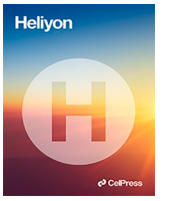
Heliyon 10 (2024) e36839

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Tumor-associated macrophages within the immunological milieu: An emerging focal point for therapeutic intervention

Yanchi Shao [a,1], Song Han [b,1], Zhenxin Hou [a], Chen Yang [a], Yanbin Zhao [a,*]

[a] Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, China
[b] The First Hospital of Jilin University, Changchun, China

ARTICLE INFO

Keywords:
TAMs
Tumor
Targeted therapy
Immunity

ABSTRACT

Tumor-associated macrophages play an important role in the tumor immune microenvironment, and regulating the function of tumor-associated macrophages has important therapeutic potential in tumor therapy. Mature macrophages could migrate to the tumor microenvironment, influencing multiple factors such as tumor cell proliferation, invasion, metastasis, extracellular matrix remodeling, immune suppression, and drug resistance. As a major component of the tumor microenvironment, tumor-associated macrophages crosstalk with other immune cells. Currently, tumor-associated macrophages have garnered considerable attention in tumor therapy, broadening the spectrum of drug selection to some extent, thereby aiding in mitigating the prevailing clinical drug resistance dilemma. This article summarizes the recent advances in tumor-associated macrophages concerning immunology, drug targeting mechanisms for tumor-associated macrophages treatment, new developments, and existing challenges, offering insights for future therapeutic approaches. In addition, this paper summarized the impact of tumor-associated macrophages on current clinical therapies, discussed the advantages and disadvantages of targeted tumor-associated macrophages therapy compared with existing tumor therapies, and predicted and discussed the future role of targeted tumor-associated macrophages therapy and the issues that need to be focused on.

1. Introduction

Macrophages, acknowledged as the most adaptable cells within the hematopoietic system, are widely distributed across tissues, distinguished by their remarkable phenotypic diversity and multifaceted functionality. They play pivotal roles spanning from developmental processes to homeostasis maintenance and tissue repair, serving as essential contributors to both innate and adaptive immune responses [1]. In certain tumors, tumor-associated macrophages (TAMs) predominantly derive from local monocytes and tissue-specific embryonic-derived resident macrophages. TAMs can be classified into two distinct phenotypes: M1 and M2. M1 macrophages are responsible for proinflammatory activities, bactericidal functions, and anti-tumor actions. Conversely, the M2 phenotype is associated with anti-inflammatory responses, tissue regeneration, and regulation of immune balance [1]. M2 macrophages exhibit an immunosuppressive phenotype induced by interleukin 13 (IL13), interleukin 4 (IL4), interleukin 10 (IL10), macrophage colony-stimulating factor (M-CSF), among others. The functional and phenotypic diversity within M2 macrophages can be

* Corresponding author.
E-mail address: zhaoyanbin1978@sina.com (Y. Zhao).
[1] These authors contributed as the co-first authors.

https://doi.org/10.1016/j.heliyon.2024.e36839
Received 3 February 2024; Received in revised form 21 August 2024; Accepted 22 August 2024
Available online 23 August 2024

subdivided into distinct subtypes: M2a, M2b, M2c, and M2d, with surface markers like CD163 and CD206 used for identification purposes. Secretion of factors like vascular endothelial growth factor (VEGF), Arg-1, IL-10, transforming growth factor β (TGF-β), and IDO among others can induce the activation of Th2 cells, promoting tumor immune evasion, aberrant angiogenesis, invasion, and metastasis[2–4]. Nevertheless, under specific conditions, they can undergo mutual transformation. Numerous substances participate in this process, and identifying those that influence it can aid in regulating their polarization, thereby controlling tumor progression. Furthermore, the phagocytic activity of TAMs is governed by specific factors. The considerable adaptability of TAMs underscores their selection as a primary therapeutic target.

TAMs represent a crucial constituent of the tumor microenvironment (TME), being extensively distributed across different tumor types. The immunosuppressive milieu facilitates intricate interactions with TME. TAMs exert their influence on the TME through the release of humoral factors and regulatory molecules. This promotes tumor progression, metastasis, invasion, and immune evasion, while simultaneously suppressing immune responses. In recent years, tumor therapy has transitioned from merely targeting tumor cells to focusing on immune cells, with TAMs garnering considerable attention. Numerous aspects pertaining to cytokines linked to TAMs and the pathways governing tumor growth remain elusive. Over the past decade, researchers have devoted significant efforts to exploring the role of TAMs in antitumor immunity, encompassing their interactions with immune cells, induced polarization in tumor immunity, and the investigation of TAMs' therapeutic mechanisms. This paper provides a summary of recent discoveries concerning TAMs in immunology, alongside an exploration of TAMs as focal points in tumor treatment research. Additionally, it discusses the potential and limitations of targeting TAMs, concluding with an overview of future challenges.

2. Phenotypic changes in TAMs promote tumor development

Under specific conditions, M1 and M2 macrophages have shown the capacity to undergo transformation. Prior research has demonstrated that tumor cell-secreted factors, including sonic hedgehog (SHH), succinate, and bone morphogenetic proteins, can induce the polarization of TAMs toward the M2 phenotype[5–7]. Moreover, local Th1 and Th2 cytokines govern macrophage polarization [8]. In the TME, colony-stimulating factor-1 (CSF-1) and chemokine ligand-2 (CCL2) play pivotal roles in regulating macrophage polarization [9]. Moreover, microRNAs (miRNAs) are pivotal in epigenetically regulating the characteristics of macrophages [10]. Recent investigations have uncovered the involvement of novel substances in this process. For example, in non-small cell lung cancer, increased miR-34a-5p expression inhibits KLF4 expression, thereby facilitating the conversion of macrophages from M2 to M1 phenotypes [11]. Long non-coding RNA LINC00543 exhibits high expression levels in colorectal cancer tissues. Mechanistically, LINC00543 hinders the translocation of pre-miR-506-3p via the transkaryotic transporter XPO5, leading to reduced production of mature miR-506-3p. This process up-regulates CCL2 expression mediated by FOXQ1, consequently fostering M2-type polarization of TAMs [12]. Additionally, it has been discovered that depletion of Cat D (KO) modifies cytokine secretion pathways, consequently reprogramming TAMs from M2 to M1 phenotype. The mechanism underlying this phenomenon revealed that transforming growth factor beta-induced protein (TGFBI) acts as a specific target protein of Cat D, influencing TAMs polarization. Enhanced TGFBI expression in Cat D KO cancer cells resulted in reduced polarization of M2-like TAMs [13]. Vinblastine (VBL), a microtubule-targeting drug, has been demonstrated to induce the conversion of TAMs into an M1 phenotype. This process is facilitated by the upregulation of cytochrome expression and the enhancement of reactive oxygen species (ROS) production [14]. MEM147 induces the polarization of M2-type macrophages through the regulation of cellular cholesterol homeostasis and the increase in 27HC secretion. These findings propose the TMEM147/STAT2/DHCR7/27HC axis within the TME as a potential therapeutic target for hepatocellular carcinoma (HCC) [15]. JMJD6, recognized as a phosphatidylserine receptor (PSR or Ptdsr), is expressed on the macrophage surface, enabling the uptake of apoptotic cells. Deletion of JMJD6 has demonstrated a reduction in LLC tumor and B16F10 melanoma growth by reverting macrophage activation to an M2-like state, potentially through modulation of the STAT3/IL10 signaling pathways [16]. The BCL-2 inhibitor APG-2575 has been discovered to reprogram TAMs to adopt the M1 phenotype [17]. Lactic acid generated by cancer cells has been demonstrated to promote M2 polarization and trigger high mobility group box 1 protein (HMGB1) secretion in macrophages, consequently worsening the carcinogenic behavior of cancer cells [18]. Moreover, arachidonic acid mediates SLC3A2-induced macrophage polarization towards M2-type differentiation in the TME, observed both in vitro and in vivo [19]. A groundbreaking discovery revealed that the long non-coding RNA NR-109 facilitates M2-like macrophage polarization and tumor progression by establishing a positive feedback loop involving NR-109, distal upstream element binding protein 1 (DUBP1), and c-Myc [20]. Many substances are involved in regulating TAMs polarization, and their phenotypes can undergo transformation under specific conditions. Discovering additional substances involved in this process will aid in developing more therapeutic drugs and alleviating the clinical issue of drug resistance.

3. Alterations in TAMs' phagocytic function facilitate tumor development

Macrophages, as essential innate immune cells, are pivotal in upholding body homeostasis, defense, and tissue restoration. Among their crucial functions, macrophages excel in the phagocytosis of extracellular materials, including pathogens, dying or dead cells, as well as tumor cells [21]. Specific signaling pathways have been identified to facilitate tumor growth and metastasis by dampening macrophage-mediated phagocytosis. In the initial phases of tumor invasion, macrophages vigorously engage in the phagocytosis of tumor cells. However, as the tumor progresses, this process is impeded by suppressive signals originating from the tumor. The leukocyte immunoglobulin-like receptor subfamily B (LILRB) comprises inhibitory receptors found on myeloid cells. These receptors engage with ligands resembling major histocompatibility complex class I (MHC-I)-like molecules [22]. As the expression of LILRB1 escalates on the surface of TAMs, cancer cells simultaneously express the MHCI-like component, β2-microglobulin. This interaction

offers direct protection against phagocytosis [23]. Therefore, the inhibition of MHC class I molecules and LILRB1 promotes TAMs phagocytosis. The CD47-SIRPα pathway is the most extensively researched anti-phagocytosis mechanism; its blockade induces and enhances macrophage phagocytosis of tumor cells. Integrin-associated proteins (IAP or CD47) serve as receptors for various members of the platelet reactivity protein family, overseeing a range of cellular functions including platelet activation, cell motility, adhesion, white blood cell adhesion, migration, and phagocytosis. CD47, an immunoglobulin widely expressed on the cell surface, is known to inhibit macrophage phagocytosis of tumors, thereby fostering tumor growth and metastasis. Moreover, CD47 plays a role in mediating cell proliferation, migration, apoptosis, and immune homeostasis. Signal-regulatory protein alpha (SIRPα), a transmembrane protein highly expressed, acts as a major ligand for CD47, binding to its extracellular NH2 terminal region. CD47, an immunoglobulin abundantly present on the cell surface, is recognized for its role in inhibiting macrophage phagocytosis of tumors, consequently fostering tumor growth and metastasis. Moreover, CD47 regulates cell proliferation, migration, apoptosis, and immune homeostasis. SIRPα, a prominently expressed transmembrane protein, acts as a primary ligand for CD47, with its extracellular NH2 terminal region forming a bond with CD47. Induction of tyrosine residues on the immunoreceptor tyrosine-based inhibitory motif (ITIM) leads to the release of an inhibitory phagocytosis signal within cells, thereby hindering macrophage-mediated phagocytosis. This protects the body's normal cells from damage caused by immune system activity. This signaling mechanism efficiently inhibits macrophage-mediated phagocytosis, thus safeguarding the body's normal cells from potential damage induced by immune system activation. CD47 is significantly overexpressed in various solid tumors and correlates with poor tumor prognosis [24]. Consequently, inhibiting the CD47-SIRPα pathway is beneficial for enhancing the body's adaptive immune response and boosting macrophage phagocytosis. A recent study revealed that olaparib augments TAMs-mediated phagocytosis of cancer cells, with this enhancement dependent on the "Don't eat me" signal mediated by CD47/SIRPα [25]. BMS-986351, an anti-SIRPα antibody, binds to opsonizing antibodies, thereby enhancing macrophage-mediated tumor phagocytosis. It exhibits broad binding across SIRPα polymorphisms and efficiently disrupts the CD47-SIRPα interaction at the CD47 binding site in a dose-dependent manner. In vitro studies have demonstrated that BMS-986351 augments phagocytic activity against both solid tumor and hematological malignancy cell lines [26]. However, hypoxia-induced zinc-finger E-box binding homeobox 1 (ZEB1) further facilitates immune evasion in squamous cell carcinoma of the cervix (SCC) by reinforcing the CD47-SIRPα axis. The combination of ZEB1-targeted therapy with CD47-SIRPα immune checkpoint immunotherapy could improve the prognosis of squamous cell carcinoma (SCC) patients by alleviating innate immunity suppression [27]. Studies have shown that hybrid nanocarriers (hEL-RS17), derived from extracellular vesicles of M1 macrophages, alter the RS17 peptide. Studies have shown that hybrid nanocarriers (hEL-RS17), derived from extracellular vesicles of M1 macrophages, alter the RS17 peptide. This mechanism triggers increased infiltration of M1-like TAMs into tumor tissue, ultimately resulting in enhanced engulfment of tumor cells [28]. Besides activating SIRP-α, CD47 also hampers phagocytosis via a SIRP-α-independent mechanism. This mechanism is attributed to the cis-interaction between CD47 and SLAMF7, which inhibits the phagocytosis of the pro-phagocytic ligand SLAMF7 on tumor cells. Disruption of the interaction between CD47 and SLAMF7 can be achieved by targeting CD47 or using a first-class agonist, such as the SLAMF7 antibody, instead of targeting SIRP-α. Consequently, this process enhances antitumor immunity. Consequently, CD47 inhibits phagocytosis by binding to SIRPα and masking endogenous phagocytic ligands on tumor cells [29]. Furthermore, NLRP3, functioning as a "macrophage phagocytosis checkpoint" for androgen receptor regulatory genes, is upregulated in TAMs after androgen deprivation therapy (ADT) and activated by NLRP3a treatment. This activation results in TAM-mediated phagocytosis and subsequent tumor control [30]. Studies have shown that the co-dependent metabolism of cholesterol (CHO) and probucol in tumors leads to monocyte-derived TAMs phagocytosis dysfunction, thus promoting disease progression. To solve this problem, Apolipoprotein A1(ApoA1), the reverse transporter of CHO-Probucol, can be used to regulate the outflow of CHO-Probucol and restore the phagocytic function of TAMs [31]. Recent studies have demonstrated that inhibiting lactic acid production in tumor cells via a specific signaling pathway effectively eliminates aggressive prostate cancer with PTEN/p53 deletion in mice, primarily through macrophage phagocytosis [32]. Discovering new substances and pathways that affect TAMs phagocytosis is essential for developing drugs targeting this process. This approach holds promise for addressing drug resistance in clinical practice and enhancing the survival rates of tumor patients.

