

Tumor-associated macrophages activated in the tumor environment of hepatocellular carcinoma: Characterization and treatment (Review)

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Abstract. Hepatocellular carcinoma (HCC) tissue is rich in dendritic cells, T cells, B cells, macrophages, natural killer cells and cellular stroma. Together they form the tumor microenvironment (TME), which is also rich in numerous cytokines. Tumor-associated macrophages (TAMs) are involved in the regulation of tumor development. TAMs in HCC receive stimuli in different directions, polarize in different directions and release different cytokines to regulate the development of HCC. TAMs are mostly divided into two cell phenotypes: M1 and M2. M1 TAMs secrete pro-inflammatory mediators, and M2 TAMs secrete a variety of anti-inflammatory and pro-tumorigenic substances. The TAM polarization in HCC tumors is M2. Both direct and indirect methods for TAMs to regulate the development of HCC are discussed. TAMs indirectly support HCC development by promoting peripheral

angiogenesis and regulating the immune microenvironment of the TME. In terms of the direct regulation between TAMs and HCC cells, the present review mainly focuses on the molecular mechanism. TAMs are involved in both the proliferation and apoptosis of HCC cells to regulate the quantitative changes of HCC, and stimulate the related invasive migratory ability and cell stemness of HCC cells. The present review aims to identify immunotherapeutic options based on the mechanisms of TAMs in the TME of HCC.

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1. Introduction

Multidimensional analysis has indicated that a special tumor microenvironment (TME) exists in liver cancer tissues (1). The study of treatment protocols for tumors in modern medicine from the perspective of cancer biology no longer considers cancer cells as the central link, but evolved from the study of cancer cells to the study of the TME in which cancer cells are located, categorizing cancer cells in the stromal cell network (2). The molecular mechanisms involved in tumor development can be elucidated by analyzing the characteristics of different cell types in the TME (3): Tumor-associated macrophages (TAMs), CD4⁺ cells, cytotoxic T lymphocytes

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(CD8⁺ cells), regulatory T cells (Tregs), dendritic cells, natural killer cells (NK cells), tumor-associated endothelial cells, cancer-associated fibroblasts (CAFs) and myeloid-derived immunosuppressive cells (MDSCs) (4). Kupffer cells (KCs) and monocyte-derived hepatic macrophages are among the innate immune-responsive cells that are widely present in the human body (5). Macrophages exert immunomodulatory effects through phagocytosis, exogenous antigen presentation, and cytokine and growth factor secretion (6).

2. TAM description

Classical macrophage phenotypes. Macrophage polarization is a process that occurs in response to changes in microenvironmental stimuli and signals. Functionally polarized subpopulations acquire substantially different functional attributes after the action of different stimuli (7). Lipopolysaccharides (LPS) and interferon- γ direct macrophage polarization towards the M1 phenotype by activating the Janus kinase (JAK)/STAT, toll-like receptor 4 (TLR4)/NF- κ B and NOTCH signaling pathways (8). The types of macrophage polarization are classified into two groups according to their functions (classically activated M1-polarized macrophages and alternatively activated M2-polarized macrophages), with different expression levels of proteins on the cell surface (9). Proinflammatory cytokines, including IL-1 β , IL-6, IL-12, IL-18, IFN- γ , inducible nitric oxide synthase (iNOS) and TNF- α , are highly expressed in M1-polarized macrophages. These cytokines also function as tumor suppressors in hepatocellular carcinoma (HCC) (10). By contrast, M2 macrophages secrete anti-inflammatory cytokines such as IL-4, TGF- β and IL-10 (11). M2 macrophages exert complex immunomodulatory functions depending on these cytokines, which possess cancer-promoting and inflammation-inhibiting effects by triggering immunosuppression (12). M2 polarization is induced by factors that activate the TGF- β /Smads and peroxisome proliferator-activated receptor γ (PPAR γ) signaling pathways, such as TGF- β and growth differentiation factor 3 (13). M2 macrophages induced by diverse stimulatory factors are further subdivided into four types: M2a, M2b, M2c and M2d (14).

The M4 macrophage phenotype is induced by chemokine C-X-C motif ligand (CXCL)4 in atherosclerosis, and characterized by MMP7, CD68 and S100 calcium binding protein A8 expression (15). Hemoglobin and oxidized phospholipids polarize M0 macrophages to hemoglobin-stimulated macrophages and Mox macrophages (16). Mantovani *et al* (17) hypothesized that regulatory M3 macrophages are a bridge for the mutual transformation of M1 and M2 macrophages. Fig. 1 shows a summary of the directions of macrophage polarization.

Regulation of macrophage polarization by HCC cells. Hypoxic conditions in the HCC TME inhibit the xanthine oxidoreductase (XOR)/isocitrate dehydrogenase (NAD (+)) 3 catalytic subunit α (IDH3 α) axis of TAMs and increase the ratio of M2 TAMs to total TAMs (18). Hematopoietic stem cells (HSCs) are induced to differentiate into CAFs in HCC (4). The expression levels of IL-6, which is associated with the polarization of the M0 cell phenotype to the M2 phenotype, are increased in CAFs-conditioned medium compared with

HSCs. In addition, high levels of CXCL12 expression by CAFs regulate the expression of plasminogen activator (PA) inhibitor-1 (PAI-1) in polarized M2 TAMs by specifically binding to C-X-C chemokine receptor type 4 (CXCR4) on the macrophage surface (19). Angiopoietin (Ang)-like protein 8 (ANGPTL8) is expressed in HCC cells and ANGPTL8 expression is positively associated with the degree of malignancy of HCC. The interaction of ANGPTL8 with the leukocyte Ig-like receptor subfamily B/paired Ig-like receptor results in the inhibition of the M1 polarization and promotes the polarization towards the M2 phenotype of TAMs (20). A related study using HCC as a model has indicated that iron restriction due to HCC activates TAM polarization towards the M2 phenotype. TAMs in HCC exhibit upregulated expression levels of the apolipoprotein C1 (APOC1) gene. APOC1 inhibition activates apoptosis in TAMs, reverses the M2 phenotype to the M1 phenotype and alters the phenotypic proportion of TAMs in HCC (21). Metabolism-related RNA expression in HCC is an important regulator of the activation of TAM polarization. Long non-coding RNAs (lncRNAs/lncs), microRNAs (miRNAs/miRs) and circular RNAs (circRNAs/circs) are regulated by gene expression to alter the polarization of TAMs (22,23). lncRNA is a type of RNA that is >200 nucleotides long and does not encode proteins (24). ZNNT1 is a lncRNA, and its high expression is associated with the infiltration of M2-polarized macrophages, promoting HCC cell proliferation, migration and invasion, and inhibiting HCC cell apoptosis (25). S100A9 secreted by M2 macrophages upregulates ZNNT1 expression in HCC cells through the activation of advanced glycosylation end-product specific receptor (AGER)/NF- κ B signaling, a process that is related to the regulation of ZNNT1 transcript stability by m⁶A modification (26). MEG3 lncRNA is widely distributed in a range of solid tumors. Its silencing promotes drug resistance in various malignant tumors (27,28). Human antigen R (HuR), also known as embryonic lethal anomalous visual-like 1, is an RNA-binding protein (29). Chemokine (C-C motif) ligand (CCL)5, also known as RANTES, participates in inflammatory and immune responses as a chemokine. HuR is a target RNA of MEG3 and inhibits CCL5 expression in bone marrow-derived macrophages by suppressing CCL5 transcription and promoting M2 macrophage polarization. MEG3 inhibits HuR expression in M1 and M2 macrophages, leading to a change in the direction of macrophage polarization (30,31). Thus, MEG3 regulates HuR at the post-transcriptional level in HCC, being a potential therapeutic target for liver disease (32). Furthermore, lncRNA MEG3 is linked to miR-145-5p in HCC cells, and MEG3 overexpression leads to a decrease in miR-145-5p mRNA expression. High miR-145-5p expression is positively associated with M2 macrophage polarization. DAB adaptor protein 2 (DAB2) is a downstream target of miR-145-5p, and DAB2 upregulation is a hallmark of M1 polarization. MEG3 inhibits M2 macrophage polarization through the upregulation of DAB2 (33). Insulin like growth factor 2 mRNA binding protein 3 (IGF2BP3) is highly expressed in human solid tumors and promotes the differentiation, proliferation, invasion and metastasis of HCC cells (34). When highly expressed, it binds to the mRNAs of CCL5 or TGF- β 1 in HCC cells, promotes the secretion of cytokines, and induces macrophage M2 polarization. IGF2BP3 knockdown combined with anti-CD47

