N, Soldani C, Di Tommaso L, Franceschini B, et al. Macrophage morphology correlates with single-cell diversity and prognosis in colorectal liver metastasis. *J Exp Med* 2020;**217**:e20191847.
139. Wang C, Yu Q, Song T, Wang Z, Song L, Yang Y, et al. The heterogeneous immune landscape between lung adenocarcinoma and squamous carcinoma revealed by single-cell RNA sequencing. *Signal Transduct Target Ther* 2022;**7**:289.
140. Chen AX, Gartrell RD, Zhao J, Upadhyayula PS, Zhao W, Yuan J, et al. Single-cell characterization of macrophages in glioblastoma reveals MARCO as a mesenchymal pro-tumor marker. *Genome Med* 2021;**13**:88.
141. Georgoudaki AM, Prokopec KE, Boura VF, Hellqvist E, Sohn S, Ostling J, et al. Reprogramming tumor-associated macrophages by antibody targeting inhibits cancer progression and metastasis. *Cell Rep* 2016;**15**:2000−11.
142. Gu C, Wiest M, Zhang W, Halder K, Zurawski S, Zurawski G, et al. Cancer cells promote immune regulatory function of macrophages by upregulating scavenger receptor MARCO expression. *J Immunol* 2023;**211**:57−70.
143. La Fleur L, Botling J, He F, Pelicano C, Zhou C, He C, et al. Targeting MARCO and IL37R on immunosuppressive macrophages in lung cancer blocks regulatory T cells and supports cytotoxic lymphocyte function. *Cancer Res* 2021;**81**:956−67.
144. Ding L, Qian J, Yu X, Wu Q, Mao J, Liu X, et al. Blocking MARCO$^+$ tumor-associated macrophages improves anti-PD-L1 therapy of hepatocellular carcinoma by promoting the activation of STING−IFN type I pathway. *Cancer Lett* 2024;**582**:216568.
145. La Fleur L, Boura VF, Alexeyenko A, Berglund A, Ponten V, Mattsson JSM, et al. Expression of scavenger receptor MARCO defines a targetable tumor-associated macrophage subset in non-small cell lung cancer. *Int J Cancer* 2018;**143**:1741−52.
146. Shi B, Chu J, Huang T, Wang X, Li Q, Gao Q, et al. The scavenger receptor MARCO expressed by tumor-associated macrophages are highly associated with poor pancreatic cancer prognosis. *Front Oncol* 2021;**11**:771488.
147. Xing Q, Feng Y, Sun H, Yang S, Sun T, Guo X, et al. Scavenger receptor MARCO contributes to macrophage phagocytosis and clearance of tumor cells. *Exp Cell Res* 2021;**408**:112862.
148. Nalio Ramos R, Missolo-Koussou Y, Gerber-Ferder Y, Bromley CP, Bugatti M, Núñez NG, et al. Tissue-resident FOLR2$^+$ macrophages associate with CD8$^+$ T cell infiltration in human breast cancer. *Cell* 2022;**185**:1189−207.
149. Xiang C, Zhang M, Shang Z, Chen S, Zhao J, Ding B, et al. Single-cell profiling reveals the trajectory of FOLR2-expressing tumor-associated macrophages to regulatory T cells in the progression of lung adenocarcinoma. *Cell Death Dis* 2023;**14**:493.
150. Matusiak M, Hickey JW, Luca B, Lu G, Kidzinski L, Shu S, et al. A spatial map of human macrophage niches links tissue location with function. *Res Sq* 2023. Available from: https://doi.org/10.21203/rs.3.rs-2393443/v1.
151. Obradovic A, Chowdhury N, Haake SM, Ager C, Wang V, Vlahos L, et al. Single-cell protein activity analysis identifies recurrence-associated renal tumor macrophages. *Cell* 2021;**184**:2988−3005.
152. Braun DA, Street K, Burke KP, Cookmeyer DL, Denize T, Pedersen CB, et al. Progressive immune dysfunction with advancing disease stage in renal cell carcinoma. *Cancer Cell* 2021;**39**:632−48.
153. Roumenina LT, Daugan MV, Noe R, Petitprez F, Vano YA, Sanchez-Salas R, et al. Tumor cells Hijack macrophage-produced complement C1q to promote tumor growth. *Cancer Immunol Res* 2019;**7**:1091−105.