4. TAMs are involved in mediating immunosuppression

4.1. TAMs and cytokines

Tumor-secreted cytokines bind to surface receptors on TAMs, regulating the expression of immunosuppressive genes and inducing the secretion of various pro-cancer factors. Concurrently, they inhibit the secretion of antitumor factors, thereby influencing the immune responses of cells within TME and facilitating tumor immune evasion. Numerous studies have validated the involvement of these TAM-related cytokines in tumor development.

4.1.1. IL-1、IL-8、L-10

Interleukin 1 (IL-1) is an immunosuppressive cytokine that exists in two types: interleukin-1α (IL-1α) and interleukin-1β (IL-1β). It is primarily secreted within the TME by both tumor cells and immunomodulatory cells through autocrine or paracrine signaling pathways [33]. Mechanistically, upon binding of IL-1α or IL-1β to IL-1R, the signaling adaptor protein myeloid differentiation factor 88 (MyD88) is recruited, initiating sustained activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) via the MyD88-IRAK signaling cascade. Furthermore, IL-1β stimulates CCL2 expression in both TAMs and tumor cells, resulting in the recruitment of myeloid-derived suppressor cells (MDSCs) and additional TAMs into the TME [34]. Hence, additional research is warranted to elucidate the mechanism through which IL-1 promotes immunosuppression via TAMs. Current experiments have shown

that knockdown of interferon induction of nucleoprotein 16 (IFI16) suppresses the malignant phenotype of esophageal squamous cells and reduces IL-1α secretion in these cells. Furthermore, recombinant IL-1α exacerbates the malignant phenotype of esophageal squamous cell carcinoma (ESCC) cells via the Erk and NF-κB signaling pathways [35]. Presently, in lung cancer, the IL-1β-mediated phosphorylation of PAK1 decreases in the absence of Ton EBP. Additionally, Ton EBP is crucial for IL-1β-induced invasion of A549 cells through the PAK1 pathway [36]. IL-8 functions as a proinflammatory chemokine. Typically, environmental stressors such as chemotherapy or hypoxia can upregulate IL-8 and its receptor expression in TAMs. Furthermore, the stimulation of NF-κB by TNF-α and IL-1α has the potential to trigger the secretion of IL-8 by tumor cells. After binding with IL-8, G protein-coupled receptors undergo conformational alterations, which then initiate coupling with heterotrimer G proteins to activate either phosphatidylinositol 3-kinase (PI3K) or phospholipase C. Subsequently, this activation triggers the threonine kinase (AKT), protein kinase C (PKC), and MAPK signaling cascades, ultimately resulting in the upregulation of various oncogene transcription factors, including signal transducer and activator of transcription 3 (STAT3) phosphorylation [37]. IL-8 production has been confirmed in osteosarcoma, where TAMs within TME contribute to the proliferation and metastasis of osteosarcoma via the FAK pathway [38]. IL-10, classified as an anti-inflammatory cytokine, exhibits dual roles depending on the specific tissue environment: it can either enhance an antitumor immune response or promote tumor immune evasion [39]. Increasingly, experiments are demonstrating that IL-10 directs TAMs towards an immunosuppressive M2 phenotype, leading to increased IL-10 secretion. The IL-10 receptor (IL-10R) consists of two distinct receptor chains: IL-10R1 and IL-10R2. When IL-10 binds to IL-10R1, IL-10R2 serves as an auxiliary subunit, initiating the activation of JAK1 and tyrosine kinase 2 (Tyk2). This leads to the phosphorylation of STAT3 and signal transducer and activator of transcription 1 (STAT1), subsequently promoting the production of BCL3. BCL3 critically modulates the dose-dependent effect of IL-10 on the expression of M1-related genes. Recent research confirms that the JMJD6/STAT3/IL-10 axis serves as the critical switch for TAMs activation [16].

4.1.2. M − CSF、TGF − β、Exosomes

Upon binding to its receptor, M-CSF initiates downstream pathways, including PKC, PI3K, and SFK, which facilitate macrophage migration to the tumor region and induce a shift towards the M2 phenotype. Additionally, as previously mentioned, it regulates VEGF secretion by macrophages, thereby promoting tumor angiogenesis [34]. Recent studies indicate that gastric cancer cells' secretion of M-CSF accelerates gastric cancer progression by upregulating protein tyrosine phosphatase 2 (SHP2) expression in TAMs [40]. Additionally, research indicates that cannabinol therapy decreases CSF-1 secretion in melanoma, reprograms regulatory medullary cells, and inhibits tumor progression [41]. Targeting M-CSF represents a promising direction for tumor therapy. TGF-β is produced via

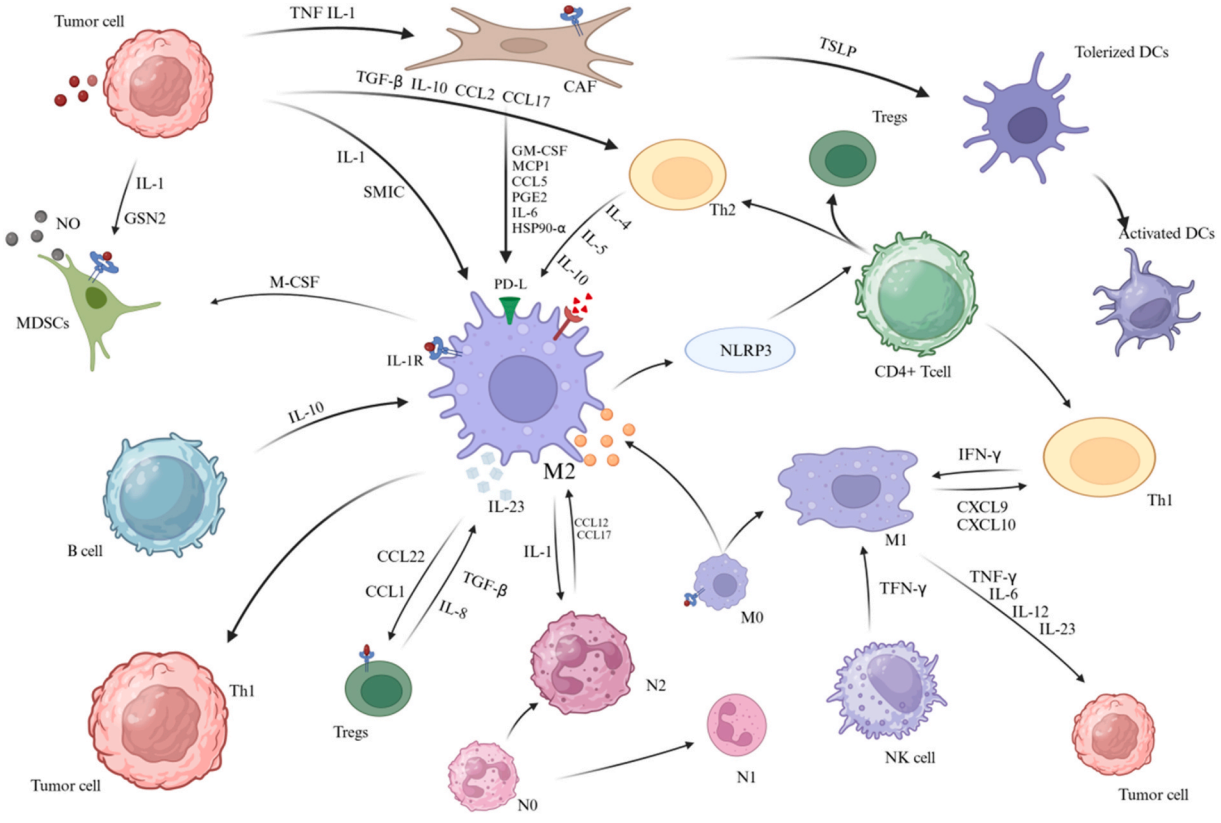


Fig. 1. The interplay between TAMs and immune cells within the TME involves intricate crosstalk, which significantly influences the tumor's immune landscape and therapeutic outcomes.

autocrine or paracrine mechanisms by leukocyte lineages including lymphocytes and macrophages, regulating their differentiation, proliferation, and activation. The tumor glycochain structure antigen sialyl-Tn preferentially binds to Siglec-15 expressed on TAMs, thereby enhancing the secretion of TGF-β. Siglec-15 exhibits high expression in M2-type macrophages, and TGF-β can induce macrophage polarization towards the M2-type, thereby enhancing TGF-β secretion and establishing a positive feedback loop. Studies have demonstrated that cathepsin D facilitates the polarization and metastasis of TAMs via the TGFBI-CCL20 signaling pathway. Moreover, disruption of TGFBI has shown to inhibit the polarization of macrophages to the M2 phenotype and to suppress macrophage-mediated stimulation of pancreatic cancer (PaC) growth. This interference has also significantly enhanced antitumor immunity and the sensitivity of PaC to chemotherapy. These effects are linked to the regulation of fibronectin 1, Cxcl10, and Ccl5 [42]. Therefore, the importance of TGF-β in TAM-mediated immune evasion cannot be overstated. Exosomes are extracellular vesicles that encapsulate proteins, nucleic acids, and cytokines. They are regarded as the third mechanism for cellular information exchange and play a crucial role in mediating interactions between tumor cells and macrophages. Certain studies have indicated that exosomes derived from TAMs, particularly those containing LINC01592, induce immune evasion in esophageal cancer by downregulating MHC-I surface expression [43]. Besides facilitating interactions between tumor cells and macrophages, exosomes are also involved in communication among macrophages, T cells, dendritic cells (DCs), and various other cell types. The expression of the NADPH oxidase 1 (NOX1) gene leads to ROS generation, promoting the migration and invasion of cervical cancer cells. Exosomal NOX1 additionally advances cancer progression by inducing TAMs M2 polarization in cervical cancer through ROS stimulation [44]. Therefore, delving deeper into the mechanisms and patterns of exosomal involvement in interactions among tumor cells and various other cell types is vital for fully comprehending their indispensable role in tumor initiation and progression. This endeavor will also provide theoretical insights for exosome-based tumor therapy.

4.2. Crosstalk between TAMs and other immune cells

TAMs act as pivotal components of immunosuppressive cellular and cytokine networks, significantly contributing to tumor immune evasion. Hence, understanding the interactions between macrophages and other immune cells is imperative, as it holds promise for enhancing current anticancer therapies (Fig. 1).

4.2.1. TAMs、MDSCs、DCs、TANs

MDSCs are bone marrow-derived precursor cells capable of differentiating into DCs, macrophages, and granulocytes. They are recruited to tumor sites via chemokines like CCL2 and CCL5, where they exert immunosuppressive functions [45]. IL-1 can recruit MDSCs via the IL-1R-MYD88-Tet2 pathway, which promotes the immunosuppressive polarization of TAMs in melanoma. This process facilitates immune evasion within the tumor microenvironment [33]. Neutrophils are categorized into two subgroups: N1 and N2. N1 neutrophils demonstrate antitumor activity, either directly through antibody-dependent cytotoxicity or indirectly via the production of proinflammatory cytokines and the activation of T cells [46]. Tumor-associated neutrophils (TANs), predominantly of the N2 phenotype, are thought to promote tumor progression. However, the precise interaction mechanism between TANs and TAMs during tumorigenesis and immune evasion remains elusive. Immunohistochemical observations from a murine model co-injected with HCC cells and TANs indicate that TANs enhance the intratumoral accumulation of TAMs and regulatory T cells (Tregs), which are recruited via the CCL12/CCR2 and CCL17/CCR4 signaling pathways [47]. Nevertheless, recent experiments have demonstrated that depleting neutrophils does not impact tumor formation. Hence, further experimental investigations are warranted to delve deeper into the interplay between TAMs and TANs. Recent studies have suggested that in breast cancer, autoimmune regulatory factor (AIRE) is predominantly localized within TANs, with limited expression observed in TAMs and tumor cells. The expression of AIRE in both TANs and TAMs correlates with an unfavorable prognosis. AIRE in neutrophils and macrophages functions in modulating the expression of immune mediators and regulating exogenous apoptotic pathways via Fas/TNFR death receptors and cathepsin G [48].