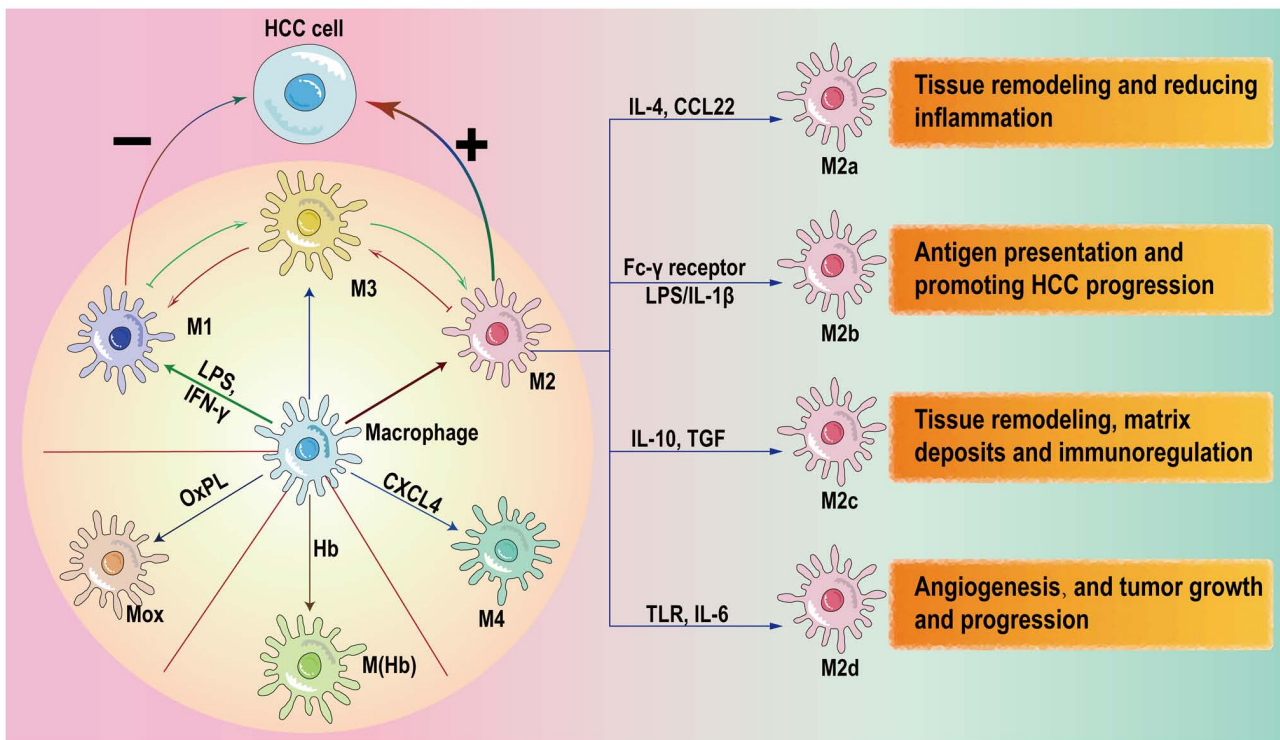


Figure 1. Classical macrophage phenotypes. Macrophages have M1, M2, M3, M4, M(Hb) and Mox polarization phenotypes. The M1 and M2 phenotypes are the two main macrophage polarization phenotypes. M3 macrophages are an intermediate phenotype that bridges the interconversion between M1 and M2 macrophages. Macrophages are referred to as TAMs in the tumor microenvironment. TAMs can also be divided into M1 and M2 subtypes. Pre-tumor macrophages polarize to the M1 subtype and inhibit tumorigenesis and progression, while more macrophages polarize to the M2 subtype in the later stages and exert pro-tumorigenic effects. M1 macrophages are mainly induced by LPS and IFN- γ . M2 macrophages are stimulated by different regulatory factors and differentiate into four subtypes: M2a, M2b, M2c and M2d. IL-4 and CCL22 are responsible for M2a macrophage polarization, and M2a macrophages focus on tissue remodeling and reducing inflammation. Fc- γ receptor and LPS/IL-1 β cause M2b macrophage polarization, and M2b macrophages serve a role in antigen presentation and promoting HCC progression. M2c macrophages are polarized by TGF and IL-10 and have functions in matrix deposits and immunoregulation. TLR and IL-6 drive M2d macrophage polarization, and M2d macrophages contribute to angiogenesis, and tumor growth and progression. CXCL4 can drive macrophage polarization toward the M4 phenotype. In Hb and OxPL pathological tissue, macrophages are polarised to M(Hb) and Mox, respectively. CCL22, C-C motif chemokine ligand 22; CXCL4, chemokine C-X-C motif ligand 4; M(Hb), hemoglobin-stimulated macrophage; HCC, hepatocellular carcinoma; LPS, lipopolysaccharide; OxPL, oxidized phospholipid; TAMs, tumor-associated macrophages; TLR, toll-like receptor.

therapy slows down tumor growth (35). A combination of *in vivo* and *in vitro* experiments revealed the role of IGF2BP3 as a specific migration factor in HCC (36). Evidence indicates that circRNAs absorb miRNAs via the 'sponge adsorption' effect and interact with RNA-binding proteins. circ_0010882 is an upstream regulatory factor of miR-382. circ_0010882 silencing inhibits M2 macrophage polarization by targeting miR-382 (37). miR-21-5p in HCC cell exosomes affects SP1/X-box binding protein 1 (XBP1) protein expression and promotes M2 polarization in TAMs (38).

The upregulation of tripartite motif containing 65 (TRIM65) is associated with the high grading of HCC tumors (39). The JAK1/STAT1 signaling pathway is activated and the expression of pro-inflammatory M1 markers is increased in TAMs after culturing with conditioned medium from the supernatant of Hep1-6 cells with TRIM65 knock-down. This suggests that TRIM65 could serve as a unique tumor immunotherapeutic target (40). Although *in vivo* and *in vitro* experiments have validated the therapeutic efficacy of targeting TRIM65 in the treatment of HCC, there is no evidence that has associated the effect of TRIM65 knockdown on HCC with its distribution in macrophages (41). Zinc-fingers and homeoboxes 2 is a regulator of a number of liver-enriched genes and it maintains macrophage polarization by regulating

interferon regulatory factor (IRF)1 transcription, which could therefore be a potential target for macrophage-based cancer immunotherapy (42). CCL16 is a factor with strong chemotactic properties. C-C chemokine receptor type 1 (CCR1) is a receptor that positively regulates the extent of M2 TAM infiltration in HCC. CCL16 produced by hepatocytes in the normal liver binds to CCR1 expressed by human KCs. Cancer cells bind to the CCR1 receptor on macrophages and release CCL16 to increase the number of CD68⁺ CCR1⁺ cells, which induces M2 polarization in TAMs (43). Auxiliary proteins are involved in IL-4-induced M2 polarization. Major vault protein (MVP) is the main component in vault nanoparticles. Its expression is increased in HCC compared with that in the normal liver (44). IL-4 activates the dimerization of IL-4 receptor (IL-4R) α and γ chains by binding to the macrophage surface receptor IL-4R. Activation of the JAK1/STAT6 signaling pathway increases the M2 polarized subtype of TAMs (45). MVP interacts with JAK1 and recruits STAT6 to form the ternary complex JAK1/MVP/STAT6, which enhances IL-4-induced STAT6 activity. The degree of infiltration of M2 TAMs is increased in HCC with high MVP expression (46). xCT (encoded by SLC7A11) is a heavy chain subunit of the system x that provides a nutrient environment for tumor development by reducing glutathione biosynthesis and antioxidant defense

Table I. Rough classification of factors that activate macrophage polarization in HCC tissues according to specificity.

Polarization factors unique to HCC	Co-polarizing factors in tumors
lncRNA ZNNT1, miR-21-5P, miR-382, IRF1, CCL9, ANGPTL8, IGF2BP3	lncRNA MEG, IL-6, IL-4, IL-10, IL-12, IL-18, CXCL12, TGF- β , IFN- γ

ANGPTL8, angiopoietin-like protein 8; CCL9, chemokine (C-C motif) ligand 9; CXCL12, chemokine C-X-C motif ligand 12; HCC, hepatocellular carcinoma; IGF2BP3, insulin like growth factor 2 mRNA binding protein 3; IRF1, interferon regulatory factor 1; lncRNA, long non-coding RNA; miR, microRNA.

in tumor cells. xCT activates the suppressor of cytokine signaling 3/STAT6/PPAR γ signaling axis and regulates the pro-tumorigenic M2-like phenotypic shift in the TME caused by IL-4 (47). Therefore, xCT knockdown in macrophages inhibits the pro-tumorigenic phenotypic activation of IL-4. In addition to IL-4, STAT6 mediates M2 cell polarization via different mechanisms of activation (48). Myeloid differentiation factor 88 (MyD88) is a ligand for TLR and activates a pro-inflammatory cascade, while it promotes CCL9/CCL15 secretion in HSCs, which enhances M2 polarization in macrophages via the activation of the STAT6/PPAR β signaling pathway in HCC cells (49). Specific deletion of MyD88 in myofibroblasts reduces the secretion of CCL9, a macrophage inflammatory protein, in nonalcoholic fatty liver disease-associated HCC (50). STAT3, another component of the STAT family, is also involved in the regulation of TAM polarization in HCC (51). The proteasome subunit α (PSMA) family of proteins mediates the synthesis of the 20S proteasome core complex and is present in exosomes secreted by metastatic HCC tissues (52). PSMA5 is a member of the PSMA family of proteins, and differences in its expression are critical for tumor growth and development. PSMA5 is activated after the activation of JAK2 and JAK1 in TAMs (53). M2 macrophages receive exosomes from HCC tissues (54). Formimidoyltransferase cyclodeaminase (FTCD) mediates enzymatic reactions and cellular biofilm ligation in tumor cells. As a downstream target of hypoxia-inducible factor-1 α (HIF-1 α), FTCD-stimulated macrophages are polarized toward the M1 type, and M1 TAMs secrete pyruvate kinase M2 (PKM2) to inhibit HCC cell proliferation (55). Macrophage glucose metabolism is also a factor inducing M2 polarization in TAMs in the TME. XOR mediates the regulation of α -ketoglutarate (α -KG) synthesis and mediates the activation of an M1 promoter in macrophages (NLR family containing pyrin structural domain 3), leading to increased IL-1 β expression (56). Tumor cells suppress XOR mRNA and protein expression in macrophages. In macrophages, XOR binds to the active structural domain of IDH3 α . IDH3 is a regulatory enzyme in the tricarboxylic acid cycle and is involved in the catalytic synthesis of α -KG (57). XOR knockdown in macrophages mediates the regulation of IDH3 activity, leading to an increase in α -KG, and activation of IDH3 α / α -KG/jumonji domain containing 3 signaling, thus enhancing M2 polarization (18). There are numerous factors that activate macrophage polarization in HCC. Table I shows the classification of polarization factors based on whether they also promote macrophage differentiation in other tumor tissues.