154. Zhang Q, He Y, Luo N, Patel SJ, Han Y, Gao R, et al. Landscape and dynamics of single immune cells in hepatocellular carcinoma. *Cell* 2019;**179**:829−45.
155. Li X, Zhang Q, Chen G, Luo D. Multi-omics analysis showed the clinical value of gene signatures of C1QC$^+$ and SPP1$^+$ TAMs in cervical cancer. *Front Immunol* 2021;**12**:694801.
156. Dong L, Chen C, Zhang Y, Guo P, Wang Z, Li J, et al. The loss of RNA $N^6$-Adenosine methyltransferase Mettl14 in tumor-associated macrophages promotes CD8$^+$ T cell dysfunction and tumor growth. *Cancer Cell* 2021;**39**:945−57.
157. Zhang L, Li Z, Skrzypczynska KM, Fang Q, Zhang W, O'Brien SA, et al. Single-cell analyses inform mechanisms of myeloid-targeted therapies in colon cancer. *Cell* 2020;**181**:442−59.
158. Yang Q, Zhang H, Wei T, Lin A, Sun Y, Luo P, et al. Single-cell RNA sequencing reveals the heterogeneity of tumor-associated macrophage in non-small cell lung cancer and differences between sexes. *Front Immunol* 2021;**12**:756722.
159. Shao YJ, Ni JJ, Wei SY, Weng XP, Shen MD, Jia YX, et al. IRF1-mediated immune cell infiltration is associated with metastasis in colon adenocarcinoma. *Medicine (Baltim)* 2020;**99**:e22170.
160. Revel M, Sautes-Fridman C, Fridman WH, Roumenina LT. C1q+ macrophages: passengers or drivers of cancer progression. *Trends Cancer* 2022;**8**:517−26.
161. Huang H, Tan M, Zheng L, Yan G, Li K, Lu D, et al. Prognostic implications of the complement protein C1Q and its correlation with immune infiltrates in osteosarcoma. *Onco Targets Ther* 2021;**14**:1737−51.
162. Yang J, Lin P, Yang M, Liu W, Fu X, Liu D, et al. Integrated genomic and transcriptomic analysis reveals unique characteristics of hepatic metastases and pro-metastatic role of complement C1q in pancreatic ductal adenocarcinoma. *Genome Biol* 2021;**22**:4.

163. Mantovani A, Allavena P, Marchesi F, Garlanda C. Macrophages as tools and targets in cancer therapy. *Nat Rev Drug Discov* 2022;**21**: 799−820.
164. Choi TH, Yoo RJ, Park JY, Kim JY, Ann YC, Park J, et al. Development of finely tuned liposome nanoplatform for macrophage depletion. *J Nanobiotechnol* 2024;**22**:83.
165. Tyner JW, Uchida O, Kajiwara N, Kim EY, Patel AC, O'Sullivan MP, et al. CCL5−CCR5 interaction provides antiapoptotic signals for macrophage survival during viral infection. *Nat Med* 2005;**11**: 1180−7.
166. Opperman KS, Vandyke K, Clark KC, Coulter EA, Hewett DR, Mrozik KM, et al. Clodronate-liposome mediated macrophage depletion abrogates multiple myeloma tumor establishment *in vivo*. *Neoplasia* 2019;**21**:777−87.
167. Shen L, Li H, Shi Y, Wang D, Gong J, Xun J, et al. M2 tumour-associated macrophages contribute to tumour progression *via* legumain remodelling the extracellular matrix in diffuse large B cell lymphoma. *Sci Rep* 2016;**6**:30347.
168. Piaggio F, Kondylis V, Pastorino F, Di Paolo D, Perri P, Cossu I, et al. A novel liposomal clodronate depletes tumor-associated macrophages in primary and metastatic melanoma: anti-angiogenic and anti-tumor effects. *J Control Release* 2016;**223**:165−77.
169. van Rooijen N, Hendrikx E. Liposomes for specific depletion of macrophages from organs and tissues. *Methods Mol Biol* 2010;**605**: 189−203.
170. Sanchez-Paulete AR, Mateus-Tique J, Mollaoglu G, Nielsen SR, Marks A, Lakshmi A, et al. Targeting macrophages with CAR T cells delays solid tumor progression and enhances antitumor immunity. *Cancer Immunol Res* 2022;**10**:1354−69.