4.2.2. TAMs and T cells

Mature $CD4^+$ T cells can be activated in diverse cytokine environments and then differentiate into distinct helper T cells subsets, such as Th1, Th2, Th17, and Treg cells, which are critical in adaptive immunity [49]. Conversely, macrophages transition towards the M1 phenotype upon exposure to interferon-gamma, which is secreted by Th1 cells, natural killer cells, and cytotoxic T lymphocytes (CTLs) [50]. Polarized M1 macrophages release numerous proinflammatory cytokines and generate electron paramagnetic resonance to induce tumor cells death. Furthermore, M1 macrophages have the capability to recruit Th1 cells by secreting chemokines such as CXCL9 and CXCL10. This recruitment causes Th1 cells to cluster, establishing a positive feedback loop that boosts the type I immune response [51]. Interactions among macrophages and other immune cells, such as Th2 cells and regulatory T cells, hold the potential to augment the type II immune response, thus contributing to the acquisition of a malignant tumor phenotype [52]. Treg cells suppress interferon-γ secretion by $CD8^+$ T cells and induce the differentiation of M2 macrophages [53]. Macrophages can impact Th1/Th2 cell differentiation as well. TAMs within pancreatic tumor tissue not only hinder CTLs activation and Th1 cells polarization but also prompt $CD4^+$ T cells differentiation towards Th2 cells or Treg cells [54]. Furthermore, tumor-activated HIF1α induces TAMs to release IL-23, which boosts Treg proliferation, elevates IL-10 and TGF-β expression, and dampens lymphocyte cytotoxicity against tumor cells [55]. In ovarian cancer, macrophages secrete CCL22, recruiting Tregs to migrate towards the tumor site. This recruitment results in the suppression of T cell-mediated immunity, thus facilitating tumor progression [56]. Recent experiments have revealed that TAMs exhibit selective expression of MS4A4A across various tumor types. Blockade therapy targeting MS4A4A has demonstrated the ability to remodel the tumor immune microenvironment. This therapy reduces M2-type TAMs infiltration and depletes T cells while simultaneously enhancing the infiltration of effector $CD8^+$ T cells [57]. Furthermore, recent experiments have demonstrated that tumor cells

induce Irg1 expression in macrophages through activation of the NF-κB pathway. Additionally, itaconate (ITA) produced by aconitate decarboxylase 1 (ACOD1) inhibits TET DNA dioxygenase, thereby impeding the repression of inflammatory genes and hindering the infiltration of $CD8^+$ T cells into the tumor microenvironment [58].

4.2.3. TAMs and CAFs

Cancer-associated fibroblasts (CAFs) constitute the primary stromal cell population within the TME. They can release various cytokines and participate in the synthesis and remodeling of the extracellular matrix, thereby establishing a tumor-promoting fibrous microenvironment. Research has demonstrated that tumor cells secrete TNF-α and IL-1β, prompting CAFs to generate thymic stromal lymphopoietin (TSLP). Subsequently, TSLP activates resident DCs, inducing the release of Th2 chemokines like CCL2 and CCL17, which attract Th2 cells to the tumor site. Subsequently, Th2 cells secrete Th2 cytokines, promoting M2 polarization [59]. CAFs also secrete interleukin-6 (IL-6), M-CSF, monocyte chemoattractant protein-1 (MCP-1), and stromal cell-derived factor-1 (SDF-1) to facilitate the recruitment and differentiation of macrophages [60]. M2 macrophages secrete TGF-β, promoting the transition of endothelial cells to a mesenchymal phenotype. This process enhances the activation of CAFs, consequently promoting the aggressiveness of cancer cells [61]. For instance, utilizing TGF-β-based immunomodulator vaccines to target TAMs and CAFs has emerged as an innovative approach to alleviate immunosuppression and immune evasion in pancreatic tumors. This strategy shows promise for treating pancreatic cancer [62]. Moreover, recent experiments have demonstrated that DIF-1 exerts anticancer effects in breast cancer by disrupting communication between tumor-associated fibroblasts and cancer cells via the CXCLs/CXCR2 axis [63]. This discovery enhances our comprehension of the interplay between TAMs and CAFs. Additionally, macrophages can form a physical barrier by clustering CAFs within the TME. They deposit fibro-collagen, hyaluronic acid, fibronectin, and other molecules while producing lysyl oxidase to induce crosslinking of type I collagen, thus establishing a physical obstruction. Furthermore, TAMs can express FAS-L and secrete active soluble FAS-L, inducing apoptosis of Fas^+ lymphocytes. Additionally, CAFs can upregulate the expression of FAS-L and programmed cell death ligand 2 (PD-L2), thereby suppressing $CD8^+$ T cells activity through MHC-I antigen cross-presentation [64].

5. Targeting TAMs may represent a novel approach for cancer treatment

Presently, the rise of drug resistance to conventional cancer therapies underscores the pressing clinical need for innovative treatments. There is significant interest in pharmaceutical agents targeting TAMs, and the subsequent sections outline and synthesize the various types and mechanisms of such drugs.

5.1. Limit recruitment of TAMs

Targeting TAMs may include restricting their recruitment to tumor sites. Tumor cells release CCL2, attracting monocytes expressing CCR2 from the bloodstream into the TME. These monocytes then differentiate into TAMs, facilitating tumor progression [65]. Thus, targeting the CCL2/CCR2 interaction holds promise as a therapeutic approach for combating tumors. Research has shown that disrupting the interaction between CCL2 and CCR2 results in a notable decrease in the recruitment and activation of M2-type TAMs, consequently leading to a significant reduction in tumor incidence.

Furthermore, targeting the CSF1/CSF1R signaling pathway represents a critical and effective strategy for treating malignancies [66]. CSF-1 is widely acknowledged as a tumor stimulator that contributes to recruiting macrophages to tumor sites and inducing the polarization of TAMs. Recent studies indicate that cannabinol therapy decreases CSF-1 secretion in melanoma, reshapes regulatory medullary cells, and mitigates tumor progression [67]. Furthermore, research has indicated that the CSF-1R inhibitor ponatinib has the potential to influence FLT3-dependent dendritic cell differentiation. This effect may counteract the effects of nivolumab in patients with advanced tumors [68].

5.2. TAMs are prevented from surviving

Synthetic and chemical compounds capable of inducing apoptosis have the potential to reduce TAMs survival [69]. In an in vivo study, Roth et al. employed ribonucleic acid (RNA) aptamers to target and eliminate TAMs via the ILR α/IL-4 receptor α (IL4Rα) pathway in Balb/C4T1 mice. This therapeutic strategy, in hormonally influenced mice, impedes tumor growth by targeting the ILR α - STAT6 signaling pathway, boosting T cells counts, and eradicating TAMs [70]. Additionally, M2pp, a unique peptide with a proapoptotic structure, selectively targets and eliminates TAMs, thereby enhancing survival in hormonally influenced mice. This study illustrates that the peptide predominantly binds to TAMs in live mice. Administering apoptosis-inducing peptides that specifically target TAMs, even without anticancer drugs, effectively delayed mortality and selectively reduced M2-like TAMs [71]. Trabectedin, an alternative anticancer agent, induces apoptosis by activating the caspase-8 pathway through the TNF-related apoptosis-inducing ligand (TRAIL) receptor. This demonstrates its effectiveness in reducing TAMs. However, the lack of specificity of this drug not only affects TAMs but also compromises the host's immune defenses by causing damage to macrophages [72].

Moreover, in vivo experiments have shown that TAMs can engulf disodium clodronate liposomes (Clo-LipoDOTAP), releasing clodronate disodium. This compound metabolizes into nonhydrolyzable ATP analogs, disrupting the mitochondrial respiratory chain and inducing cytotoxicity against M2-type TAMs. Treatment of solid tumors in mice with Clo-LipoDOTAP resulted in the eradication of M2-type TAMs from tumor tissue and substantially improved the survival of the mice [73,74]. Targeting TAMs' viability represents a potential strategy in tumor therapy; however, it is crucial to assess whether these agents might also adversely affect other healthy cells in the body.

5.3. Limiting the polarization of TAMs

M1-type TAMs suppress tumor progression, whereas M2-type TAMs promote it. Currently, there is considerable emphasis on inhibiting TAMs polarization. Drug development aimed at targeting TAMs polarization can partially hinder tumor advancement. For instance, imatinib inhibits STAT6 phosphorylation and nuclear translocation, resulting in a notable reduction in IL-13- and IL-4-induced M2-like polarization in vitro. Imatinib treatment also reduced the expression of the M2 marker antigen cluster 206 (CD206) and M2-like gene expression. In vivo experiments confirmed a decrease in M2-like macrophages in both tumor and lung tissues [75]. CD163 is recognized as one of the molecules responsible for regulating M2 polarity. Corosolinic acid reduces CD163 expression in TAMs, thereby promoting their transition to an M1-like phenotype [76]. NF-κB, STAT3, and STAT6 play pivotal roles in regulating the differentiation of TAMs towards the M2 phenotype [77].

Moreover, addressing the metabolic processes of tumors can be pivotal. The metabolic processes of long-chain fatty acids, particularly unsaturated ones, play a significant role in shaping the immunosuppressive characteristics of TAMs. These fatty acids drive the polarization of bone marrow-derived stem cells (BMDMs) towards a more suppressive M2 phenotype [78]. As a result, chemical inhibitors have demonstrated efficacy in impeding TAMs polarization in laboratory settings and suppressing tumor growth in animal models.

5.4. Reprogramming of M2 TAMs

5.4.1. Stimulation of TLRs

Toll-like receptors (TLRs), classified as innate immune receptors for pattern recognition, can be triggered by lipopolysaccharides present in viral nucleic acids and bacterial components [79,80]. Within the TME, TLRs activation effectively induces TAMs to adopt a phenotype reminiscent of M1 polarization [81,82]. Nanoparticles loaded with TLRs agonists assist in achieving more effective reprogramming of TAMs. For example, nanoparticles containing R848, a TLR7/TLR8 agonist, promote TAMs accumulation and transition them from an M2-type to an M1-type phenotype [83]. In an alternative study aimed at overcoming resistance to tumor immunotherapy, nanogels containing TLRs agonists and extended-chain peptide antigens were utilized. This combination stimulated TAMs in antigen presentation, transitioning immunosuppressive M2-type TAMs toward an immunosensitive M1-type phenotype [84].

5.4.2. Suppression of phosphatidylinositol 3-kinase expression

Molecular switches impede both "immunosuppressive and immunostimulatory programs" by inhibiting PI3K [85,86]. In the absence of PI3K activity in TAMs, there is heightened expression of major histocompatibility complex class II (MHC-II) and inflammatory mediators, alongside reduced levels of IL-10 and arginase. These changes contribute to a shift away from immunosuppressive functions [87]. Consequently, PI3K inhibition can modulate the shift from immunosuppression to immune activation in M2 TAMs, thereby augmenting the efficacy of combination immunotherapy with other checkpoint inhibitors [88].

5.4.3. Transitioning TAMs from M2 phenotype to M1 phenotype

Various siRNAs have been employed to redirect TAMs, inducing their transition into an M1-like TAMs phenotype [89]. Additionally, numerous lncRNAs, circRNAs, and miRNAs, including miR-1155, miR-23b-3p, and lncRNA-0243, have been utilized to reprogram M2-like TAMs. These TAMs, recognized for their anti-inflammatory and tumor-promoting properties, convert into anti-tumor M1-like TAMs [90]. Theoretical propositions indicate that the autophagy inhibitor hydroxychloroquine (HCQ) might increase the pH level of lysosomes in tumor cells, thereby facilitating drug transport from the lysosome to the nucleus. TAMs subjected to HCQ treatment demonstrated heightened expression of common molecules (Ifng, IL12b, IL1b, and IL6) typically secreted by M1-like macrophages, along with reduced expression of M2-like molecules (Tgfb1, IL10, and Ido1). Furthermore, HCQ-treated TAMs facilitated the infiltration of $CD3^+$ and $CD8^+$ T cells, suggesting that the bolstered $CD8^+$ T cell immunity stemmed from the repolarization of M2-like TAMs into an M1-like phenotype induced by HCQ [91]. Moreover, liposomal nanoparticles delivering guanosine monophosphate-adenosine monophosphate (GAMP) demonstrated the capacity to inhibit triple-negative breast cancer (TNBC) proliferation by reprogramming, transitioning M2-like macrophages into the M1 phenotype [92].