3. Direct modulation of the HCC TME by TAMs

Role of TAMs in regulating cancer stem cell (CSC) differentiation in HCC. Primary liver cancer includes HCC, intrahepatic cholangiocarcinoma (iCCA) and combined HCC-CCA (cHCC-CCA). IgGfC-binding protein⁺ secreted phosphoprotein 1 (SPP1)⁺ TAMs are mainly observed in primary HCC and are commonly distributed in areas of HCC and iCCA, and the poorly differentiated areas in cHCC-CCA. The necroptotic apoptotic microenvironment is associated with HCC differentiation, and IgGfC-binding protein⁺ SPP1⁺ TAMs promote HCC to gradually acquire CCA features, which are important for intrahepatic biliary metastasis of HCC cells (58).

CSCs in the TME are a type of self-renewing undifferentiated cells with tumorigenic and stem cell-like characteristics (59). CSCs are essential for tumor development and migration (60). Stemness markers, including NANOG, OCT4, SOX2, MYC oncogene and krüppel-like factor 4 (KLF4), are essential transcription factors in the pluripotent stemness of CSCs (61). M2 TAMs act as a 'HCC stemness regulatory complex' by secreting VEGFA, integrin subunit β 3 binding protein and ADAM metalloproteinase domain 9 ligands (62,63). The CXCL12-integrin subunit β 1 and VEGFA-integrin subunit α V pairs in M2 TAMs are involved in the initiation of tumor cells and the stem-like properties of OV6 CSCs, which are important assistants in the stemness of HCC (64).

TAMs produce IL-6, which promotes the expansion of these CSCs and tumorigenesis (65). Exploiting the interaction between TAMs and CSCs in HCC represents a novel approach for the development of tumor suppressors. S100 calcium binding protein A4 (S100A4) and collagen I enhance HCC stem cell properties by relying on the receptor for advanced glycation endproducts/ β -catenin signaling pathway. S100A4⁺ macrophages are a subtype of M2 macrophages in HCC tissues (66). The stemness markers Oct-4, Nanog, CD133, SOX2 and CD44 are upregulated in HuH7 liver cancer cells after stimulation by S100A4. *In vivo* experiments suggest that S100A4 knockdown in a mouse model of HCC decreases the level of CSC markers (67). S100A9, also belonging to the S100 family, is a common factor expressed in exosomes of TAMs and CSCs. S100A9 stimulates CCL2 and tumor stemness-related gene production via the AGER/NF- κ B signaling pathway in HepG2 and MHCC-97H cells. In addition to the effect of S100A9 expressed by TAMs in malignancy development, S100A9 in the TME serves a role in the recruitment and polarization of TAMs (68).

A sharp drop in the size of subcutaneous tumors in a tumor mouse model was observed after intracardiac injection of HCC cells co-cultured with M2 TAMs. Furthermore, co-culture of HCC cells with M2 TAMs resulted in a decrease in the expression levels of characteristic stem cell surface markers of HCC cells, including CD133, master transcription factors Oct-4 and SOX-2, N-cadherin, and vimentin. The *in vitro* approach revealed that TNF- α secreted by M2 TAMs activated the Wnt/ β -catenin signaling pathways, leading to epithelial-to-mesenchymal transition (EMT) and the stemness features of HCC (69).

TGF- β 1 is a central regulator of inflammation and liver cancer (70). RAW264.7 macrophages are induced to differentiate into M2 macrophages by IL-4, resulting in an increase in TGF- β 1 expression, which is linked to the action of the TGF- β 1/Smad signaling pathway for EMT and the levels of Bmi1 and KLF4, which are two genes characterizing HCC stem cells (71,72). TGF- β type II receptor gene (TGFB2) is the receptor of TGF- β 1 and TGF- β 2 (73). TAMs increase lncRNA H19 expression by regulating TGFB2, downregulating miR-193b expression in HCC cells. Finally, MAPK1 signaling is activated, regulating the EMT pathway and the conversion of non-CSCs to CSCs (74).

Role of TAMs in regulating the proliferation and apoptosis of HCC cells. The properties of HCC cells depend on the stimulation of various components in the TME, especially cytokines, chemotactic cytokines and exosomes. IL-6 is a critical cytokine for HCC cell proliferation (75). There are numerous cells in the TME secreting the inflammatory factor IL-6 (76). By contrast, the scavenger receptor cysteine-rich type 1 protein M130 activates CD163⁺ TAMs, a type of M2 TAMs expressing IL-6. This effect in the HCC TME involves the IL-6/STAT3 signaling pathway activated by M2 TAMs and their exosomes (77).

Autophagy protects the viability of cells and maintains the steady state of cells (78). Macrophage autophagy has the dual function of inhibiting and promoting tumor growth in the TME. The PI3K/Akt/mTOR signaling pathway is a classical pathway in autophagy. M2 TAMs are involved in the activation of this pathway in HCC cells, resulting in the inhibition of M2 TAM autophagy (79). miRNA-210 is an autophagy agonist acting on the downregulation of PI3K/Akt/mTOR signaling in macrophages, as a consequence of which, M2 TAMs increase the expression levels of IL-10 and TGF- β 1, promoting HCC cell proliferation (80).

The proliferation of HCC cells is also associated with the cell cycle. M2 TAMs induced by CAFs regulate the HCC cell cycle directly by inducing PAI-1 expression. PAI-1 downregulates FAS and Fas ligand, resulting in the decrease of the antiapoptotic abilities of liver cancer cells and in the promotion of HCC (19). Extracellular ubiquitin (eUb) regulates cell apoptosis with the assistance of TAMs. eUb is not a regulator of TAM activation and polarization. The absence of TAMs affects the effect of eUb in regulating HCC cell apoptosis. After inhibition by the pro-inflammatory factor TNF- α released by M1 TAMs, HCC cells receive the signal from eUb. and activate the Akt/mTOR signaling pathway and suppress apoptosis (81). In addition, large tumor suppressor kinase 1 activates the Hippo signaling pathway in HCC cells. The

Hippo signaling pathway is critical for cell apoptosis and mitochondrial damage (82). Arsenate induces M2-type polarization of macrophages by inducing miR-15b expression to inhibit HCC cell apoptosis activated by LAST1 (83). Upregulation of the EZH2-associated lncRNA HEIH is associated with poor prognosis in patients with HCC. HEIH promotes macrophage M2 polarization by targeting the miR-98-5p/STAT3 axis, and promotes tumor growth and metastasis induced by M2 TAMs (84). Lysosomal acid lipase (LAL) inhibition leads to the accumulation of cellular lipid content and reduces the expression levels of CD36 and ATP binding cassette subfamily a member 1 in macrophages. LAL inhibition slows down monocyte cholesterol metabolism, which reduces the number of M2 TAMs and decreases the HCC tumor growth-promoting axis in which M2 TAMs are involved (85).

M1 TAMs polarized by the signal NORCH-recombination signal binding protein for immunoglobulin κ J region (RBPJ) release exosomes with high RBPJ expression. Hsa-cir-004658 in RBPJ+/+exosome secreted by M1 TAMs is involved in the miR499b-5p/junctional adhesion molecule 3 signaling pathway and promotes the apoptosis of liver cancer cells, while it inhibits the increase in the number of HCC cells (86). Under the stimulation of hepatoma cells, macrophages increase the expression of the classical M1 TAM chemotactic cytokine interleukin-8 (CXCL8) (87). CXCL8 facilitates HCC cell proliferation by changing the percentage of miRNA-17, which is a potent proliferative molecule in the miRNA clusters (88). TAM cell glycolysis in HCC is involved in the proliferative ability of HCC (89). The glycolytic enzymes 6-phosphofructo-2-kinase, hexokinase 2, triose-phosphate isomerase, PKM2, glucose transporter type 1 and lactate dehydrogenase A negatively regulate the apoptosis of H22 tumor cells. Dectin3, a C-type lectin-like receptor, increases HCC cell proliferation by activating cell glycolysis (90,91). HCC cells undergo circ fucosyltransferase 8 (FUT8) m6A modification mediated by METTL14, which promotes the translocation of circFUT8 to the cytoplasm and the recognition of the specific protein YTH N6-methyladenosine RNA binding protein C1, and positively regulates the tumor growth cycle. M1 TAMs competitively bind cytoplasmic circFUT8 through the exosomal miR-628-5p to inhibit HCC progression (92).

Role of TAMs in regulating the invasion and metastasis of HCC cells. According to several studies, the polarized orientation of TAMs in the TME is closely associated with the invasive and metastatic ability of HCC cells through the regulation of multiple signaling pathways (5,43,45,93). M2 TAMs activate the ability of HCC cells to invade and migrate (5). M1 type macrophages antagonize the action of M2 type macrophages by inhibiting HCC progression (9). EMT is an important process in cancer progression, and the prediction of cancer cell metastasis based on the expression of EMT markers is a well-established and effective method (11).