171. Rodriguez-Garcia A, Lynn RC, Poussin M, Eiva MA, Shaw LC, O'Connor RS, et al. CAR-T cell-mediated depletion of immunosuppressive tumor-associated macrophages promotes endogenous antitumor immunity and augments adoptive immunotherapy. *Nat Commun* 2021;**12**:877.
172. Mantovani A, Allavena P, Sozzani S, Vecchi A, Locati M, Sica A. Chemokines in the recruitment and shaping of the leukocyte infiltrate of tumors. *Semin Cancer Biol* 2004;**14**:155−60.
173. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol* 2017;**14**:399−416.
174. He Z, Zhang S. Tumor-associated macrophages and their functional transformation in the hypoxic tumor microenvironment. *Front Immunol* 2021;**12**:741305.
175. Boutilier AJ, Elsawa SF. Macrophage polarization states in the tumor microenvironment. *Int J Mol Sci* 2021;**22**:6995.
176. Zuo C, Baer JM, Knolhoff BL, Belle JI, Liu X, Alarcon De La Lastra A, et al. Stromal and therapy-induced macrophage proliferation promotes PDAC progression and susceptibility to innate immunotherapy. *J Exp Med* 2023;**220**:e20212062.
177. Anderson NR, Minutolo NG, Gill S, Klichinsky M. Macrophage-based approaches for cancer immunotherapy. *Cancer Res* 2021;**81**: 1201−8.
178. Pyonteck SM, Akkari L, Schuhmacher AJ, Bowman RL, Sevenich L, Quail DF, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. *Nat Med* 2013;**19**:1264−72.
179. Erkes DA, Rosenbaum SR, Field CO, Chervoneva I, Villanueva J, Aplin AE. PLX3397 inhibits the accumulation of intra-tumoral macrophages and improves bromodomain and extra-terminal inhibitor efficacy in melanoma. *Pigment Cell Melanoma Res* 2020;**33**: 372−7.
180. Lamb YN. Pexidartinib: first approval. *Drugs* 2019;**79**:1805−12.
181. Tap WD, Gelderblom H, Palmerini E, Desai J, Bauer S, Blay JY, et al. Pexidartinib *versus* placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet* 2019; **394**:478−87.
182. Wesolowski R, Sharma N, Reebel L, Rodal MB, Peck A, West BL, et al. Phase Ib study of the combination of pexidartinib (PLX3397), a CSF-1R inhibitor, and paclitaxel in patients with advanced solid tumors. *Ther Adv Med Oncol* 2019;**11**:1758835919854238.
183. Autio KA, Klebanoff CA, Schaer D, Kauh JS, Slovin SF, Blinder VS, et al. Phase 1 study of LY3022855, a colony-stimulating factor-1 receptor (CSF-1R) inhibitor, in patients with metastatic breast cancer (MBC) or metastatic castration-resistant prostate cancer (MCRPC). *J Clin Oncol* 2019;**37**:2548.
184. Wiehagen KR, Girgis NM, Yamada DH, Smith AA, Chan SR, Grewal IS, et al. Combination of CD40 agonism and CSF-1R blockade reconditions tumor-associated macrophages and drives potent antitumor immunity. *Cancer Immunol Res* 2017;**5**:1109−21.
185. Li X, Yao W, Yuan Y, Chen P, Li B, Li J, et al. Targeting of tumour-infiltrating macrophages *via* CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma. *Gut* 2017;**66**:157−67.
186. Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. *Nat Rev Immunol* 2017;**17**:559−72.
187. Tu MM, Abdel-Hafiz HA, Jones RT, Jean A, Hoff KJ, Duex JE, et al. Inhibition of the CCL2 receptor, CCR2, enhances tumor response to immune checkpoint therapy. *Commun Biol* 2020;**3**:720.
188. Yang H, Zhang Q, Xu M, Wang L, Chen X, Feng Y, et al. CCL2−CCR2 axis recruits tumor associated macrophages to induce immune evasion through PD-1 signaling in esophageal carcinogenesis. *Mol Cancer* 2020;**19**:41.
189. Möckel D, Bartneck M, Niemietz P, Wagner M, Ehling J, Rama E, et al. CCL2 chemokine inhibition primes the tumor vasculature for improved nanomedicine delivery and efficacy. *J Control Release* 2024;**365**:358−68.