5.4.4. Metabolic reprogramming of TAMs

Rapamycin, a selective mTOR inhibitor, holds promise in converting M2-type TAMs into M1-type TAMs by suppressing mitochondrial ROS and promoting the generation of NLRP3 inflammatory vesicles. This implies that targeting upstream glucose metabolism molecules could enhance the antitumor effects of TAMs [93,94]. Activation of caspase-1 induces TAMs to accumulate lipids and acquire a tumorigenic phenotype. Compounds that target caspase-1, including nitroaspirin (NCX-4016), YVAD, and VAD, have shown efficacy in reversing TAMs to an anti-tumorigenic phenotype, thus hindering tumor growth in vivo [95]. Tumor cells employ ATP-binding transporters, particularly ABC transporters, to promote cholesterol efflux from the membrane of M2-TAMs. This process aids in IFN-γ-mediated gene suppression in M2-TAMs and triggers the activation of M1-TAMs. Genetic deletion or specific inhibition of ABC transporter proteins has been observed to impede membrane sterol efflux in M2-like TAMs across various mouse models, including bladder, melanoma, and ovarian cancer. This intervention has demonstrated efficacy in facilitating their transition from a pro-tumor to an antitumor phenotype [96]. Macrophages expressing C1q in malignant pleural effusion contribute to immunosuppression through fatty acid metabolic reprogramming facilitated by fatty acid binding protein 5 (FABP5). Inhibiting FABP5 markedly alleviates the immunosuppressive tumor microenvironment and enhances the efficacy of immune checkpoint-blocking therapy [97].

6. Future challenges for targeted drugs against TAMs

Presently, several drugs targeting TAMs are undergoing clinical trials. The following table summarizes the latest clinical trials focusing on TAMs (Table 1). However, TAMs accumulation in the TME is often inadequate, leading to off-target effects or adverse reactions, and the therapeutic outcomes remain limited [98]. Some challenges must be addressed before TAM-targeting drugs can be extensively employed in clinical settings. Firstly, CSF-1R antagonists manage tumor development by impeding TAMs recruitment. Nonetheless, several studies have documented relapse or deterioration in certain patients following cessation of CCL2 inhibition therapy. Hence, this aspect necessitates consideration when devising clinical treatment strategies for patients. Secondly, therapies targeting TAMs not only reduce the number of macrophages but also lead to decreased counts of $CD4^+$ T cells and an increase in $CD8^+$ T cells populations in tumor patients [99]. Further research is needed in the future to address this issue if the balance of T cells subpopulations is to be maintained while targeting TAMs. Moreover, the rapid advancements in spatial transcription sequencing and single-cell sequencing are significantly enhancing our understanding of TAMs heterogeneity and function. Nevertheless, current studies suggest that future research should continue to prioritize the exploration of the complex regulatory mechanisms of TAMs and strategies for reprogramming macrophages, rather than simply selecting between BMDMs or medulla cell lines. Given the heterogeneity of cell types in the TME, current studies on their interactions need to be comprehensive [100].

Nano immunotherapy has garnered significant attention in this field in recent years. Nano immunotherapy, a drug formulation based on nanomaterials, holds significant promise in cancer treatment due to its ability to selectively target TAMs, thus increasing precision and minimizing side effects. TAMs demonstrate mobility and exhibit specific distribution patterns, allowing them to effectively transport drugs to precise sites within the tumor microenvironment. This ability boosts local drug accumulation and facilitates enhanced drug penetration [101]. Furthermore, the secretory capacity of TAMs enhances the efficacy of drugs. Nanoparticles facilitate precise drug delivery to TAMs and modulation of their polarization state. For example, microparticles derived from tumor cells loaded with the chemotherapeutic drug methotrexate (TMP-MTX), nanoparticles delivering viologen, siRNA targeting programmed cell death ligand 1 (PD-L1) for knockdown (SK/siR-NPs), and Gado fullerene (GF-Ala) nanoparticles have demonstrated the ability to reprogram M2-type TAMs into an M1-like phenotype. This reprogramming results in increased cytotoxic T lymphocyte (CTL) infiltration and effectively inhibits tumor growth[102–104]. Nevertheless, it possesses certain limitations. Firstly, macrophages share several receptors with other immune cells, which to some extent hinders the recognition of target cells by nanomaterials. Secondly, the absence of a precise delivery mechanism might result in the uptake of nanomaterials by cells in unintended locations within the body. Thirdly, regulating the rate of drug release presents a challenge, potentially impacting the drug's effectiveness. Addressing this challenge, researchers are striving to create a drug release mechanism that is highly responsive to temperature and pH variations. However, its widespread applicability necessitates further investigation [105]. Safety trials of material and drug combinations are currently in the laboratory stage and require significant advancement before transitioning to the clinical stage.

Moreover, the emergence of cellular immunotherapy, notably Chimeric antigen receptor M (CAR-M), offers a new and promising

Table 1
Clinical trial of cancer treatment against TAMs. (This record was obtained from the Clinical Trials website:http://clinicaltrials.gov).

Cancer	Clinical trial	Clinical phases	Interventions
Advanced Nonsmall Cell Lung Cancer	NCT01551251	/	/
Colorectal Liver Metastases	NCT03888638	/	Procedure: Hepatectomy
Metastatic Breast Cancer With Active Brain Metastasis	NCT01770353	I	Drug: Ferumoxytol,MM-398
Wilms Tumor and Other Childhood Kidney Tumors	NCT01493817	/	Other: laboratory biomarker analysis
Colorectal Cancer	NCT00262808	II	Biological: sargramostim, fluorouracil,leucovorin calcium, oxaliplatin|Procedure: adjuvant therapy, conventional surgery, neoadjuvant therapy
Stage I/II/III Prostate Adenocarcinoma	NCT02472275	I	Drug: Antiandrogen Therapy, Multitargeted Tyrosine Kinase Inhibitor PLX3397| Other: Laboratory Biomarker Analysis|Radiation: Radiation Therapy
Ovarian Cancer	NCT01309230	II	Biological: Vigil™
Advanced Malignancy|Advanced Solid Tumors	NCT01444404	I	Drug: AMG 820
Thyroid Cancer	NCT03397238	/	/
Colorectal Cancer|Pancreatic Cancer	NCT03184870	I-II	Drug: BMS-813160|Biological: Nivolumab|Drug: Nab-paclitaxel,Gemcitabine,5-fluorouracil (5-FU), Leucovorin, Irinotecan
Head and Neck Squamous Carcinoma	NCT04361409	I	Drug: Rituximab, Cisplatin, Gemcitabine
Advanced Triple Negative Breast Cancer (TNBC) With High Tams	NCT02435680	II	Drug: MCS110,carboplatin, gemcitabine
Metastatic Cancer	NCT01316822	I	Drug: ARRY-382, cFMS inhibitor; oral
Bone Cancer	NCT01336803	II	Drug: Feraheme|Procedure: Magnetic Resonance Imaging (MRI) scan
Advanced Solid Tumors	NCT01494688	I	Drug: Paclitaxel,RO5509554
Solid Cancers	NCT02323191	I	Drug: Atezolizumab, Emactuzumab
Neoplasms	NCT02760797	I	Drug: Emactuzumab,RO7009789
Pancreatic Cancer	NCT03415854	II	Drug: Paricalcitol (Zemplar)
Glioblastoma	NCT02887417	/	/
Malignant Mesothelioma	NCT02300883	/	/
Clear Cell Renal Cell Carcinoma	NCT03680521	II	Drug: Sitravatinib, Nivolumab

avenue for cancer treatment. CAR-M technology stands out as an innovative therapeutic strategy capable of converting M2 macrophages into the M1 phenotype. This reprogramming not only enhances phagocytic activity but also enables the specific targeting of cancer cells. Genetic manipulation can convert M2 macrophages into the anti-inflammatory M1 phenotype, resulting in the secretion of various proinflammatory cytokines and beneficial alterations within the tumor microenvironment. Furthermore, CAR-M stimulate dendritic cell activation, recruit T cells, and enhance the presentation of new antigens by T cells, thereby promoting sustained adaptive immune responses [25].

Prior to clinical implementation, several considerations must be addressed. Firstly, the effectiveness of gene reprogramming plays a pivotal role in determining the therapeutic potential of CAR-Ms. Hence, nano biomaterials may be necessary to ensure efficient target cells transfection. For example, viral vector-mediated infection of macrophages in vitro is notably less efficient than T cells infection, necessitating larger virus doses to achieve the desired therapeutic effect, thereby substantially increasing treatment costs. Secondly, studies indicate that following in vivo administration of the CAR-M program throughout the body, a significant portion of foreign carriers will accumulate in the liver, hindering their ability to reach tumor lesions and thereby impacting therapeutic efficacy. Moreover, the safety of CAR cells immunotherapy in vivo depends on the specificity of solid tumor-specific targets. Similar to CAR-T therapy, insufficient specificity of the selected target could lead to severe toxic side effects. Moreover, tumor cells exhibiting low expression of the target antigen might evade CAR-M treatment, potentially leading to tumor recurrence. Hence, addressing the challenge of designing vehicles that precisely target specific cells is paramount for future advancements. Furthermore, the complex microenvironment of solid tumors could potentially compromise the therapeutic efficacy of CAR-M. Despite the superior tumor invasion ability of macrophages compared to T cells, achieving therapeutic efficacy remains a challenge. While certain clinical trials have shown promising results, it is imperative to tackle the intricacies of the human tumor microenvironment to enhance CAR-M infiltration and therapeutic efficacy. Crucially, future advancements in CAR-M technology should diverge from the conventional CAR-T approach. Research into innovative CAR molecules for activating macrophage function should be prioritized, considering that the CAR structure was initially devised to enhance T cells activity. Since macrophages fulfill diverse roles in maintaining homeostasis, future CAR-M applications may extend beyond simple cell or reprogramming factor infusions. These distinctive characteristics offer a fresh perspective for advancing the next generation of CAR-M technology [106]. Furthermore, CAR-M therapy could be integrated with other treatment modalities.

7. Therapeutic approaches directed at TAMs can be integrated with various other treatment modalities

Currently, there has been notable progress in single targeted therapy for TAMs, and several experiments have demonstrated that TAMs also exert a distinct influence on other tumor treatments. These findings support the future advancement of targeted therapy for TAMs in conjunction with conventional treatments like chemotherapy and radiotherapy to address the clinical challenge of drug resistance.

7.1. TAMs and immune checkpoint inhibitors

Immune checkpoint inhibitors have emerged as a significant advancement in cancer treatment, offering some enhancements in patient survival rates. Nevertheless, the emergence of drug resistance poses an inevitable challenge that requires effective addressing. Within the TME, the interaction between PD-L1 on tumor cells and PD-1 on T cells leads to T cells dysfunction, thereby facilitating immune evasion. Monoclonal antibodies (mAbs) engineered to target the PD-1/PD-L1 pathway have shown significant antitumor effects in various solid tumors [1]. Resistance to PD-1/PD-L1 blockade primarily arises from factors such as dysfunctional and inadequately activated T cells, T cells depletion, and alterations in PD-L1 expression. T cells infiltration is crucial for antitumor immunity, whereas immunosuppressive cells assist tumors in evading immune responses. TAMs, acting as immunosuppressive cells, contribute to resistance to PD-1/PD-L1 therapy. TAMs exhibit immunosuppressive traits through the secretion of cytokines and metabolites[107–109]. Elevated PD-L1 expression in both tumor and immunosuppressive cells hinders T-cell function and leads to depletion. During anti-PD-1/PD-L1 immunotherapy, M2-type TAMs suppress T-cell activity and increase PD-L1 expression in the TME, thereby compromising the therapeutic efficacy of immunotherapy[110–112]. M2-type TAMs release anti-inflammatory cytokines such as TGF-β and prostaglandin E2 (PGE2), along with exosomes containing miRNAs. As a result, these cytokines upregulate the expression of immune checkpoint ligands such as VISTA, thereby impairing the efficacy of PD-1/PD-L1 blockers [113]. Targeting TPAMS dependent PD-1/PD-L1 is a viable strategy to improve the efficacy of PD-1/PD-L1 inhibitors. For example, research has indicated that cellular particles containing tumor antigens and receptors can reprogram tumor-associated macrophages and facilitate the development of stem-like $CD8^+$ T cells. This process enhances the effectiveness of anti-PD-1 therapy [114]. Furthermore, studies conducted in liver cancer have provided experimental evidence suggesting that the absence of CacyBP (calcium cyclin-binding protein) diminishes TAM infiltration and alleviates the immunosuppressive conditions within the tumor microenvironment. Consequently, this enhances the responsiveness of liver cancer to anti-PD-1 therapy [115]. Recent studies have demonstrated that blocking tumor-associated macrophages through the C-type lectin receptor Dectin-1 can enhance the efficacy of anti-PD-1 therapy in gastric cancer [116]. The combination of TAMs targeted therapy with immune checkpoint therapy can significantly improve the efficiency of immunotherapy, thus creating new opportunities for tumor treatment.