M2 TAM secretion of the cytokines CXCL12, CXCL16, epidermal growth factor (EGF), CCL18 and CCL22 enhances the invasion of HCC cells (94,95). The level of macrophage-derived chemokine (MDC)/CCL22 secretion is increased in M2 TAMs (96). CCL22 selectively interacts with C-C motif chemokine receptor 4, and is involved in the direct activation of EMT in HCC cells (95). In a previous

study, the further away the colony-stimulating factor (CSF)-1 receptor (CSF-1R) was from the peri-carcinoma tissue, the less expressed it was. The main drawback of the study was that it did not specifically investigate the mechanisms associated with CSF-1 affecting intrahepatic metastasis of tumors (97). High CSF-1R expression in peritumoral HCC tissues results in an increase in macrophage infiltration in HCC through CSF-1, affecting the intrahepatic metastasis of tumors. Specifically, CSF-1 mediates the upregulation of AIF1 in M0 macrophages, induces M2 macrophage polarization and increases the secretion of the cytokine CXCL16, thereby leading to the migration of Hepa1-6 cells (98). M2 TAMs secrete IL-8, activate the JAK2/STAT3/Snail signaling pathway, upregulate the expression of the mesenchymal marker N-cadherin and are involved in the induction of EMT in the HepG2 cell line (99). TGF- β -treated M2 TAMs upregulate the expression of T cell immunoglobulin and mucin structural domain-containing protein-3, activate the NF- κ B signaling pathway, upregulate the expression of the classical cytokines IL-6, colony stimulating factor 2 (CSF2) and IL-10, and promote tumor migration (100,101). GSK3 β is upregulated in macrophages, which in turn activates the NF- κ B pathway-mediated direction of M2 TAM polarization, and upregulates the secretion of STAT1, CCL5, IL-6 and CSF2 in macrophages, promoting HCC metastasis and invasion (102). The activation of the STAT3 signaling pathway in HCC cells mediated by the secretion of IL-6 by M2 TAMs is necessary for HCC invasion and metastasis (103). Clinicopathological analysis has revealed that CD163-positive macrophages aggregate around STAT3-positive HCC cells. M2 TAMs activate the STAT3 tyrosine phosphorylation (p-STAT3) signaling pathway through IL-6 upregulation and participate in HCC cell migration and invasion (104,105). The expression of the homologous heterotrimeric transcription factor sine oculis homeobox homolog 1 (SIX1) is increased in tumor tissue TAMs (106). Co-culture of macrophages with high SIX1 expression with HCC cells increases the levels of p-STAT3, HCC cell migration and invasion, and the extent of EMT. Specifically, in HCC, macrophages alter the transcriptional level of the p65 gene in the nucleus, increase IL-6 secretion, activate the STAT3 signaling pathway in HCC cells, and lead to an increase in MMP-9 expression through upregulation of SIX1 expression, regulating the migration, invasion and EMT of HCC cells (107). A study has demonstrated that MMP-9 degrades the extracellular matrix (ECM) at an early tumor stage and is a classical pro-metastatic invasive factor for HCC cells (108). Furthermore, M2 TAM exosomes participate in HCC metastasis by activating the TLR4/STAT3 signaling pathway (109,110).

Exosomes work as a messaging link for TAMs to regulate the extent of the invasive migration of HCC cells (111). The ratio of CD11b/CD18 is increased in M2 macrophage exosomes. CD11b/CD18 upregulates MMP9 expression in HCC cells, and mediates the metastatic invasion of HepG2 and Huh7 cells (112). Integrins are proteins that regulate the function of HCC cells. Upregulation of integrins in HCC regulates tumor cell proliferation, metastasis, invasion and survival (113). S100A4 secretion by M2 TAMs regulates ECM remodeling in the TME via the ERK signaling pathway (65). The heterogeneous nuclear ribonucleoprotein A1 in M2 TAMs

is a component of miR-23a-3p-containing exosomes, and the formed exosomes mainly act on the targets PTEN and tight junction protein 1 in HCC, leading to the secretion of CSF2, VEGF, granulocyte-colony stimulating factor, monocyte chemoattractant protein-1 (MCP-1) and IL-4, accelerating the EMT process in HCC cells (114).

By contrast, miR326 expression is abundant in the exosomes of M1 TAMs and is involved in the tumor-suppressive effects of M1 TAM exosomes. Specifically, HCC cells receive exosomes from M1 macrophages, and miR326 in the exosomes decreases the expression levels of twist family BHLH transcription factor 1 in HCC cells, hindering the metastatic invasion of HCC (115). lnc-Ma301 expression is higher in M1 TAMs than in M2 TAMs, but lower in HCC tissues. lnc-Ma301 is an inhibitor of the invasive migration of HCC cells in mouse HCC lung metastasis. lnc-Ma301 regulates the Akt/Erk1 signaling pathway downstream proteins by silencing caprin1, and inhibits the migration and invasion HCC cells, as well as the EMT (116). M2 TAMs secrete the cytokines IL-6, TNF- α , CSF2 and intercellular cell adhesion molecule-1 to mediate the Akt/proline-rich Akt substrate of 40 kDa signaling pathway and activate EMT in interstitial cells of Cajal. Akt inhibitor VII has a reversal effect on the aforementioned cytokines, upregulating EMT markers (117). This mechanism provides a potential approach for Akt-targeted therapy, which might turn into a main method to cure HCC. Fig. 2 shows the mechanistic process of the crosstalk of HCC cells and TAMs.

4. Indirect control of HCC development by TAMs

Role of TAMs in promoting angiogenesis of HCC. The angiogenesis of new blood vessels is necessary to supply oxygen and nutrition, and remove carbon dioxide and other metabolic waste during the proliferation and migration of tumor cells. The formation of new blood vessels and recruitment of pre-existing vessels are two main causes of vascular hyperplasia in the tumor (118). There is a positive relationship between the increase in macrophage numbers and high micro-vessel density. The recruitment of TAMs stimulated by hypoxia is associated with a wide range of roles in the formation of new blood vessels. After stimulation by hypoxia, TAMs secrete vascular endothelial growth factor, which binds to receptors, and promote the movement and direct migration of endothelial cells (114). Subsequently, TAMs, regulated by HIF-1 α in the hypoxic lactate-enriched TME, express multiple genes for the fine-tuning of the polarized M2 macrophage phenotype and secrete several proangiogenic factors to activate pro-angiogenic signaling pathways in HCC (119). M2 TAMs produce miR-23a-3p-containing exosomes that are taken up by HUVECs, leading to their migration to form new blood vessels (114).

M2d macrophages are the main pro-angiogenic phenotype in HCC. They form numerous new blood vessels through the secretion of several vasoactive substances, such as VEGF-A, EGF, placenta growth factor (PIGF), TGF- β , TNF- α , IL-1 β , IL-8, CCL2, CXCL8, CXCL12, MMP2, MMP9, MMP12, thymidine phosphorylase (TP), cathepsins and Plas (120,121). HCC TAM infiltration into tissues inhibits the antiangiogenic factors endostatin and angiostatin, while it upregulates the expression of angiogenic factors. VEGFs serve a dominant