190. Sandhu SK, Papadopoulos K, Fong PC, Patnaik A, Messiou C, Olmos D, et al. A first-in-human, first-in-class, phase I study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 in patients with solid tumors. *Cancer Chemother Pharmacol* 2013;**71**:1041−50.
191. Brana I, Calles A, LoRusso PM, Yee LK, Puchalski TA, Seetharam S, et al. Carlumab, an anti-C−C chemokine ligand 2 monoclonal antibody, in combination with four chemotherapy regimens for the treatment of patients with solid tumors: an open-label, multicenter phase 1b study. *Target Oncol* 2015;**10**:111−23.
192. Pienta KJ, Machiels JP, Schrijvers D, Alekseev B, Shkolnik M, Crabb SJ, et al. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. *Invest N Drugs* 2013; **31**:760−8.
193. Pathria P, Louis TL, Varner JA. Targeting tumor-associated macrophages in cancer. *Trends Immunol* 2019;**40**:310−27.
194. Vergunst CE, Gerlag DM, Lopatinskaya L, Klareskog L, Smith MD, van den Bosch F, et al. Modulation of CCR2 in rheumatoid arthritis: a double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2008;**58**:1931−9.
195. Noel MS, Hezel AF, Linehan D, Wang-Gillam A, Eskens F, Sleijfer S, et al. Orally administered CCR2 selective inhibitor CCX872-b clinical trial in pancreatic cancer. *J Clin Oncol* 2017;**35**:276.
196. Christenson E, Lim SJ, Wang H, Ferguson A, Parkinson R, Cetasaan Y, et al. Nivolumab and a CCR2/CCR5 dual antagonist (BMS-813160) with or without GVAX for locally advanced pancreatic ductal adenocarcinomas: results of phase I study. *J Clin Oncol* 2023;**41**:730.
197. Guo F, Wang Y, Liu J, Mok SC, Xue F, Zhang W. CXCL12/CXCR4: a symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. *Oncogene* 2016;**35**:816−26.
198. Hughes R, Qian BZ, Rowan C, Muthana M, Keklikoglou I, Olson OC, et al. Perivascular M2 macrophages stimulate tumor relapse after chemotherapy. *Cancer Res* 2015;**75**:3479−91.
199. Sun R, Sun Y, Wu C, Liu Y, Zhou M, Dong Y, et al. CXCR4-modified CAR-T cells suppresses MDSCs recruitment *via* STAT3/NF-kappaB/SDF-1alpha axis to enhance efficacy against pancreatic cancer. *Mol Ther* 2023;**31**:3193−209.

200. Guillot A, Tacke F. Liver macrophages: old dogmas and new insights. *Hepatol Commun* 2019;**3**:730−43.
201. Baghdadi M, Wada H, Nakanishi S, Abe H, Han N, Putra WE, et al. Chemotherapy-induced IL34 enhances immunosuppression by tumor-associated macrophages and mediates survival of chemoresistant lung cancer cells. *Cancer Res* 2016;**76**:6030−42.
202. Nakasone ES, Askautrud HA, Kees T, Park JH, Plaks V, Ewald AJ, et al. Imaging tumor-stroma interactions during chemotherapy reveals contributions of the microenvironment to resistance. *Cancer Cell* 2012;**21**:488−503.
203. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* 2010;**376**:1164−74.
204. Travers M, Brown SM, Dunworth M, Holbert CE, Wiehagen KR, Bachman KE, et al. DFMO and 5-azacytidine increase M1 macrophages in the tumor microenvironment of murine ovarian cancer. *Cancer Res* 2019;**79**:3445−54.
205. Ma F, Zhang J, Zhang J, Zhang C. The TLR7 agonists imiquimod and gardiquimod improve DC-based immunotherapy for melanoma in mice. *Cell Mol Immunol* 2010;**7**:381−8.
206. Machiels JP, Kaminsky MC, Keller U, Brummendorf TH, Goddemeier T, Forssmann U, et al. Phase Ib trial of the Toll-like receptor 9 agonist IMO-2055 in combination with 5-fluorouracil, cisplatin, and cetuximab as first-line palliative treatment in patients with recurrent/metastatic squamous cell carcinoma of the head and neck. *Invest N Drugs* 2013;**31**:1207−16.
207. Zhou J, Xu Y, Wang G, Mei T, Yang H, Liu Y. The TLR7/8 agonist R848 optimizes host and tumor immunity to improve therapeutic efficacy in murine lung cancer. *Int J Oncol* 2022;**61**:81.