7.2. TAMs and radiotherapy

Radiotherapy is a frequently utilized local tumor treatment, and its effect on TAMs primarily hinges on the radiation dose and

modality employed. Exposure to low-dose irradiation (LDI, less than 2 Gy) usually prompts TAMs to polarize towards the M2 phenotype [117,118]. Moderate doses of irradiation (2–8 Gy) typically result in TAM polarization towards the M1 phenotype [119]. High doses of irradiation (HDI, >8 Gy) generally trigger the polarization of TAMs towards the M2 phenotype [120]. M2-type TAMs can counteract the effects of radiation therapy, as radiation induces macrophage infiltration and M2-type polarization through IL-4 or CSF-1 signaling pathways[121–123]. Recent research indicates that inhibiting SIRPα expression in TAMs significantly improves the efficacy of radiotherapy across different types of tumors. SIRPα-negative macrophages activated by radiotherapy primarily elicit tumor-specific T-cell responses through inflammation and antigen presentation. This process overcomes radiotherapy resistance and fosters long-term humoral and cellular immunity to eradicate cancer cells [124]. Moreover, the combination of radiotherapy with CSF-1R inhibitors exhibits superior efficacy in suppressing tumor growth compared to radiotherapy alone [125]. Furthermore, recent research has demonstrated that varying doses of ionizing radiation (IR) can induce polarization of macrophages, leading to proinflammatory M1-like characteristics in xenograft tumor models and human rectal cancer specimens from patients undergoing neoadjuvant chemoradiotherapy. This effect is associated with IR-induced activation of interferon regulatory Factor 5 (IRF5), which undergoes regulation of mRNA levels and post-translational modifications facilitated by ATM kinase. ATM kinase activation not only contributes significantly to the radiation-induced polarization of macrophages but also plays a pivotal role in macrophage reprogramming following drug treatments, including cisplatin, gamma-interferon, and lipopolysaccharide [126]. Additional clinical trials are necessary to investigate radiotherapy protocols that induce the polarization of TAMs towards the M2 phenotype, as the effectiveness may vary among different regimens. Furthermore, research should persist in exploring the interaction between radiotherapy and TAMs. These investigations offer valuable insights for integrating TAMs-targeted therapy with radiotherapy.

7.3. TAMs and chemotherapy

The role of macrophages in chemotherapy outcomes is complex. TAMs, acting as antigen-presenting cells (APCs), have the ability to amplify immunogenic cell death by stimulating T cells responses. This mechanism enhances the efficacy of chemotherapy. Conversely, TAMs' immunosuppressive traits can lead to chemotherapy resistance in patients [127]. Decreasing TAMs presence with drugs like trabectedin can alleviate resistance and boost the tumor-killing effects of chemotherapy [128]. Macrophage responses to different chemotherapeutic agents may vary, leading to either enhanced or diminished antitumor activity [129]. Targeting drug-accessible sites on $CCR2^+$ TAMs and $CXCR2^+$ TANs can enhance immune function and overcome chemotherapy resistance [130].

For example, TAMs upregulate cytidine deaminase expression and release resistin. Subsequently, resistin interacts with CAP-1 and TLR-4 receptors on tumor cells, exacerbating the resistance of pancreatic ductal adenocarcinoma to gemcitabine, a CSF-1 receptor blocker [131,132]. The ample secretion of TAMs activates insulin-like growth factor 1 (IGF-1) receptors present on pancreatic ductal adenocarcinoma cells, thereby inducing resistance to gemcitabine [133]. TAMs trigger antiapoptotic signaling pathways in tumor cells by releasing cytokines like IL-6, STAT-3 factors, histone B, and S, ultimately leading to resistance against chemotherapy [134]. The elevated secretion of IL-10 by TAMs exacerbates their multidrug resistance to paclitaxel and other chemotherapeutic agents.

Moreover, in breast cancer cells, TAMs exacerbate resistance to chemotherapy by influencing the IL-10/STAT3/Bcl-2 signaling pathway [135]. TAMs impact tumor growth by regulating the population of tumor stem cells. Research suggests that macrophages engage with tumor cells through various factors, including M-CSF, intercellular adhesion molecule-1 (ICAM-1), and ephrin, potentially promoting the survival of cancer stem cells (CSCs). The increased survival, self-renewal capacity, and tumorigenic potential of CSCs significantly contribute to tumor growth and confer resistance to chemotherapy [136,137]. Research experiments have shown that vinblastine has the capacity to reset TAMs to the M1 phenotype, thereby fostering an antitumor immune response [14]. These trials have demonstrated the significance of TAMs in chemotherapy for tumors. At present, the treatment of TAMs combined with chemotherapy has aroused wide attention. The advantages of the combination of the two are reflected in the following aspects. First, treatment with TAMs targeted drugs and traditional chemotherapy drugs will enhance efficacy. One potential example involves the inhibition of CSF-1R on M2-like TAMs, which amplifies the intratumoral production of type I interferon. This collaborative action with chemotherapy could bolster the effectiveness of platinum-based treatments, potentially enhancing therapeutic outcomes [138]. Moreover, the utilization of CSF1R inhibitors alongside bortezomib or melphalan exhibits augmented effectiveness in treating myeloma, showcasing promising prospects for enhanced therapeutic outcomes in this context [139]. Furthermore, directing attention towards TAMs holds potential for mitigating chemotherapy resistance. Take, for instance, the use of TLR 7/8 agonists, which could potentially diminish chemotherapy resistance in colorectal cancer through the stimulation of myelosuppressor cell polarization into M1-like TAMs, thus indicating a promising avenue for therapeutic intervention [140]. However, whether the adverse reactions of the combined treatment are aggravated and whether the patient's body tolerance is a problem that needs attention in future clinical application. In the future, additional clinical trials and experimental research are necessary to evaluate the feasibility of combining TAMs-targeting agents with chemotherapy.

7.4. TAMs and anti-angiogenic therapy

Typical growth factors that stimulate angiogenesis consist of members of the EGF family, VEGF, FGF, CSF, human epidermal growth factor receptors 2 and 3 (HER2 and HER3), and platelet-derived growth factor. Anti-angiogenic medications regulate TAMs activity, facilitating TAMs reprogramming and transitioning them from an M2 to an M1 phenotype. This process effectively impedes tumor progression and metastasis, leading to improved patient outcomes and offering potential for enhanced survival rates. Recent studies, both in laboratory settings and animal models, have pinpointed several anti-angiogenic drugs with the ability to halt TAMs polarization toward M2 or induce the transformation of M2 TAMs into M1. For instance, following lapatinib treatment and co-culture

of THP-1 cells with A549 or H1299 conditioned medium for 4 h, Western blot or q-PCR revealed reduced PD-L1 expression on macrophage surfaces, indicating Apatinib's positive regulatory effect on the immunosuppressive tumor microenvironment. Furthermore, low doses of Apatinib were found to more effectively inhibit MDSCs recruitment [141]. Additionally, studies have shown that endostatin, known for its anti-angiogenic and antitumor properties, hinders macrophage migration and alternative activation by suppressing the P38 MAP kinase and Erk1/2 signaling pathways. Additionally, endostatin suppresses tumor cell proliferation and blood vessel density induced by TAMs [142]. The role of TAMs in the context of anti-angiogenic drugs against tumors deserves attention. Further research is warranted to investigate the feasibility of integrating targeted therapy for TAMs with anti-angiogenic medications. Moreover, research indicates that TAMs can compromise the efficacy of anti-angiogenic treatments by fostering resistance to such therapies [143]. Understanding the relationship between TAMs and anti-angiogenic therapy could pave the way for addressing drug resistance in patients.

7.5. Advantages and disadvantages of targeting TAMs therapies compared to current therapies

The emergence of targeted TAMs therapy provides a new way to alleviate the drug resistance problem in traditional clinical treatment. Traditional treatment can control the progression of tumor to a certain extent, but its drug resistance and adverse reactions are always urgent problems in clinical practice. Despite advancements in immune checkpoint inhibitors, which have led to some extension in survival rates in recent years, the response rate among patients undergoing PD-1/PD-L1 immunotherapy remains modest, hovering around 30 %. Because PD-L1 expression varies widely across tissues, the detection outcomes of PD-L1 expression are susceptible to false negatives, hindering the development of tailored treatment strategies for patients [139]. Otherwise, some patients were forced to terminate treatment after adverse reactions such as immune pneumonia and immune myocarditis occurred after the application of PD-1/PD-L1 immunotherapy. However, TAMs, as the main components of the tumor microenvironment, exist in large quantities in the body, and targeted tams can produce better results for the treatment of tumor patients. Conventional treatments like chemotherapy and radiotherapy unavoidably target normal cells alongside tumor cells, leading to myelosuppression and significantly impacting patients' prognosis and quality of life. In recent years, TAMs have garnered significant attention in the realm of nano-immunotherapy. TAMs primarily contribute to cancer treatment through two principal strategies. Firstly, nanomedicine can be engineered to directly target TAMs, exerting a profound influence on tumor growth. Through this approach, drugs can remodel TME, hindering tumor progression. However, challenges persist regarding the biological distribution of nanomedicine in normal tissues and its efficacy in penetrating tumor sites. Secondly, compared to the former method, drug delivery platforms based on TAMs hold the potential to extend drug circulation time and enhance drug penetration into tumor tissues. Nonetheless, there are potential immune-related risks associated with this strategy. With regard to the characteristics of macrophage cell membranes and the fluidity exhibited by TAMs, they undergo reprogramming to serve as an efficient delivery platform. This reprogramming enables them to traverse immune barriers, prolong blood circulation time, and mitigate toxicity associated with drug delivery. Furthermore, the recruitment of TAMs can facilitate the accumulation of nanomedicine at the tumor site, leading to elevated drug concentrations and enhanced therapeutic effects. The profound infiltration of TAMs aids in enhancing the permeability of nanomedicine, enabling the transportation of drugs to challenging regions such as hypoxic areas and tumor stem cells, which are typically hard to access using other delivery platforms [144]. The emergence of targeted TAMs therapy breaks the limitations of traditional therapy and lays a good foundation for future precision therapy. In addition, TAMs is intricately related to tumor metastasis, angiogenesis and immunosuppression, and influences tumor progression through a large number of cytokines and pathways as media. This phenomenon provides us with more research directions, deepen our understanding of tumor microenvironment, and find more drugs targeting TAMs.

While TAMs have significantly influenced cancer treatment, they have emerged as direct targets in certain cancer therapies. Nevertheless, the high toxicity to non-cancerous cells and the lack of specificity of drugs employed to target TAMs are recognized as notable side effects of TAMs-based therapies. In addition, TAMs targeted therapies do not appear to eradicate cancer on their own, and overdoses can be toxic to patients [143]. At the same time, we can not ignore that there are still some technical difficulties in targeted tams therapy at this stage, which we need to focus on and solve in the future. First, the proliferation capacity of macrophages is limited, and it is almost impossible to expand in vitro, and the output is difficult to increase, which greatly limits its clinical application. Second, macrophages are highly plastic and susceptible to microenvironment, and macrophage-mediated cancer therapy alone is not enough to eradicate tumors. Third, the innate tumor-targeting ability of macrophages has limited effectiveness in treating metastatic tumors. Furthermore, the role of TAMs in cancer is diverse across different cancer types, and individual variances among patients are often underestimated, resulting in unpredictable treatment efficacy [139]. At present, targeted TAMs are more in the clinical trial stage, and its safety and related adverse reaction rate need more clinical trials.

8. TAMs: potential diagnostic markers in cancer

Currently, TAMs research is advancing towards increased complexity and precision. However, representative biomarkers associated with TAMs remain unsuitable for clinical applications. While some studies propose that TAMs infiltration predicts a favorable prognosis for certain cancers, such as colorectal and gastric cancers, it generally correlates with a poor prognosis in most cancers, including lung, breast, bladder, prostate, head and neck, glioma, melanoma, and non-Hodgkin lymphoma [145]. The association between TAMs and cancer patient prognosis remains contentious, possibly due to several factors. Firstly, it's essential to note that the most common marker for identifying TAMs, the CD68 antibody, is expressed not only in TAMs but also in other tumor tissue components such as malignant epithelial cells and stromal cells. Therefore, relying solely on a CD68-based marker may not effectively differentiate the TAMs subpopulation. Secondly, studies included in analyses often utilize varied antibodies and markers to label

TAMs. Thirdly, tumor cells exhibit heterogeneity and complex spatial distributions, with many studies failing to account for tumor typing and TAMs distribution location. Lastly, diverse methodologies are adopted across studies [145]. Furthermore, recent studies indicate that substances linked to TAMs can influence tumor patient prognosis. The synergistic effect of CXCL9 and phosphoprotein 1 (SPP1) has been identified as jointly influencing the polarity of TAMs, significantly affecting tumor progression and treatment response. The mutually exclusive expression of CXCL9 and SPP1 in the tumor microenvironment not only regulates TAMs polarity but also demonstrates a strong correlation with the immune cell spectrum, antitumor factors, and patient prognosis, thereby exerting a significant impact on patient outcomes [146]. SPP1, commonly referred to as osteopontin, is a multifunctional secreted phosphorylated glycoprotein. Its expression on TAMs has been linked to poor prognosis and chemotherapy resistance in lung adenocarcinoma. Additionally, SPP1 serves as a potentially valuable marker for identifying monocyte-derived TAMs [147]. Currently, high-resolution analysis of mononuclear phagocytes has identified Gpnm b as a prognostic marker for liver metastasis in human colorectal cancer [148].