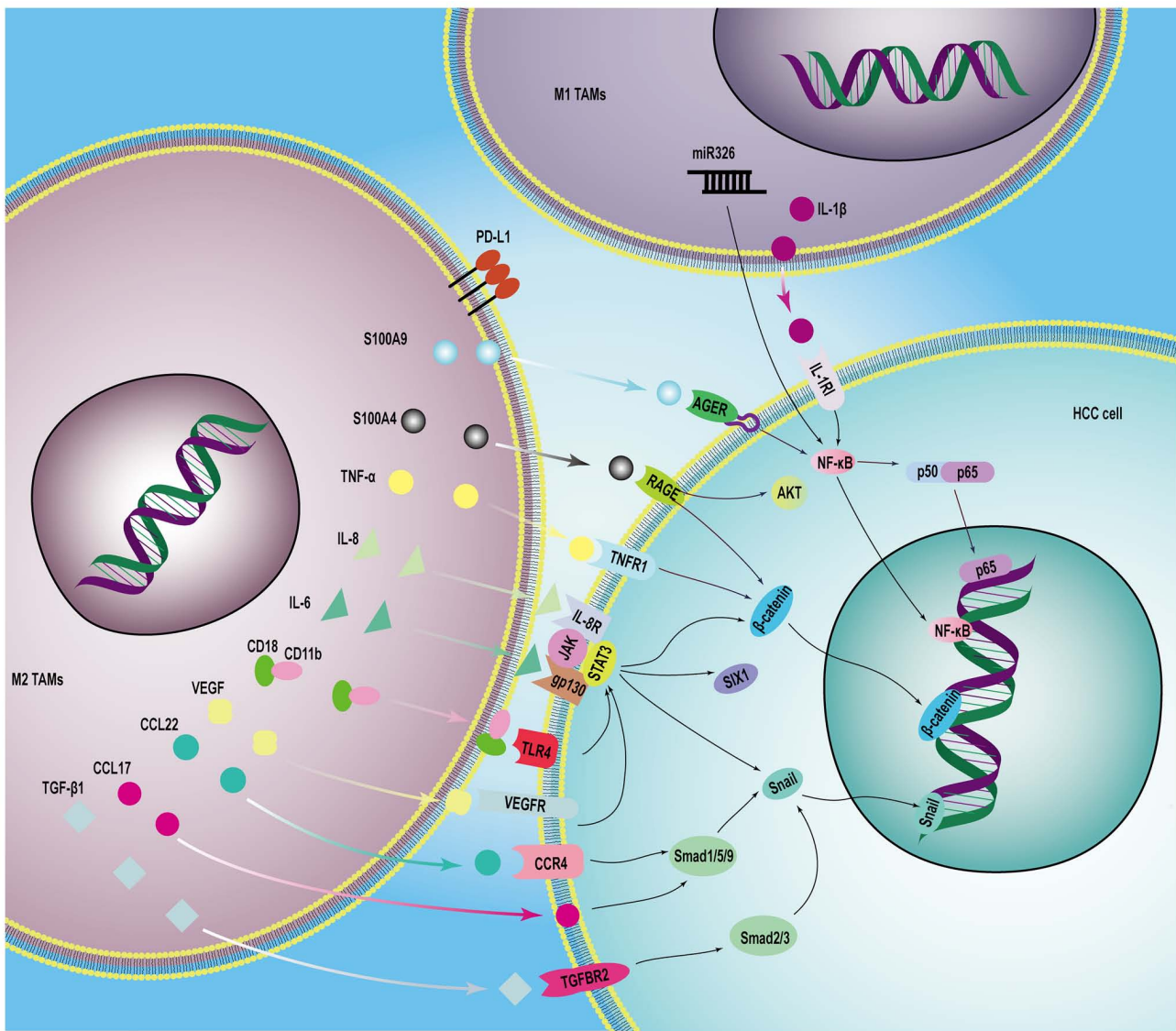


Figure 2. Direct modulation of the HCC tumor microenvironment by TAMs. Molecular mechanisms by which TAMs affect HCC cells. M1 TAMs mainly act to control hepatocarcinogenesis. M2 TAMs can enable faster adaptation of HCC cells to the tumor microenvironment through activation of multiple complexes and signaling pathways in HCC cells. AGER, advanced glycosylation end-product specific receptor; CCL17, C-C motif chemokine ligand 17; CCL22, C-C motif chemokine ligand 22; CCR4, C-C motif chemokine receptor 4; HCC, hepatocellular carcinoma; JAK, Janus kinase; miR, microRNA; PD-L1, programmed death ligand 1; RAGE, receptor for advanced glycation endproducts; S100A4, S100 calcium binding protein A4; S100A9, S100 calcium binding protein A9; SIX1, sine oculis homeobox homolog 1; TAMs, tumor-associated macrophages; TGFBR2, TGF- β type II receptor gene; TLR4, toll-like receptor 4; TNFR1, TNF receptor superfamily member 1A.

role in promoting tumor angiogenesis (122,123). The VEGF family is comprises five members: VEGF-A, VEGF-B, VEGF-C, VEGF-D and PlGF. Increased lncRNA-cyclooxygenase-2 (COX2), H3-AS1 and MALAT1 levels are present in malignant liver tumors (124). These lncRNAs are the messengers for the increase in the proportion of M2-like TAMs, and the density and growth of tumor vessels (125). TAMs activate the STAT3 signaling pathway to stimulate VEGF expression in liver cancer cells through the regulation of B7-H3 expression (126). VEGFs are involved in tumor angiogenesis after being secreted, and bind to the cognate receptors VEGFR-1, VEGFR-2, VEGFR-3 and recombinant neuropilin protein (127). The proteolytic modification of the ECM, contributing to the degradation of the vascular basement membrane, relies on MMPs, TP, cathepsins and PA, which promote liver fibrosis and angiogenesis (128). Urokinase-type

PA and TP found in the TAM tumor-promoting secretions increase the perivascular space (129).

In addition to the classical angiogenic factor VEGF, the TME contains other angiogenetic factors, including the S100 protein family, semaphorin (SEMA) family, COX-2, SPP1, secreted protein acidic and rich in cysteine, chitinase-like proteins found mainly in cartilage and connective tissues [chitinase 3-like-2 and chitinase 3-like-1 (YKL-40)] and Tie-2. These cytokines mainly target TAMs, increase their infiltration in HCC and are involved in the increase of proangiogenic factor expression (130-132). For example, S100 calcium binding protein, frequently identified at the site of tissue injury, is associated with the recruitment of inflammatory cells, regulating the inflammatory microenvironment and remodeling vessels (133). In addition, inhibition of the SEMA3A/neuropilin 1 signaling pathway inhibits the high

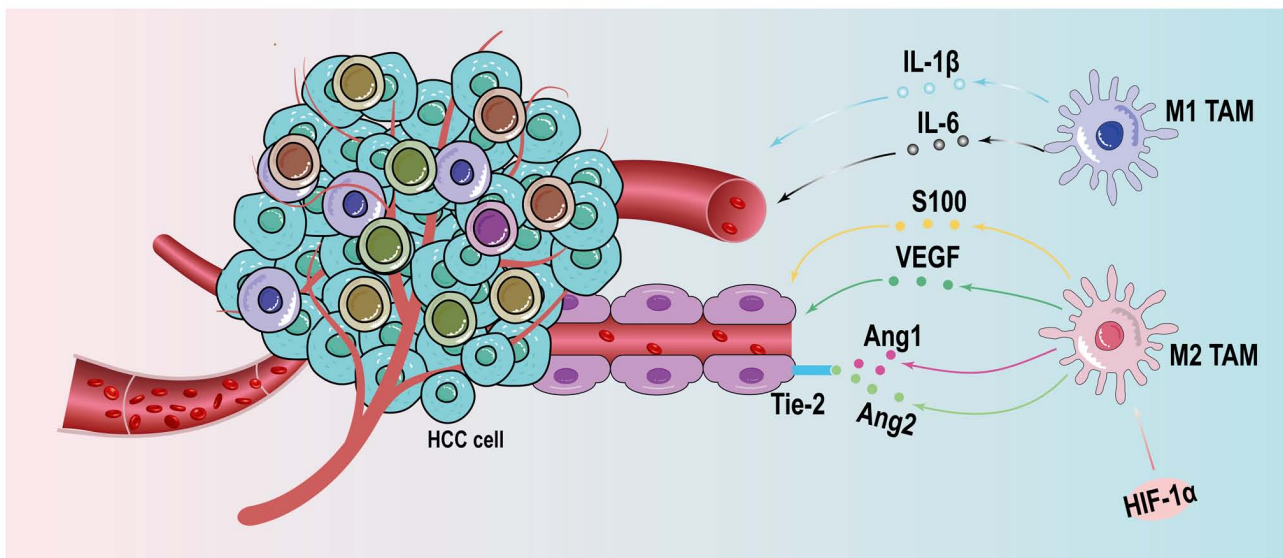


Figure 3. Role of TAMs in promoting angiogenesis of HCC. The indirect regulation of HCC tissues by TAMs mainly lies in the suppression of immune system function and pro-angiogenesis. In terms of angiogenesis, TAMs receive stimulation from HIF-1 α in the tumor microenvironment, and act on endothelial cells and mediate tumor angiogenesis via S100, VEGF, Ang1 and Ang2. Ang, angiopoietin; HCC, hepatocellular carcinoma; HIF-1 α , hypoxia-inducible factor-1 α ; TAM, tumor-associated macrophage.

level of TAM infiltration response to the hypoxic microenvironment in HCC (134). Furthermore, the increase in the number of TAMs results in increased YKL-40 protein expression in HCC precancerous tissue sections (135). Tie-2-expressing TAMs, a special subtype of TAMs, are involved in the sustenance of the tumor vasculature by regulating the Ang-2/Ang-1 ratio, thus exerting pro-angiogenic effects (136). However, VEGF-A takes part in the functional transformation of the pro-angiogenic effects of Ang-2 that leads to the degeneration of blood vessels (137).

C-C motif chemokine receptor 2 (CCR2), the chemokine receptor of CCL2, is essential for the recruitment of TAMs. The inhibition of the MCP-1-CCR2 (CCL2-CCR2) axis reduces the TAM (CCR2⁺) response and suppresses angiogenesis, controlling the development of HCC. CCR2⁺ TAMs, which are deprived of most of the properties of M2-type macrophages, are a novel M1-type macrophage. The high level of CCR2⁺ TAM infiltration in the boundaries of HCC increases the liver blood volume and pathogenic neoangiogenesis (138). In addition, M1 TAMs are involved in the NF- κ B, STAT3 and activator protein-1 (AP-1) signaling pathways in HCC cells through the production of inflammatory cytokines (IL-1 β and IL-6). M1 TAMs activate an angiogenic response, which is one of the antitumoral proinflammatory effects (139). Fig. 3 shows the effect of TAMs on angiogenesis in HCC. Table II shows the key differences in the molecular mechanisms by which TAMs directly vs. indirectly regulate HCC progression.