208. Adams S, Kozhaya L, Martiniuk F, Meng TC, Chiriboga L, Liebes L, et al. Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer. *Clin Cancer Res* 2012;**18**:6748−57.
209. Kobold S, Wiedemann G, Rothenfusser S, Endres S. Modes of action of TLR7 agonists in cancer therapy. *Immunotherapy* 2014;**6**: 1085−95.
210. Smith DA, Conkling P, Richards DA, Nemunaitis JJ, Boyd TE, Mita AC, et al. Antitumor activity and safety of combination therapy with the Toll-like receptor 9 agonist IMO-2055, erlotinib, and bevacizumab in advanced or metastatic non-small cell lung cancer patients who have progressed following chemotherapy. *Cancer Immunol Immunother* 2014;**63**:787−96.
211. Harney AS, Arwert EN, Entenberg D, Wang Y, Guo P, Qian BZ, et al. Real-time imaging reveals local, transient vascular permeability, and tumor cell intravasation stimulated by TIE2hi macrophage-derived VEGFA. *Cancer Discov* 2015;**5**:932−43.
212. Jakab M, Rostalski T, Lee KH, Mogler C, Augustin HG. Tie2 receptor in tumor-infiltrating macrophages is dispensable for tumor angiogenesis and tumor relapse after chemotherapy. *Cancer Res* 2022;**82**:1353−64.
213. Mazzieri R, Pucci F, Moi D, Zonari E, Ranghetti A, Berti A, et al. Targeting the ANG2/TIE2 axis inhibits tumor growth and metastasis by impairing angiogenesis and disabling rebounds of proangiogenic myeloid cells. *Cancer Cell* 2011;**19**:512−26.
214. Gupta VG, Roby KF, Pathak HB, Godwin AK, Gunewardena S, Khabele D. Abstract 3457: Rebastinib, a TIE2 antagonist improves chemotherapy response in homologous recombination proficient epithelial ovarian cancer murine models. *Cancer Res* 2022;**82**:3457.
215. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;**389**:56−66.
216. Lombardi G, De Salvo GL, Brandes AA, Eoli M, Ruda R, Faedi M, et al. Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet Oncol* 2019;**20**:110−9.
217. Wang S, Yang Y, Ma P, Zha Y, Zhang J, Lei A, et al. CAR-macrophage: an extensive immune enhancer to fight cancer. *EBioMedicine* 2022;**76**:103873.
218. Li N, Geng S, Dong ZZ, Jin Y, Ying H, Li HW, et al. A new era of cancer immunotherapy: combining revolutionary technologies for enhanced CAR-M therapy. *Mol Cancer* 2024;**23**:117.
219. Klichinsky M, Gabrusiewicz K, Anderson N, Schmierer M, Best A, Zeeman M, et al. Abstract 3242: CT-0508 is an anti-HER2 chimeric antigen receptor (CAR) macrophage with targeted anti-tumor activity that promotes a pro-inflammatory solid tumor microenvironment. *Cancer Res* 2020;**80**:3242.
220. Annunziata CM, Ghobadi A, Pennella EJ, Vanas J, Powell C, Pavelova M, et al. Feasibility and preliminary safety and efficacy of first-in-human intraperitoneal delivery of MCY-M11, anti-human-mesothelin CAR mRNA transfected into peripheral blood mononuclear cells, for ovarian cancer and malignant peritoneal mesothelioma. *J Clin Oncol* 2020;**38**:3014.
221. Wang YN, Wang YY, Wang J, Bai WJ, Miao NJ, Wang J. Vinblastine resets tumor-associated macrophages toward M1 phenotype and promotes antitumor immune response. *J Immunother Cancer* 2023; **11**:e007253.
222. Lei A, Yu H, Lu S, Lu H, Ding X, Tan T, et al. A second-generation M1-polarized CAR macrophage with antitumor efficacy. *Nat Immunol* 2024;**25**:102−16.
223. Barclay AN, Van den Berg TK. The interaction between signal regulatory protein alpha (SIRPalpha) and CD47: structure, function, and therapeutic target. *Annu Rev Immunol* 2014;**32**:25−50.