9. Summary and future prospects

Although substantial advancements have been achieved in current TAMs research, the intricate nature of the TME underscores the need for continued exploration into the quantitative and functional alterations of its constituent elements during tumor development. Our understanding of TAMs remains limited, with many pathways and related factors yet to be elucidated. The relationship between TAMs and neutrophils remains contentious and warrants further investigation. Despite numerous targeted drugs for TAMs, most remain in the experimental stage, with the human body's immune mechanism being more intricate than that of mice. Therefore, selecting appropriate drug applications for clinical trials is crucial. Moreover, before widespread clinical application, considerations such as administration mode, cycle, toxicity, side effects, and cost should be addressed. However, reports suggest that TAM-targeting drugs may encounter resistance issues, warranting further exploration of resistance mechanisms. Additionally, due to the limited efficacy and potential for drug resistance with single drugs, future efforts should focus on exploring combination therapies to mitigate treatment shortcomings. Furthermore, identifying more TAM-associated markers will aid in prognostication and provide better clinical guidance. The rapid advancement of single-cell sequencing has provided a newfound understanding of TAMs subsets. Future research should aim to conduct more comprehensive analyses of their heterogeneity and function and develop targeted treatments accordingly. Ongoing advancements in anticancer therapies targeting TAMs are continuously evolving and refining, holding the promise of surpassing traditional tumor-related treatments and attaining favorable clinical therapeutic outcomes. Looking ahead, targeted anti-TAM cancer therapies will increasingly emerge as a crucial frontier in combination therapy. The targeted approach to TAMs holds immense potential in tumor treatment, capable of being synergistically combined with chemotherapy, radiotherapy, and immune checkpoint inhibitors in clinical practice, thereby further extending patients' survival outcomes. Furthermore, both upstream and downstream pathways of TAMs can serve as targets for modulating macrophage function. Particularly promising is the utilization of genetic engineering to reprogram macrophages, converting TAMs that promote tumor growth into macrophages that inhibit tumor growth. Currently, the integration of TAM-targeted therapy with immunotherapy and nanotechnology has enhanced clinical anticancer efficacy. However, a significant challenge in the future lies in designing vectors capable of targeting specific macrophage populations while evading absorption by macrophages. Moreover, the intricate interactions between macrophages and nanoparticles, encompassing internalization, cytotoxicity, immune activation, and regulation, remain enigmatic. Therefore, it is crucial to delve into the nano/biological interface events between nanomaterials and macrophages to unravel these complexities. Furthermore, the complex interplay between macrophages and nanoparticles, involving processes such as internalization, cytotoxicity, immune activation, and regulation, remains poorly understood. It is imperative to explore the nano/biological interface events between nanomaterials and macrophages to untangle these intricacies. Hence, targeting TAMs holds promise as an innovative treatment approach for precision cancer therapy in the future. As research progresses, our comprehension of TAMs' role in cancer treatment will advance, paving the way for further breakthroughs in therapeutic strategies.

Statement

I promise that all information will be open and accessible to everyone. I also promise that the picture is copyrighted from Biorender.

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because there are no human subjects or animal experiments in this paper. Ethical approval is not applicable.

Data availability statement

All data generated or analysed during this study are included in article/supplementary material/referenced in article. All data generated or analysed during this study are included in article/supplementary material/referenced in article. Support the results of the data from the public sector of the available resources of the following: clinical trial website: http://clinicaltrials.gov.

CRediT authorship contribution statement

Yanchi Shao: Writing – original draft. **Song Han:** Writing – original draft. **Zhenxin Hou:** Writing – review & editing. **Chen Yang:** Visualization. **Yanbin Zhao:** Project administration.

Declaration of competing interest

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

Acknowledgements

The study was supported by the Haiyan Science Fund of Harbin Medical University Cancer Hospital (JJZD2023-02 to Yanbin Zhao).

References

[1] U. Basak, T. Sarkar, S. Mukherjee, et al., Tumor-associated macrophages: an effective player of the tumor microenvironment, Front. Immunol. 14 (2023) 1295257.
[2] H. Zhang, L. Liu, J. Liu, et al., Roles of tumor-associated macrophages in anti-PD-1/PD-L1 immunotherapy for solid cancers, Mol. Cancer 22 (1) (2023) 58.
[3] S. Wang, G. Liu, Y. Li, et al., Metabolic reprogramming induces macrophage polarization in the tumor microenvironment, Front. Immunol. 133 (2022) 840029.
[4] H. Hu, R. Cheng, Y. Wang, et al., Shaping polarization of tumor-associated macrophages in cancer immunotherapy, Front. Immunol. 13 (2022) 888713.
[5] S.J. Lee, M.J. Kim, I.C. Kwon, et al., Hedgehog signaling promotes tumor-associated macrophage polarization to suppress intratumoral $CD8^+$ T cell recruitment, J. Clin. Invest. 129 (12) (2019) 5151–5162.
[6] J.Y. Wu, T.W. Huang, Y.T. Hsieh, et al., Cancer-derived succinate promotes macrophage polarization and cancer metastasis via succinate receptor, Mol. Cell 77 (2) (2020) 213–227.e5.
[7] Y. Zhu, J. Yang, D. Xu, et al., Disruption of tumour-associated macrophage trafficking by the osteopontin-induced colony-stimulating factor-1 signalling sensitises hepatocellular carcinoma to anti-PD-L1 blockade, Gut 68 (9) (2019) 1653–1666.
[8] A. Shapouri-Moghaddam, S. Mohammadian, H. Vazini, et al., Macrophage plasticity, polarization, and function in health and disease, J. Cell. Physiol. 233 (9) (2018) 6425–6440.
[9] T. Tsukui, K.H. Sun, J.B. Wetter, et al., Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis, Nat. Commun. 11 (1) (2020) 1920.
[10] K. Movahedi, D. Laoui, C. Gysemans, et al., Different tumor microenvironments contain functionally distinct subsets of macrophages derived from Ly6C(high) monocytes, Cancer Res. 194 (11) (2021) 648–661.
[11] S. Arora, P. Singh, S. Ahmad, et al., Comprehensive integrative analysis reveals the association of KLF4 with macrophage infiltration and polarization in lung cancer microenvironment, Cells 10 (8) (2021) 2091.
[12] J. Zheng, R. Dou, X. Zhang, et al., LINC00543 promotes colorectal cancer metastasis by driving EMT and inducing the M2 polarization of tumor associated macrophages, J. Transl. Med. 21 (1) (2023) 153.
[13] S.G. Lee, S.M. Woo, S.U. Seo, et al., Cathepsin D promotes polarization of tumor-associated macrophages and metastasis through TGFBI-CCL20 signaling, Exp. Mol. Med. 56 (2) (2024) 383–394.
[14] W.S. Ho, I. Mondal, B. Xu, et al., Vinblastine resets tumor-associated macrophages toward M1 phenotype and promotes antitumor immune response, Journal for ImmunoTherapy of Cancer 11 (8) (2023) e007253.
[15] J. Huang, H. Pan, J. Sun, et al., TMEM147 aggravates the progression of HCC by modulating cholesterol homeostasis, suppressing ferroptosis, and promoting the M2 polarization of tumor-associated macrophages, J. Exp. Clin. Cancer Res. 42 (1) (2023) 286.
[16] S. Chen, M. Wang, T. Lu, et al., JMJD6 in tumor-associated macrophage regulates macrophage polarization and cancer progression via STAT3/IL-10 axis, Oncogene 42 (37) (2023) 2737–2750.
[17] F. Luo, H. Li, W. Ma, et al., The BCL-2 inhibitor APG-2575 resets tumor-associated macrophages toward the M1 phenotype, promoting a favorable response to anti-PD-1 therapy via NLRP3 activation, Cell. Mol. Immunol. 21 (1) (2023) 60–79.
[18] X. Gao, S. Zhou, Z. Qin, et al., Upregulation of HMGB1 in tumor-associated macrophages induced by tumor cell-derived lactate further promotes colorectal cancer progression, J. Transl. Med. 21 (1) (2023) 53.
[19] Z. Li, S. Chen, X. He, et al., SLC3A2 promotes tumor-associated macrophage polarization through metabolic reprogramming in lung cancer, Cancer Sci. 114 (6) (2023) 2306–2317.
[20] C. Zhang, S. Wei, S. Dai, et al., The NR_109/FUBP1/c-myc axis regulates TAM polarization and remodels the tumor microenvironment to promote cancer development, Journal for ImmunoTherapy of Cancer 11 (5) (2023) e006230.
[21] M.A. Gonzalez, D.R. Lu, M. Yousefi, et al., Phagocytosis increases an oxidative metabolic and immune suppressive signature in tumor macrophages, J. Exp. Med. 220 (6) (2023) e20221472.
[22] L.E. Hudson, R.L. Allen, Leukocyte ig-like receptors – a model for MHC class I disease associations, Front. Immunol. 7 (2016).
[23] A.A. Barkal, K. Weiskopf, K.S. Kao, et al., Engagement of MHC class I by the inhibitory receptor LILRB1 suppresses macrophages and is a target of cancer immunotherapy, Nat. Immunol. 19 (1) (2018) 76–84.
[24] W. Zhang, Q. Huang, W. Xiao, et al., Advances in anti-tumor treatments targeting the CD47/SIRPα axis, Front. Immunol. 11 (2020) 18.
[25] Y. Liu, R. Xue, X. Duan, et al., PARP inhibition synergizes with CD47 blockade to promote phagocytosis by tumor-associated macrophages in homologous recombination-proficient tumors, Life Sci. 326 (2023) 121790.
[26] H. Chan, C.V. Trout, D. Mikolon, et al., Discovery and preclinical activity of BMS-986351, an antibody to SIRPα that enhances macrophage-mediated tumor phagocytosis when combined with opsonizing antibodies, Cancer Research Communications 4 (2) (2024) 505–515.
[27] X.J. Chen, C.H. Guo, Z.C. Wang, et al., Hypoxia-induced ZEB1 promotes cervical cancer immune evasion by strengthening the CD47-SIRPα axis, Cell Commun. Signal. 22 (1) (2024) 15.
[28] L. Tang, Y. Yin, Y. Cao, et al., Extracellular vesicles-derived hybrid nanoplatforms for amplified CD47 blockade-based cancer immunotherapy, Adv. Mater. 35 (35) (2023) 2303835.
[29] Z. Tang, M.C. Zhong, J. Qian, et al., CD47 masks pro-phagocytic ligands in cis on tumor cells to suppress antitumor immunity, Nat. Immunol. 24 (12) (2023) 2032–2041.
[30] K. Chaudagar, S. Rameshbabu, S. Mei, et al., Androgen blockade primes NLRP3 in macrophages to induce tumor phagocytosis[R], Cancer Biology (2023).
[31] S. Wang, W. Yan, L. Kong, et al., Oncolytic viruses engineered to enforce cholesterol efflux restore tumor-associated macrophage phagocytosis and anti-tumor immunity in glioblastoma, Nat. Commun. 14 (1) (2023) 4367.
[32] K Chaudagar, H M Hieromnimon, A Kelley, et al., Suppression of Tumor Cell Lactate-Generating Signaling Pathways Eradicates Murine PTEN/p53-deficient Aggressive-Variant Prostate Cancer via Macrophage phagocytosis, Clin Cancer Res 29 (23) (2023) 4930–4940.
[33] M.R. Galdiero, E. Bonavita, I. Barajon, et al., Tumor associated macrophages and neutrophils in cancer, Immunobiology 218 (11) (2013) 1402–1410.