Role of TAMs in regulating the immune environment of HCC cells. TAMs inhibit effector T cell activation and proliferation through bidirectional effects. Mitochondrial autophagy regulates cellular energy metabolism by changing the mitochondrial DNA copy number (5). Autophagy maintains the basic cellular function of keeping oxidative phosphorylation nutrient levels stable, which is essential for tumor maintenance

and progression (140). Mitochondrial function and β -oxidation production are the main energy sources for the pro-tumorigenic effects of Tregs or M2 TAMs. Upregulation of arginase 1 and IL-10 in M2 TAMs enhances mitochondrial autophagy due to polyamines, which in turn enhances the metabolic energy supply of the cell and promotes the formation of an immune-suppressive HCC microenvironment, leading to T cell depletion and NK cell inactivation, thus inhibiting the progression of HCC (141). Liu *et al* (142) investigated a novel immunotherapeutic mechanism. It was based on a reductive reactive nanoplatfrom consisting of poly (disulfide amide) and a lipid-poly (ethylene glycol) shell, which repolarizes TAMs to M1 TAMs via IFN γ and sialic acid binding Ig like lectin 15 (Siglec15) small interfering RNA. Siglec15 silencing in the repolarized TAMs enhanced CXCL9 secretion, increased T cell proliferation and infiltration, and created a tumor immunosuppressive microenvironment. Resiquimod (R848) is a novel TLR7/8 agonist, which repolarizes M2 TAMs to M1 TAMs via the TLR7 MyD88-dependent signaling pathway. Cell microparticles (MPs) are extracellular vesicles and AFP is a classical tumor marker for HCC widely used in HCC vaccine-related investigations. Targeting R848 using MPs as vectors has been used for reprogramming of TAMs after the recognition of AFP in M2 TAMs. The use of R848@M2pep-MPs_{AFP} to improve the immunosuppressive microenvironment is a novel approach for tumor immunotherapy (143).

On the one hand, TAMs positively inhibit cellular immunity by mediating the secretion of multiple cytokines that act directly on CD8⁺ cells (144). Immune checkpoint ligand programmed death ligand 1 (PD-L1) is the main acting protein that inhibits CD4⁺ and CD8⁺ cell infiltration (145). The binding of programmed cell death protein-1 (PD-1) to PD-L1 leads to CD8⁺ cell depletion, promoting the expression of regulatory molecules such as B7-H4 and Ig inhibitor of the V structural domain of T cell activation in T cells, which effectively attenuates antitumor effects due to CD8⁺ cell

Table II. Direct and indirect molecular mechanisms by which tumor-associated macrophages affect HCC development, and the cell types regulated.

First author/s, year	Direct/indirect mechanisms	Cells	Molecular signals involved in regulation	Effects	(Refs.)
Ganjalkhani Hakemi <i>et al</i> , 2020; Liu <i>et al</i> , 2022	Direct	HCC cells	TGF- β /Tim-3/NF- κ B	Promoting tumor migration	(101,103)
Wei <i>et al</i> , 2021			S100A9/AGBR/NF- κ B	Development of malignancies	(68)
Qi <i>et al</i> , 2022			S100A4/ERK	Promoting the expansion of CSCs and tumorigenesis	(65)
Li <i>et al</i> , 2020			S100A4/RAGE/ β -catenin	Development of new tumor suppressors	(66)
Chen <i>et al</i> , 2019			TNF- α /Wnt/ β -catenin	EMT and stemness features of HCC	(69)
Liu <i>et al</i> , 2023			TGF- β 1/Smad	HCC stem cell-like characteristics	(73)
Keawvilai <i>et al</i> , 2024			LAL/CD36/ACBA	Inactivation of the HCC tumor growth-promoting axis	(85)
Wu <i>et al</i> , 2021			CD11b/CD18/MMP	Invasive migration of HCC cells	(113)
Wan <i>et al</i> , 2014			SIX/P65/IL-6/STAT3/MMP9	Regulation of the migration, invasion and EMT of HCC cells	(77,106)
Dong <i>et al</i> , 2022;			IL-8/JAK2/STAT3/Snail	Induction of EMT in the HepG2 cell line	(99)
Peng <i>et al</i> , 2019			TLR4/STAT3	Invasive migration of HCC cells	(111)
Xu <i>et al</i> , 2022			CCL22/CCR4	Direct activation of EMT in HCC cells	(95)
Yeung <i>et al</i> , 2015			CXCL2/ITGB1	Initiation condition of tumor cells and stem-like properties of OV6 CSCs	(64)
Zhang <i>et al</i> , 2024					
Qu <i>et al</i> , 2022;			CXCL8/miR-17	HCC cell proliferation	(90,91)
Ji <i>et al</i> , 2023					
Ye <i>et al</i> , 2020			lncRNA H19/miR-193b/MAPK1	EMT pathway and the conversion of non-CSCs to CSCs	(74)
Wu <i>et al</i> , 2020			hsa-circ-004658/miRNA-99b-5p/JAM3	Apoptosis of liver cancer cells	(87)
Lu <i>et al</i> , 2023			miRNA-32a-3p/PTEN/TJP1	EMT process in HCC cells	(114)
Bi <i>et al</i> , 2023			PI3K/AKT/mTOR	HCC cell proliferation	(80)
Cai <i>et al</i> , 2020			eUB/AKT/mTOR	HCC cell apoptosis	(81)
Chen <i>et al</i> , 2021			PAI-1/FAS/FASLG	Antiapoptotic abilities of liver cancer cells	(19)
She <i>et al</i> , 2023			LATS1/Hippo	HCC cell apoptosis and mitochondrial damage	(82)
Wang <i>et al</i> , 2022			METTL14/cirfut8/YTHBC1	HCC progression	(92)
Cheng <i>et al</i> , 2021	Indirect	HUVECs	B7-H3/STAT3/VEGF	Promoting tumor angiogenesis	(126)
Lu <i>et al</i> , 2023			miRNA-23a-3p	Migration of HUVECs	(114)
Duran <i>et al</i> , 2021			Tie-2/Ang-1	Degeneration of blood vessels	(137)
Xiang <i>et al</i> , 2023			IL-6/NF- κ B/STAT3/AP-1	Angiogenic response	(139)
Wen <i>et al</i> , 2023		Immune cells	OIT3/NF- κ B/PD-L1	CD4 ⁺ and CD8 ⁺ cell infiltration	(148)
Wang <i>et al</i> , 2023			MyD88/CX3CR1/CX3CL1	Therapeutic efficacy of anti-PD-1 antibodies in HCC	(149)
Lu <i>et al</i> , 2021			CD39/CD73	CD8 ⁺ cell activity inhibition	(155)
Szefel <i>et al</i> , 2019			PGE2/EP2	Modulating PD-1 levels	(157)
Szefel <i>et al</i> , 2019			PGE2/EP4		(157)

Table II. Continued.

First author/s, year	Direct/indirect mechanisms	Cells	Molecular signals involved in regulation	Effects	(Refs.)
Wang <i>et al.</i> , 2023			MISP/IQGAP/STAT3	Upregulation of the levels of PD-L1 secretion	(159)
Goswami <i>et al.</i> , 2021			CCL17/CCL18/CCL5/CCL20	Recruitment of T helper 2 cells	(160)
Liu <i>et al.</i> , 2024			Arg-1/IL-10	T cell depletion and NK cell inactivation	(141)
Liu <i>et al.</i> , 2022			TGF- β /PGE2/IDO	Cytotoxicity and killing effect of NK cells on tumor cells	(162)
Ai <i>et al.</i> , 2024			CXCL2/CXCR4	Recruiting B cells	(84)

circ, circular RNA; CSC, cancer stem cell; EMT, epithelial-to-mesenchymal transition; HCC, hepatocellular carcinoma; lncRNA, long non-coding RNA; miR/miRNA, microRNA; NK, natural killer; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1.

infiltration (146). IL-10 in the TME induces high PD-L1 and PD-1 expression in monocytes (147). Oncoprotein induced transcript 3 is upregulated in M2 TAMs and involved in the activation of the NF- κ B/PD-L1 axis (148). Calcyclin binding protein (CacyBP) competes for the E3 ubiquitin ligase binding site on MyD88 in HCC cells, preventing the degradation of MyD88 via the classical E3 ubiquitin ligase E3 ubiquitin protein ligase 1, leading to increased C-X3-C motif chemokine ligand 1 (CX3CL1) expression. The activation of C-X3-C motif chemokine receptor 1/CX3CL1 signaling is critical for the infiltration of TAMs in HCC tissues. The inhibition of CacyBP has become an emerging idea to maintain the therapeutic effect of anti-PD-1 antibodies in HCC (149). In addition, mucosal-associated invariant T (MAIT) cells are MR1-restricted, innate-like T cells. There is mutual crosstalk of CD163 TAMs and MAIT cells via cell contact and a PD-L1-dependent mechanism. PD-L1 blockade and depletion of CSF-1R TAMs were involved in the functional inhibition of MAIT cells in an HCC mouse model (150).

TGF- β 1, IL-10 and prostaglandin E2 (PGE2) block Th1 cell differentiation, and CD4⁺ and CD8⁺ cell infiltration to exert an antitumor effect (151). Th1 cells assist CD8⁺ cells to participate in antitumor cellular immunity (152). *In vivo* and *in vitro* experiments have demonstrated that M2 TAMs depleted the already activated CD8 T cells, reduced the secretion of the related inflammatory factors IFN- γ and granzyme B in T cells, and activated the immune escape and immunosuppression in HCC (153). Adenosine in the HCC TME produced by the ATP-adenosine pathway is a CD8⁺ cell exhaustion promoter that interferes with CD8⁺ cell proliferation. CD39, secreted by M2 TAMs, is the key enzyme for the activation of the ATP-adenosine pathway (154). CD39 together with CD73 secreted by HCC cells increases the proportion of ATP converted to adenosine and is involved in CD8 T cell activity inhibition (155). Activation of the PGE2/prostaglandin E receptor 2 and PGE2/prostaglandin E receptor 4 signaling pathways modulates PD-1 expression during CD8⁺ cell infiltration, leading to immune tolerance in the TME (156). T cells interact with tumor antigens through the T cell receptor ζ , which is associated with L-arginine (157). M1 TAMs express

iNOS and M2 TAMs express arginase 1, which metabolizes arginine to nitric oxide and urea (158).