224. Barclay AN, Brown MH. The SIRP family of receptors and immune regulation. *Nat Rev Immunol* 2006;**6**:457−64.
225. van Duijn A, Van der Burg SH, Scheeren FA. CD47/SIRP$\alpha$ axis: bridging innate and adaptive immunity. *J Immunother Cancer* 2022; **10**:e004589.
226. Zhou H, Wang W, Xu H, Liang Y, Ding J, Lv M, et al. Metabolic reprograming mediated by tumor cell-intrinsic type I IFN signaling is required for CD47-SIRPalpha blockade efficacy. *Nat Commun* 2024; **15**:5759.
227. Wang Y, Ni H, Zhou S, He K, Gao Y, Wu W, et al. Tumor-selective blockade of CD47 signaling with a CD47/PD-L1 bispecific antibody for enhanced anti-tumor activity and limited toxicity. *Cancer Immunol Immunother* 2021;**70**:365−76.
228. Chen SH, Dominik PK, Stanfield J, Ding S, Yang W, Kurd N, et al. Dual checkpoint blockade of CD47 and PD-L1 using an affinity-tuned bispecific antibody maximizes antitumor immunity. *J Immunother Cancer* 2021;**9**:e003464.
229. Barkal AA, Weiskopf K, Kao KS, Gordon SR, Rosental B, Yiu YY, et al. Engagement of MHC class I by the inhibitory receptor LILRB1 suppresses macrophages and is a target of cancer immunotherapy. *Nat Immunol* 2018;**19**:76−84.
230. Zhou B, Yang Y, Kang Y, Hou J, Yang Y. Targeting the macrophage immunocheckpoint: a novel insight into solid tumor immunotherapy. *Cell Commun Signal* 2024;**22**:66.
231. Barkal AA, Brewer RE, Markovic M, Kowarsky M, Barkal SA, Zaro BW, et al. CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy. *Nature* 2019;**572**:392−6.
232. Zhang C, Zhang J, Liang F, Guo H, Gao S, Yang F, et al. Innate immune checkpoint Siglec10 in cancers: mining of comprehensive omics data and validation in patient samples. *Front Med* 2022;**16**: 596−609.
233. Cai J, Song L, Zhang F, Wu S, Zhu G, Zhang P, et al. Targeting SRSF10 might inhibit M2 macrophage polarization and potentiate anti-PD-1 therapy in hepatocellular carcinoma. *Cancer Commun* 2024;**44**:1231−60.
234. Molgora M, Colonna M. Turning enemies into allies-reprogramming tumor-associated macrophages for cancer therapy. *Med* 2021;**2**: 666−81.
235. Pittet MJ, Michielin O, Migliorini D. Clinical relevance of tumour-associated macrophages. *Nat Rev Clin Oncol* 2022;**19**:402−21.

236. Bergamaschi A, Tagliabue E, Sorlie T, Naume B, Triulzi T, Orlandi R, et al. Extracellular matrix signature identifies breast cancer subgroups with different clinical outcome. *J Pathol* 2008;**214**: 357−67.
237. Elomaa O, Kangas M, Sahlberg C, Tuukkanen J, Sormunen R, Liakka A, et al. Cloning of a novel bacteria-binding receptor structurally related to scavenger receptors and expressed in a subset of macrophages. *Cell* 1995;**80**:603−9.
238. Masetti M, Carriero R, Portale F, Marelli G, Morina N, Pandini M, et al. Lipid-loaded tumor-associated macrophages sustain tumor growth and invasiveness in prostate cancer. *J Exp Med* 2022;**219**: e20210564.
239. Eisinger S, Sarhan D, Boura VF, Ibarlucea-Benitez I, Tyystjarvi S, Oliynyk G, et al. Targeting a scavenger receptor on tumor-associated macrophages activates tumor cell killing by natural killer cells. *Proc Natl Acad Sci U S A* 2020;**117**:32005−16.
240. Li A-Q, Fang J-H. Anti-angiogenic therapy enhances cancer immunotherapy: mechanism and clinical application. *Interdiscipl Med* 2024;**2**:e20230025.
241. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. *Cell Mol Life Sci* 2020;**77**:1745−70.
242. Larionova I, Cherdyntseva N, Liu T, Patysheva M, Rakina M, Kzhyshkowska J. Interaction of tumor-associated macrophages and cancer chemotherapy. *OncoImmunology* 2019;**8**:1596004.