[34] Y. Qiu, T. Chen, R. Hu, et al., Next frontier in tumor immunotherapy: macrophage-mediated immune evasion, Biomark. Res. 9 (1) (2021) 72.
[35] Y. Azumi, Y. Koma, S. Tsukamoto, et al., IFI16 induced by direct interaction between esophageal squamous cell carcinomas and macrophages promotes tumor progression via secretion of IL-1α, Cells 12 (22) (2023) 2603.
[36] H.J. Song, T. Kim, H.N. Choi, et al., TonEBP expression is essential in the IL-1β–induced migration and invasion of human A549 lung cancer cells, Oncology Research 32 (1) (2024) 151–161.
[37] C. Alfaro, M.F. Sanmamed, M.E. Rodríguez-Ruiz, et al., Interleukin-8 in cancer pathogenesis, treatment and follow-up, Cancer Treat Rev. 60 (2017) 24–31.
[38] R. Tatsuno, J. Ichikawa, Y. Komohara, et al., Pivotal role of IL-8 derived from the interaction between osteosarcoma and tumor-associated macrophages in osteosarcoma growth and metastasis via the FAK pathway, Cell Death Dis. 15 (2) (2024) 108.
[39] M.H. Mannino, Z. Zhu, H. Xiao, et al., The paradoxical role of IL-10 in immunity and cancer, Cancer Lett. 367 (2) (2015) 103–107.
[40] S. Zhang, D. Ren, H. Hou, et al., M-CSF secreted by gastric cancer cells exacerbates the progression of gastric cancer by increasing the expression of SHP2 in tumor-associated macrophages, Aging 15 (24) (2023) 15525–15534.
[41] I. Wyrobnik, M. Steinberg, A. Gelfand, et al., Decreased melanoma CSF-1 secretion by cannabigerol treatment reprograms regulatory myeloid cells and reduces tumor progression, OncoImmunology 12 (1) (2023) 2219164.
[42] J. Zhou, N. Lyu, Q. Wang, et al., A novel role of TGFBI in macrophage polarization and macrophage-induced pancreatic cancer growth and therapeutic resistance, Cancer Lett. 578 (2023) 216457.
[43] X. Qiao, Z. Cheng, K. Xue, et al., Tumor-associated macrophage-derived exosomes LINC01592 induce the immune escape of esophageal cancer by decreasing MHC-I surface expression, J. Exp. Clin. Cancer Res. 42 (1) (2023) 289.
[44] L. Gu, C. Feng, M. Li, et al., Exosomal NOX1 promotes tumor-associated macrophage M2 polarization-mediated cancer progression by stimulating ROS production in cervical cancer: a preliminary study, Eur. J. Med. Res. 28 (1) (2023) 323.
[45] Z. Li, D. Maeda, M. Yoshida, et al., The intratumoral distribution influences the prognostic impact of CD68- and CD204-positive macrophages in non-small cell lung cancer, Lung Cancer 123 (2018) 127–135.
[46] C. Jackaman, F. Tomay, L. Duong, et al., Aging and cancer: the role of macrophages and neutrophils, Ageing Res. Rev. 36 (2017) 105–116.
[47] S.L. Zhou, Z.J. Zhou, Z.Q. Hu, et al., Tumor-associated neutrophils recruit macrophages and T-regulatory cells to promote progression of hepatocellular carcinoma and resistance to sorafenib, Gastroenterology 150 (7) (2016) 1646–1658.e17.
[48] E. Källberg, M. Mehmeti-Ajradini, F. Björk Gunnarsdottir, et al., AIRE is expressed in breast cancer TANs and TAMs to regulate the extrinsic apoptotic pathway and inflammation, J. Leukoc. Biol. (2023) qiad152.
[49] J. Zhu, H. Yamane, W.E. Paul, Differentiation of effector CD4 T cell populations, Annu. Rev. Immunol. 28 (1) (2010) 445–489.
[50] M. Locati, G. Curtale, A. Mantovani, Diversity, mechanisms, and significance of macrophage plasticity, Annu. Rev. Pathol. 15 (1) (2020) 123–147.
[51] S.C. Funes, M. Rios, J. Escobar-Vera, et al., Implications of macrophage polarization in autoimmunity, Immunology 154 (2) (2018) 186–195.
[52] K. Kashfi, J. Kannikal, N. Nath, Macrophage reprogramming and cancer therapeutics: role of iNOS-derived NO, Cells 10 (11) (2021) 3194.
[53] D. Sun, T. Luo, P. Dong, et al., Treg cells promote the SREBP1-dependent metabolic fitness of tumor-promoting macrophages via repression of $CD8^+$ T cell-derived interferon-γ, Immunity 51 (2) (2019) 381–397.e6.
[54] D. Daley, V.R. Mani, N. Mohan, et al., NLRP3 signaling drives macrophage-induced adaptive immune suppression in pancreatic carcinoma, J. Exp. Med. 214 (6) (2017) 1711–1724.
[55] Q. Fu, L. Xu, Y. Wang, et al., Tumor-associated macrophage-derived interleukin-23 interlinks kidney cancer glutamine addiction with immune evasion, Eur. Urol. 75 (5) (2019) 752–763.
[56] T.J. Curiel, G. Coukos, L. Zou, et al., Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival, Nat. Med. 10 (9) (2004) 942–949.
[57] Y. Li, Z. Shen, Z. Chai, et al., Targeting MS4A4A on tumour-associated macrophages restores CD8+ T-cell-mediated antitumour immunity, Gut 72 (12) (2023) 2307–2320.
[58] Y.J. Chen, G.N. Li, X.J. Li, et al., Targeting IRG1 reverses the immunosuppressive function of tumor-associated macrophages and enhances cancer immunotherapy, Sci. Adv. 9 (17) (2023) eadg0654.
[59] M.P. Protti, L. De Monte, Cross-talk within the tumor microenvironment mediates Th2-type inflammation in pancreatic cancer, OncoImmunology 1 (1) (2012) 89–91.
[60] H. Cho, Y. Seo, K.M. Loke, et al., Cancer-stimulated CAFs enhance monocyte differentiation and protumoral TAM activation via IL6 and GM-CSF secretion, Clin. Cancer Res. 24 (21) (2018) 5407–5421.
[61] V. Kumar, L. Donthireddy, D. Marvel, et al., Cancer-associated fibroblasts neutralize the anti-tumor effect of CSF1 receptor blockade by inducing PMN-MDSC infiltration of tumors, Cancer Cell 32 (5) (2017) 654–668.e5.
[62] M. Perez-Penco, L. Lara De La Torre, I. Lecoq, et al., TGFβ-specific T cells induced by a TGFβ-derived immune modulatory vaccine both directly and indirectly modulate the phenotype of tumor-associated macrophages and fibroblasts, Journal for ImmunoTherapy of Cancer 12 (2) (2024) e008405.
[63] F. Seto-Tetsuo, M. Arioka, K. Miura, et al., DIF-1 exhibits anticancer activity in breast cancer via inhibition of CXCLs/CXCR2 axis-mediated communication between cancer-associated fibroblasts and cancer cells, Int. Immunopharm. 117 (2023) 109913.
[64] E.A. De Jaeghere, H.G. Denys, O. De Wever, Fibroblasts fuel immune escape in the tumor microenvironment, Trends in Cancer 5 (11) (2019) 704–723.
[65] H. Yang, Q. Zhang, M. Xu, et al., CCL2-CCR2 axis recruits tumor associated macrophages to induce immune evasion through PD-1 signaling in esophageal carcinogenesis, Mol. Cancer 19 (1) (2020) 41.
[66] I. Lelios, D. Cansever, S.G. Utz, et al., Emerging roles of IL-34 in health and disease, J. Exp. Med. 217 (3) (2020) e20190290.
[67] I. Wyrobnik, M. Steinberg, A. Gelfand, et al., Decreased melanoma CSF-1 secretion by Cannabigerol treatment reprograms regulatory myeloid cells and reduces tumor progression, OncoImmunology 12 (1) (2023) 2219164.
[68] A. Voissière, C. Gomez-Roca, S. Chabaud, et al., The CSF-1R inhibitor pexidartinib affects FLT3-dependent DC differentiation and may antagonize durvalumab effect in patients with advanced cancers, Sci. Transl. Med. 16 (731) (2024) eadd1834.
[69] Palma M. De, C.E. Lewis, Macrophage regulation of tumor responses to anticancer therapies, Cancer Cell 23 (3) (2013) 277–286.
[70] F. Roth, A.C. De La Fuente, J.L. Vella, et al., Aptamer-mediated blockade of IL4Rα triggers apoptosis of MDSCs and limits tumor progression, Cancer Res. 72 (6) (2012) 1373–1383.
[71] M. Cieslewicz, J. Tang, J.L. Yu, et al., Targeted delivery of proapoptotic peptides to tumor-associated macrophages improves survival, Proc. Natl. Acad. Sci. USA 110 (40) (2013) 15919–15924.
[72] P. Allavena, G. Germano, C. Belgiovine, et al., Trabectedin: a drug from the sea that strikes tumor-associated macrophages, OncoImmunology 2 (6) (2013) e24614.
[73] E. Goulielmaki, M. Bermudez-Brito, M. Andreou, et al., Pharmacological inactivation of the PI3K p110δ prevents breast tumour progression by targeting cancer cells and macrophages, Cell Death Dis. 9 (6) (2018) 678.
[74] Y. Wang, W. Zhai, L. Yang, et al., Establishments and evaluations of post-operative adhesion animal models, Advanced Therapeutics 6 (4) (2023) 2200297.
[75] Z. Yao, J. Zhang, B. Zhang, et al., Imatinib prevents lung cancer metastasis by inhibiting M2-like polarization of macrophages, Cancer Commun. 133 (2018) 121–131.
[76] M.K. Skytthe, J.H. Graversen, S.K. Moestrup, Targeting of CD163+ macrophages in inflammatory and malignant diseases, Int. J. Mol. Sci. 21 (15) (2020) 5497.
[77] Y.J. Cha, J.S. Koo, Role of tumor-associated myeloid cells in breast cancer, Cells 9 (8) (2020) 1785.
[78] H. Wu, Y. Han, Y. Rodriguez Sillke, et al., Lipid droplet-dependent fatty acid metabolism controls the immune suppressive phenotype of tumor-associated macrophages, EMBO Mol. Med. 11 (11) (2019) e10698.
[79] S. Gordon, Pattern recognition receptors, Cell 111 (7) (2002) 927–930.
[80] B. Li, W. Wang, L. Zhao, et al., Multifunctional AIE nanosphere-based "nanobomb" for trimodal imaging-guided photothermal/photodynamic/pharmacological therapy of drug-resistant bacterial infections, ACS Nano 17 (5) (2023) 4601–4618.