On the other hand, TAMs exert antitumor effects on T cells through the interaction with other relevant cells in the TME. In addition to the immunosuppressive effect of PD-L1 secreted directly by TAMs, these cells also activate the mitotic spindle positioning/IQ motif containing GTPase activating protein 1/STAT3 axis in HCC cells, upregulate the levels of PD-L1 secretion and promote the immune escape of HCC (159). Regulatory T cells can be divided into naturally occurring natural regulatory T cells (nTregs) and adaptive regulatory T cells. TAMs upregulate IL-10 and TGF- β expression, and promote the expression of the chemokines thymic and activating regulatory chemokine (CCL17), CCL18, CCL5, macrophage inflammatory protein 3 α (CCL20) and small inducible cytokine subfamily A (Cys-Cys) to recruit T helper 2 cells, induced Tregs and nTregs (160). Tregs migrate toward tumors and antagonize CD8⁺ cell-mediated antitumor cellular immune functions (161). High protein expression levels of TGF- β , PGE2, indoleamine 2,3-dioxygenase and B7 in TAMs reduces the migration, proliferation and apoptotic ability of NK cells, reduces IFN- γ and TNF- α expression in the TME, and reduces the cytotoxicity and killing effect of NK cells on tumor cells (162). In addition, CAFs recruit TAMs from the peripheral blood through the macrophage migration inhibitory factor/CD74 axis and induce differentiation of TAMs into CXCL2⁺ TAMs via the activation of SMAD3. This was demonstrated *in vivo* and *in vitro*, and the binding was strong enough to explain the activation of TAMs in relation to CAFs (19). Activated TAMs possess the ability to recruit B cells via the CXCL12/CXCR4 signaling pathway and enhance cytotoxic T cell depletion through the expression of PD-L1 regulated by CXCR4 (84). Fig. 4 shows how TAMs enhance immune protection against HCC by regulating the function of other immune cells.

5. Treatment of HCC targeting TAMs

TAMs are an important type of innate immune cells in HCC. Studies have identified an inextricable relationship among polarization, recruitment of TAMs and tumor

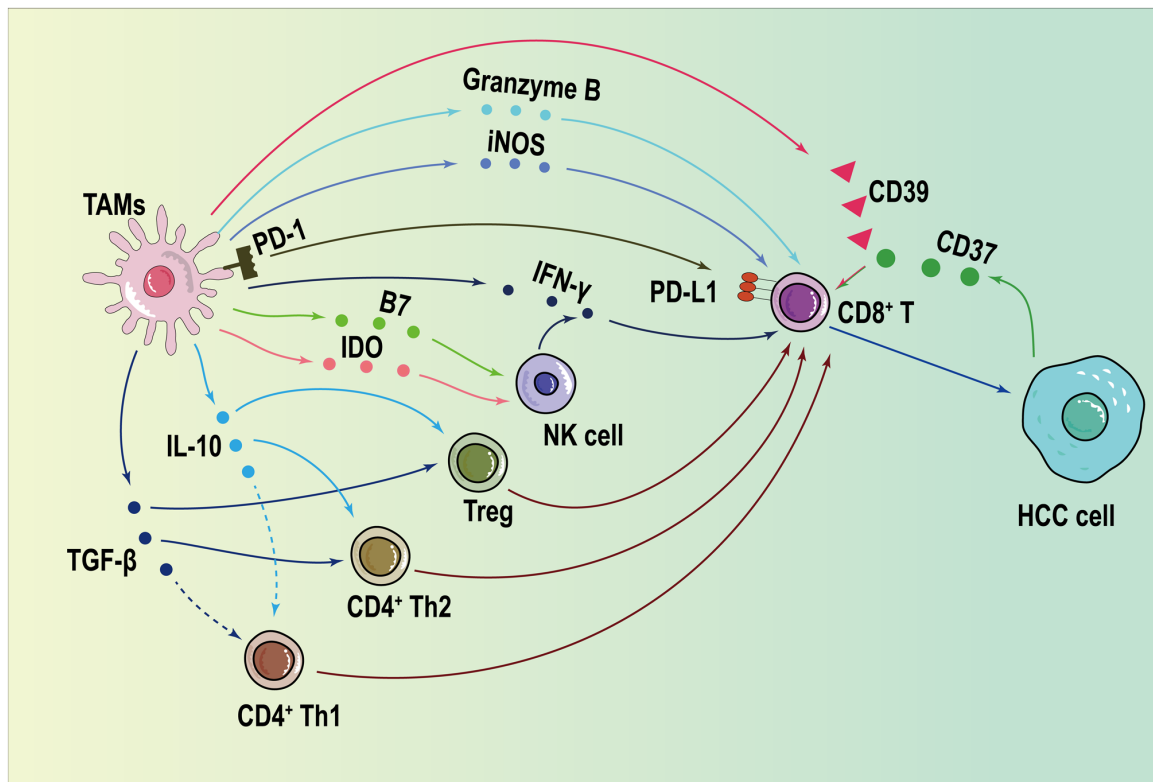


Figure 4. Role of TAMs in regulating the immune environment of HCC cells. Macrophages mainly regulate the immune environment by modulating CD8⁺ cells, thereby promoting tumor growth. TAMs not only target CD8⁺ cells through iNOS, PD-1 and granzyme B, but also through cytokines and proteins such as B7 molecules, IDO, IL-10 and TGF- α to regulate NK cells and CD4⁺ Th2 cells. Furthermore, secretions of TAMs act on CD4⁺ Th1 cells, which are helper cells for the immune function of CD8⁺ T cells, to block the immune activity of CD8⁺ cells. The dotted lines indicate the functional inhibition of CD4⁺ Th1 cells by TGF- β and IL-10. HCC, hepatocellular carcinoma; IDO, indoleamine 2,3-dioxygenase; iNOS, inducible nitric oxide synthase; NK, natural killer; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1; TAM, tumor-associated macrophage; Th, T helper; Treg, regulatory T cell.

development (163-167). Therapies targeting TAMs effectively inhibit the invasion of HCC and the proliferation of tumor cells. Targeted TAM therapy is mainly carried out as follows: i) Controlling the number of TAMs in HCC, preventing the generation of the HCC TME by reducing the infiltration of TAMs and their polarized phenotypes; ii) restoring the tumor-resistant effects of TAMs by altering the function of TAMs in the HCC TME, activating the antitumor mechanism and the synthesis of its products in TAMs; and iii) inhibition of immune escape in HCC. It has been confirmed that HCC uses the 'do not kill me' mechanism to evade the phagocytosis of tumor cells by TAMs. Therefore, tumor cells can be eliminated by cutting off the signaling pathway of HCC that interferes with the phagocytosis of TAMs (3,47,119,168-171). Fig. 5 shows the direction of treatment options targeting TAMs in HCC.

Targeting the infiltrated TAMs and their polarized subtypes

Removal of TAMs that are already present. The control of HCC by the specific depletion of TAMs is the most direct immunotherapeutic approach to target TAMs. Sorafenib is a common therapeutic agent used to treat HCC (172). CSF-1, stromal cell-derived factor 1 α (SDF-1 α) and VEGF are important chemokines for the proliferation of macrophages. Studies have indicated that plasma CSF-1 expression is increased after sorafenib treatment. CSF-1 activates macrophages, promoting macrophage-tumor interactions, ultimately leading to tumor progression. By contrast, sorafenib in combination with

chlorolipids or zoledronic acid inhibits macrophage infiltration (173,174). Tumor progression and tumor angiogenesis are inhibited after the depletion of macrophages by chlorolipids or zoledronic acid. Furthermore, the combination of these drugs controls lung metastasis of HCC (175). *In vivo* experiments were only performed using mice, and the *in vitro* experiments were performed using RAW264.7 mouse macrophages, while human macrophages such as THP-1 cells were not used; thus, the results are less representative than those using human macrophages (176). Microtubule depolymerization is specifically induced by 2'-carboxy-D-arabinitol 1-phosphate (CA1P) through the inhibition of the p150-AKT-GSK3 β signaling pathway (177). Downregulation of Akt phosphorylation activates GSK-3 β , which in turn inhibits the Wnt/ β -catenin signaling pathway in HepG2 cells (178). This signaling is abnormally activated during HCC development; thus, CA1P induces apoptosis in HCC cells *in vitro* and *in vivo*. In addition, CA1P induces apoptosis in tumor cells and TAMs via the same pathway and alters the TME by disrupting the crosstalk between tumor cells and tumor-associated immune cells. The effectiveness of CA1P in the treatment of HCC and the effect of CA1P on macrophages are mentioned in a study by Mao *et al* (179); however, to the best of our knowledge, the relationship between the two has not been confirmed in any particular study. Since TAMs have multiple polarized subtypes in HCC, their widespread clearance leads to an imbalance in immune regulation. Current therapeutic regimens