243. Kloepper J, Riedemann L, Amoozgar Z, Seano G, Susek K, Yu V, et al. Ang-2/VEGF bispecific antibody reprograms macrophages and resident microglia to anti-tumor phenotype and prolongs glioblastoma survival. *Proc Natl Acad Sci U S A* 2016;**113**:4476−81.
244. Wong EC, Lam G, Wong C, Lam RC, Lo KW, Hui EP, et al. Abstract 948: preclinical evaluation of VEGF Ang2 bispecific nanobody BI836880 in patient-derived xenograft models of nasopharyngeal carcinoma. *Cancer Res* 2021;**81**:948.
245. Deng G, Zeng F, Su J, Zhao S, Hu R, Zhu W, et al. BET inhibitor suppresses melanoma progression via the noncanonical NF-$\kappa$B/SPP1 pathway. *Theranostics* 2020;**10**:11428−43.
246. Deng G, Zeng F, He Y, Meng Y, Sun H, Su J, et al. EEF2K silencing inhibits tumour progression through repressing SPP1 and synergises with BET inhibitors in melanoma. *Clin Transl Med* 2022;**12**:e722.
247. Messex JK, Byrd CJ, Thomas MU, Liou GY. Macrophages cytokine Spp1 increases growth of prostate intraepithelial neoplasia to promote prostate tumor progression. *Int J Mol Sci* 2022;**23**:4247.
248. Liu S, Liu Z, Shang A, Xun J, Lv Z, Zhou S, et al. CD44 is a potential immunotherapeutic target and affects macrophage infiltration leading to poor prognosis. *Sci Rep* 2023;**13**:9657.
249. Juric V, Mayes E, Binnewies M, Lee T, Canaday P, Pollack JL, et al. TREM1 activation of myeloid cells promotes antitumor immunity. *Sci Transl Med* 2023;**15**:eadd9990.
250. Klesney-Tait J, Turnbull IR, Colonna M. The TREM receptor family and signal integration. *Nat Immunol* 2006;**7**:1266−73.
251. Colonna M. The biology of TREM receptors. *Nat Rev Immunol* 2023; **23**:580−94.
252. Shen ZT, Sigalov AB. Novel TREM-1 inhibitors attenuate tumor growth and prolong survival in experimental pancreatic cancer. *Mol Pharm* 2017;**14**:4572−82.
253. Benner B, Good L, Quiroga D, Schultz TE, Kassem M, Carson WE, et al. Pexidartinib, a novel small molecule CSF-1R inhibitor in use for tenosynovial giant cell tumor: a systematic review of pre-clinical and clinical development. *Drug Des Dev Ther* 2020;**14**:1693−704.
254. Guo S, Chen X, Guo C, Wang W. Tumour-associated macrophages heterogeneity drives resistance to clinical therapy. *Expet Rev Mol Med* 2022;**24**:e17.
255. Wang Y, Zhao M, Liu S, Guo J, Lu Y, Cheng J, et al. Macrophage-derived extracellular vesicles: diverse mediators of pathology and therapeutics in multiple diseases. *Cell Death Dis* 2020;**11**:924.
256. Torroella-Kouri M, Silvera R, Rodriguez D, Caso R, Shatry A, Opiela S, et al. Identification of a subpopulation of macrophages in mammary tumor-bearing mice that are neither M1 nor M2 and are less differentiated. *Cancer Res* 2009;**69**:4800−9.
257. Scott NA, Andrusaite A, Andersen P, Lawson M, Alcon-Giner C, Leclaire C, et al. Antibiotics induce sustained dysregulation of intestinal T cell immunity by perturbing macrophage homeostasis. *Sci Transl Med* 2018;**10**:eaao4755.
258. Sousa AB, Aguas AP, Barbosa MA, Barbosa JN. Immunomodulatory biomaterial-based wound dressings advance the healing of chronic wounds via regulating macrophage behavior. *Regen Biomater* 2022; **9**:rbac065.
259. Lakkis J, Schroeder A, Su K, Lee MYY, Bashore AC, Reilly MP, et al. A multi-use deep learning method for CITE-seq and single-cell RNA-seq data integration with cell surface protein prediction and imputation. *Nat Mach Intell* 2022;**4**:940−52.
260. Xu W, Wen Y, Liang Y, Xu Q, Wang X, Jin W, et al. A plate-based single-cell ATAC-seq workflow for fast and robust profiling of chromatin accessibility. *Nat Protoc* 2021;**16**:4084−107.