[81] L. Cassetta, J.W. Pollard, Targeting macrophages: therapeutic approaches in cancer, Nat. Rev. Drug Discov. 17 (12) (2018) 887–904.
[82] M. Djurfeldt, J. Hjorth, J.M. Eppler, et al., Run-time interoperability between neuronal network simulators based on the MUSIC framework, Neuroinformatics 8 (1) (2010) 43–60.
[83] C.B. Rodell, S.P. Arlauckas, M.F. Cuccarese, et al., TLR7/8-agonist-loaded nanoparticles promote the polarization of tumour-associated macrophages to enhance cancer immunotherapy, Nat. Biomed. Eng. 2 (8) (2018) 578–588.
[84] D. Muraoka, N. Seo, T. Hayashi, et al., Antigen delivery targeted to tumor-associated macrophages overcomes tumor immune resistance, J. Clin. Invest. 129 (3) (2019) 1278–1294.
[85] W. Zheng, J.W. Pollard, Inhibiting macrophage PI3Kγ to enhance immunotherapy, Cell Res. 26 (12) (2016) 1267–1268.
[86] H. Chen, Q. Wang, S. Nolen-Hoeksema, et al., Regulatory mechanisms of lipid biosynthesis in microalgae, Biol. Rev. 96 (5) (2021) 2373–2391.
[87] M.M. Kaneda, K.S. Messer, N. Ralainirina, et al., Erratum: corrigendum: PI3Kγ is a molecular switch that controls immune suppression, Nature 542 (7639) (2017), 124-124.
[88] H. Qin, H. Yu, J. Sheng, et al., PI3Kgamma inhibitor attenuates immunosuppressive effect of poly(<scp>l</scp>-glutamic acid)-combretastatin A4 conjugate in metastatic breast cancer, Adv. Sci. 6 (12) (2019) 1900327.
[89] S.J. Lee, M.J. Kim, I.C. Kwon, et al., Delivery strategies and potential targets for siRNA in major cancer types, Adv. Drug Deliv. Rev. 104 (2016) 2–15.
[90] X. Feng, S. Yang, Long non-coding RNA LINC00243 promotes proliferation and glycolysis in non-small cell lung cancer cells by positively regulating PDK4 through sponging miR-507, Mol. Cell. Biochem. 463 (1–2) (2020) 127–136.
[91] Y. Li, F. Cao, M. Li, et al., Hydroxychloroquine induced lung cancer suppression by enhancing chemo-sensitization and promoting the transition of M2-TAMs to M1-like macrophages, J. Exp. Clin. Cancer Res. 37 (1) (2018) 259.
[92] J. Ma, L. Liu, G. Che, et al., A nanoparticle-incorporated STING activator enhances antitumor immunity in PD-L1–insensitive models of triple-negative breast cancer, JCI Insight 3 (22) (2018) e120638.
[93] X. Liu, D. Chen, J. Liu, et al., Blocking modification of eukaryotic initiation 5A2 antagonizes cervical carcinoma via inhibition of RhoA/ROCK signal transduction pathway, Technol. Cancer Res. Treat. 16 (5) (2017) 630–638.
[94] J.H. Ko, S.O. Yoon, H.J. Lee, et al., Rapamycin regulates macrophage activation by inhibiting NLRP3 inflammasome-p38 MAPK-NFκB pathways in autophagy- and p62-dependent manners, Oncotarget 8 (25) (2017) 40817–40831.
[95] M. Niu, M. Yi, N. Li, et al., Predictive biomarkers of anti-PD-1/PD-L1 therapy in NSCLC, Exp. Hematol. Oncol. 10 (1) (2021) 18.
[96] P. Goossens, J. Rodriguez-Vita, A. Etzerodt, et al., Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression, Cell Metabol. 29 (6) (2019) 1376–1389.e4.
[97] S. Zhang, W. Peng, H. Wang, et al., C1q $^{+}$ tumor-associated macrophages contribute to immunosuppression through fatty acid metabolic reprogramming in malignant pleural effusion, Journal for ImmunoTherapy of Cancer 11 (8) (2023) e007441.
[98] M. Ovais, M. Guo, C. Chen, Tailoring nanomaterials for targeting tumor-associated macrophages, Adv. Mater. 31 (19) (2019) 1808303.
[99] B. Ruffell, L.M. Coussens, Macrophages and therapeutic resistance in cancer, Cancer Cell 27 (4) (2015) 462–472.
[100] H. Wang, X. Wang, X. Zhang, et al., The promising role of tumor-associated macrophages in the treatment of cancer, Drug Resist. Updates 73 (2024) 101041.
[101] J. Zheng, J. Jiang, Y. Pu, et al., Tumor-associated macrophages in nanomaterial-based anti-tumor therapy: as target spots or delivery platforms, Front. Bioeng. Biotechnol. 11 (2023) 1248421.
[102] B.A. Teicher, S.P. Fricker, CXCL12 (SDF-1)/CXCR4 pathway in cancer, Clin. Cancer Res. 16 (11) (2010) 2927–2931.
[103] R.S. Cavalcante, U. Ishikawa, E.S. Silva, et al., STAT3/NF-κB signalling disruption in M2 tumour-associated macrophages is a major target of PLGA nanocarriers/PD-L1 antibody immunomodulatory therapy in breast cancer, Br. J. Pharmacol. 178 (11) (2021) 2284–2304.
[104] J. Van Den Bulk, N.F.C.C. De Miranda, P. Ten Dijke, Therapeutic targeting of TGF-β in cancer: hacking a master switch of immune suppression, Clinical Science 135 (1) (2021) 35–52.
[105] X. Kang, Y. Huang, H. Wang, et al., Tumor-associated macrophage targeting of nanomedicines in cancer therapy, Pharmaceutics 16 (1) (2023) 61.
[106] Y. Zhang, J. Yang, T. Zhang, et al., Emerging advances in nanobiomaterials-assisted chimeric antigen receptor (CAR)-macrophages for tumor immunotherapy, Front. Bioeng. Biotechnol. 11 (2023) 1211687.
[107] L. Dong, C. Chen, Y. Zhang, et al., The loss of RNA N6-adenosine methyltransferase Mettl14 in tumor-associated macrophages promotes CD8^{+} T cell dysfunction and tumor growth, Cancer Cell 39 (7) (2021) 945–957.e10.
[108] J.A. Beaver, M. Hazarika, F. Mulkey, et al., Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis, Lancet Oncol. 19 (2) (2018) 229–239.
[109] D. Ren, Y. Hua, B. Yu, et al., Predictive biomarkers and mechanisms underlying resistance to PD1/PD-L1 blockade cancer immunotherapy, Mol. Cancer 19 (1) (2020) 19.
[110] V. Prima, L.N. Kaliberova, S. Kaliberov, et al., COX2/mPGES1/PGE_2 pathway regulates PD-L1 expression in tumor-associated macrophages and myeloid-derived suppressor cells, Proc. Natl. Acad. Sci. USA 114 (5) (2017) 1117–1122.
[111] S. Mariathasan, S.J. Turley, D. Nickles, et al., TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells, Nature 554 (7693) (2018) 544–548.
[112] X. Zhang, Y. Zeng, Q. Qu, et al., PD-L1 induced by IFN-γ from tumor-associated macrophages via the JAK/STAT3 and PI3K/AKT signaling pathways promoted progression of lung cancer, Int. J. Clin. Oncol. 22 (6) (2017) 1026–1033.
[113] Y. Pu, Q. Ji, Tumor-associated macrophages regulate PD-1/PD-L1 immunosuppression, Front. Immunol. 13 (2022) 874589.
[114] X. Zhang, Z. Wei, T. Yong, et al., Cell microparticles loaded with tumor antigen and resiquimod reprogram tumor-associated macrophages and promote stem-like CD8+ T cells to boost anti-PD-1 therapy, Nat. Commun. 14 (1) (2023) 5653.
[115] J. Wang, X. Zhang, X. Ma, et al., Blockage of CacyBP inhibits macrophage recruitment and improves anti-PD-1 therapy in hepatocellular carcinoma, J. Exp. Clin. Cancer Res. 42 (1) (2023) 303.
[116] X. Liu, K. Lv, J. Wang, et al., C-type lectin receptor Dectin-1 blockade on tumour-associated macrophages improves anti-PD-1 efficacy in gastric cancer, Br. J. Cancer 129 (4) (2023) 721–732.
[117] R. Wunderlich, A. Ernst, F. Rödel, et al., Low and moderate doses of ionizing radiation up to 2 Gy modulate transmigration and chemotaxis of activated macrophages, provoke an anti-inflammatory cytokine milieu, but do not impact upon viability and phagocytic function, Clin. Exp. Immunol. 179 (1) (2014) 50–61.
[118] B. Lödermann, R. Wunderlich, S. Frey, et al., Low dose ionising radiation leads to a NF-κB dependent decreased secretion of active IL-1β by activated macrophages with a discontinuous dose-dependency, Int. J. Radiat. Biol. 88 (10) (2012) 727–734.
[119] V. Stary, B. Wolf, D. Unterleuthner, et al., Short-course radiotherapy promotes pro-inflammatory macrophages via extracellular vesicles in human rectal cancer, Journal for ImmunoTherapy of Cancer 8 (2) (2020) e000667.
[120] Y. Meng, M.A. Beckett, H. Liang, et al., Blockade of tumor necrosis factor α signaling in tumor-associated macrophages as a radiosensitizing strategy, Cancer Res. 70 (4) (2010) 1534–1543.
[121] W ru Geng, B. Ruffell, D.G. DeNardo, et al., TH2-Polarized CD4+ T cells and macrophages limit efficacy of radiotherapy, Cancer Immunol. Res. 3 (5) (2015) 518–525.
[122] J. Xu, J. Escamilla, S. Mok, et al., CSF1R signaling blockade stanches tumor-infiltrating myeloid cells and improves the efficacy of radiotherapy in prostate cancer, Cancer Res. 73 (9) (2013) 2782–2794.
[123] M.F. Almahariq, T.J. Quinn, P. Kesarwani, et al., Inhibition of colony-stimulating factor-1 receptor enhances the efficacy of radiotherapy and reduces immune suppression in glioblastoma, In Vivo 35 (1) (2021) 119–129.
[124] Z. Bian, L. Shi, K. Kidder, et al., Intratumoral SIRPα-deficient macrophages activate tumor antigen-specific cytotoxic T cells under radiotherapy, Nat. Commun. 12 (1) (2021) 3229.

[125] A. Atala, Re: CSF1R signaling blockade stanches tumor-infiltrating myeloid cells and improves the efficacy of radiotherapy in prostate cancer, J. Urol. 191 (1) (2014) 270–271.
[126] C. Becherini, A. Lancia, B. Detti, et al., Modulation of tumor-associated macrophage activity with radiation therapy: a systematic review, Strahlenther. Onkol. 199 (12) (2023) 1173–1190.
[127] F. Marchesi, Macrophages at the crossroads of anticancer strategies, Front. Biosci. 24 (7) (2019) 1271–1283.
[128] G. Germano, R. Frapolli, C. Belgiovine, et al., Role of macrophage targeting in the antitumor activity of trabectedin, Cancer Cell 23 (2) (2013) 249–262.
[129] W ru Geng, Geng W. ru, Radiotherapy alters the polarization of tumor-associated macrophage to suppress lung cancer progression via up-regulation of lincRNA-p21, Clinical Surgery Research Communications 1 (1) (2019) 1–7.
[130] L. Bjerre Knudsen, L.W. Madsen, S. Andersen, et al., Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation, Endocrinology 151 (4) (2010) 1473–1486.
[131] R.R. Yao, J.H. Li, R. Zhang, et al., M2-polarized tumor-associated macrophages facilitated migration and epithelial-mesenchymal transition of HCC cells via the TLR4/STAT3 signaling pathway, World J. Surg. Oncol. 16 (1) (2018) 9.
[132] A.M.G. Klein Tank, J.B. Wijngaard, G.P. Können, et al., Daily dataset of 20th-century surface air temperature and precipitation series for the European Climate Assessment, Int. J. Climatol. 22 (12) (2002) 1441–1453.
[133] M. Knez, B. Sladojević, N. Oblak, et al., Vloga MEDICINSKE sestre pri OBRAVNAVI otrok Z NESAMOMORILNIM samopoškodbenim VEDENJEM in spektroavtistično motnjo ter POSEBNOSTI DAJANJA ZDRAVIL na ODDELKU za otroško PSIHIATRIJO, Slovenska pediatrija, revija pediatrov Slovenije in specialistov šolske ter visokošolske medicine Slovenije 28 (4) (2021) 223–227.
[134] S. Dallavalasa, N.M. Beeraka, C.G. Basavaraju, et al., The role of tumor associated macrophages (TAMs) in cancer progression, chemoresistance, angiogenesis and metastasis - current status, Curr. Med. Chem. 28 (39) (2021) 8203–8236.
[135] T.H. Barker, G. Baneyx, M. Cardó-Vila, et al., SPARC regulates extracellular matrix organization through its modulation of integrin-linked kinase activity, J. Biol. Chem. 280 (43) (2005) 36483–36493.
[136] Y. Komohara, Y. Fujiwara, K. Ohnishi, et al., Tumor-associated macrophages: potential therapeutic targets for anti-cancer therapy, Adv. Drug Deliv. Rev. 99 (2016) 180–185.
[137] H. Lu, K.R. Clauser, W.L. Tam, et al., A breast cancer stem cell niche supported by juxtacrine signalling from monocytes and macrophages, Nat. Cell Biol. 16 (11) (2014) 1105–1117.
[138] C. Salvagno, M. Ciampricotti, S. Tuit, et al., Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response, Nat. Cell Biol. 21 (4) (2019) 511–521.
[139] M. Li, L. He, J. Zhu, et al., Targeting tumor-associated macrophages for cancer treatment, Cell Biosci. 12 (1) (2022) 85.
[140] Z. Liu, Y. Xie, Y. Xiong, et al., TLR 7/8 agonist reverses oxaliplatin resistance in colorectal cancer via directing the myeloid-derived suppressor cells to tumoricidal m1-macrophages, Cancer Lett. 469 (2020) 173–185.
[141] C. Xie, X. Zhou, C. Liang, et al., Apatinib triggers autophagic and apoptotic cell death via VEGFR2/STAT3/PD-L1 and ROS/Nrf2/p62 signaling in lung cancer, J. Exp. Clin. Cancer Res. 40 (1) (2021) 266.
[142] M. Xu, S. Zhang, L. Jia, et al., E-M, an engineered endostatin with high ATPase activity, inhibits the recruitment and alternative activation of macrophages in non-small cell lung cancer, Front. Pharmacol. 8 (2017) 532.
[143] P. Moeini, P. Niedźwiedzka-Rystwej, Tumor-associated macrophages: combination of therapies, the approach to improve cancer treatment, Int. J. Mol. Sci. 22 (13) (2021) 7239.
[144] J. Zheng, J. Jiang, Y. Pu, et al., Tumor-associated macrophages in nanomaterial-based anti-tumor therapy: as target spots or delivery platforms, Front. Bioeng. Biotechnol. 11 (2023) 1248421.
[145] J. Song, T. Xiao, M. Li, et al., Tumor-associated macrophages: potential therapeutic targets and diagnostic markers in cancer, Pathol. Res. Pract. 249 (2023) 154739.
[146] X. Su, C. Liang, R. Chen, et al., Deciphering tumor microenvironment: CXCL9 and SPP1 as crucial determinants of tumor-associated macrophage polarity and prognostic indicators, Mol. Cancer 23 (1) (2024) 13.
[147] E. Matsubara, H. Yano, C. Pan, et al., The significance of SPP1 in lung cancers and its impact as a marker for protumor tumor-associated macrophages, Cancers 15 (8) (2023) 2250.
[148] N. Cortese, R. Carriero, M. Barbagallo, et al., High-resolution analysis of mononuclear phagocytes reveals GPNMB as a prognostic marker in human colorectal liver metastasis, Cancer Immunol. Res. 11 (4) (2023) 405–420.