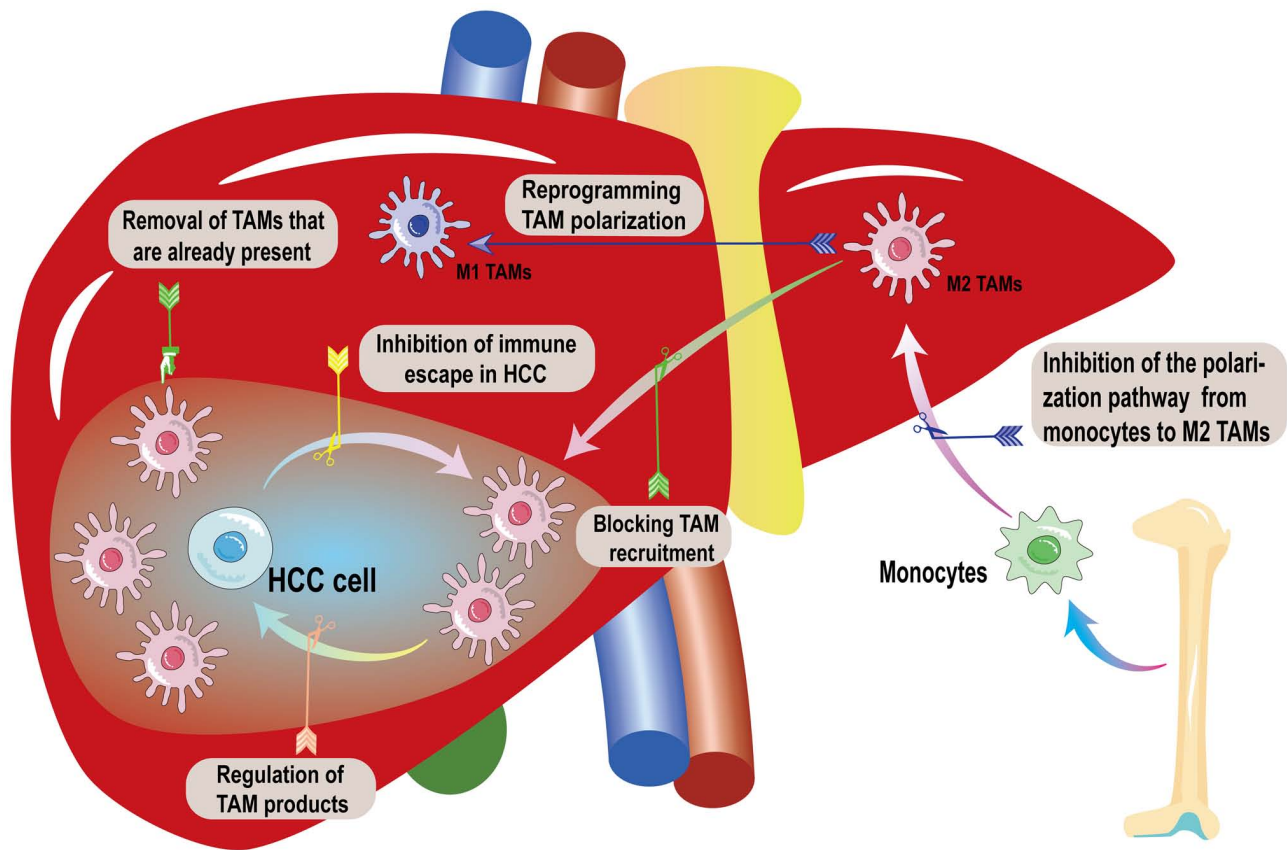


Figure 5. Treatment of HCC targeting TAMs. Targeting the infiltrated TAMs and their polarized subtypes: i) Removal of TAMs that already exists; and ii) inhibition of monocyte/macrophage recruitment. Restoration of tumor-resistant effects of TAMs: i) Inhibition of the polarization pathway from monocytes to M2 TAMs; ii) regulation of TAM polarization; and iii) reprogramming of TAM products. Inhibition of immune escape in HCC. HCC, hepatocellular carcinoma; TAM, tumor-associated macrophage.

targeting the removal of TAMs fail to specifically target M2 TAMs, resulting in the unavoidable removal of antitumor M1 TAMs (180).

Inhibition of monocyte/macrophage recruitment. CCL2 is a feature of inflammatory monocytes, and its only known receptor CCR2 is expressed in hepatic macrophages. CCL2-CCR2 signaling is involved in the infiltration of TAMs and the polarization of M2 TAMs. HCC can be treated at a biomacromolecular level by targeting CCR2 signaling blockade. A natural product called 747 has been found to act as a CCR2 antagonist. It reduces macrophage infiltration by activating the CD8 T cell population (181). Genipin, also derived from herbal origins, is a natural cyclic enol ether terpene glycoside commonly used in clinical practice for the treatment of inflammatory diseases and heat-associated HCC. Genipin directly binds to PPAR γ and activates PPAR signaling in post-operative hepatic macrophages in mice (182,183). Activated PPAR γ triggers the degradation of p65/RelA by acting as an E3 ligase (184). p65/RelA is a transcription factor for CCL2, and its inhibition results in the blockade of the CCL2-CCR2 signaling pathway. These effects in turn inhibit the recruitment of the hepatic macrophage population, as well as macrophage pro-inflammatory cytokine and chemokine expression, and postoperative HCC recurrence, resulting in a reduction in postoperative patient survival (5). Cenicriviroc (CVC) is a novel oral dual CCR2/CCR5 antagonist. CVC reduces macrophage infiltration in the liver of patients with autoimmune liver

disease. CVC treatment blocks the release of LPS-induced macrophage cytokines. The oral administration of genipin after CVC treatment in an experimental mouse model of HCC reduced the risk of lung metastasis of HCC cells. In addition, CVC prevents pro-inflammatory signaling and macrophage activation in the liver, blocking the TAM polarization pathway in the treatment of HCC (185). A total of 10 CCL2 inhibitors (MK0812, PF04634817, PF04136309, INCB3344, cenicriviroc, JNJ2714149, CCR2-ra-[R], CAS-445479-97-0, RS504393 and RS102895) are commercially available at present and are used in clinical HCC therapy (186). Pharmacological experiments have confirmed that MK0812 inhibits tumor metastasis in humanized mice, with the lowest IC₅₀ (1.73 nM) being the most potent human CCR2 inhibitor. Oral administration of MK0812 in human CCR2B knock-in mice did not result in weight loss or other serious side effects (187). The cytidine analog gemcitabine (GEM) is a first-line chemotherapeutic agent in the treatment of parenchymal tumors, functioning by inhibiting DNA replication. However, GEM has some limitations such as poor delivery and susceptibility to cytidine deaminase-induced degradation, which hamper its clinical therapeutic application. The poor delivery of GEM was addressed by constructing GEM-conjugated polymers (PGEMs) showing high tumor penetration in several pancreatic ductal adenocarcinoma models. PGEM has a reduced particle size, being a small and acceptable polymer drug complex. A study has demonstrated that PGEM induces double-stranded DNA damage

in tumor cells and activates the cyclic GMP-AMP synthase (cGAS)-interferon gene-stimulating factor (STING) pathway (188). STING is an endoplasmic reticulum transmembrane protein that activates CCL2 and CCL7 expression, leading to a marked increase in the percentage of MDSCs and TAMs, thus regulating tumor innate immunity. PF-6309 is an optimal CCR2 inhibitor for loading PGEM micelles. It was also evident that free PF-6309 and PGEM/PF-6309 treatments led to a decrease in the percentage of MDSCs and TAMs, the latter also leading to a decrease in the percentage of M2-type macrophages and an increase in the percentage of M1-type macrophages and the M1/M2 ratio, suggesting that macrophages infiltrating the tumors are polarized from a tumor-promoting to a tumor-suppressing phenotype (189). Hypoxic conditions in HCC lead to the upregulation of SDF-1 α expression, leading to the recruitment of M2 macrophages and the promotion of tumor progression (19,190). The expression levels of CXCR4 and VEGF in TAMs, as well as the expression levels of M2 TAM markers CCL22 and arginase 1 are more than 2-fold higher in TAMs after sorafenib treatment than in TAMs without sorafenib treatment. AMD3100 is a classical inhibitor of the SDF-1 α receptor (CXCR4), which blocks the SDF-1 α /CXCR4 axis that arrests the recruitment of TAMs, prevents polarization to an immunosuppressive microenvironment after sorafenib treatment, inhibits tumor growth, reduces lung metastasis and improves survival. AMD3100 alone or in combination with sorafenib reduces the expression levels of M2 type markers in TAMs but does not affect the expression of M1 type markers. This combined therapeutic approach exerts an anticancer effect not through reprogramming M2 TAMs but by cutting off the recruitment channel of M2 TAMs (191). CXCL17 is a selective inhibitor of CXCR4 signaling with low potency. Binding of CXCL17 to neuropilin-1, a VEGFR2 co-receptor containing glycosaminoglycans, blocks endogenous CXCL12 binding to CXCR4, thereby inhibiting ligand binding to NanoLuc/CXCR4 and inhibiting β -arrestin 2 recruitment to CXCR4 (192). The differentiation of human M2 macrophages results in the upregulation of the expression levels of P2Y11, a G protein-coupled ATP receptor that activates the IL-1 receptor in a cyclic AMP-dependent manner, upregulating the expression levels of CECR7 through increased EGFR expression, along with the upregulation of CXCR4 expression. The antagonist NF340 is a specific inhibitor of P2Y11, and this inhibition controls macrophage infiltration by suppressing CXCR4 expression (193).

Restoration of tumor-resistant effects of TAMs

Inhibition of the polarization pathway from monocytes to M2 TAMs. Some chemotherapeutic agents, such as Adriamycin (Dox) and oxaliplatin are effective in tumor immunotherapy regimens. These drugs applied in combination therapy are effective in treating the development of HCC (194,195). Manganese (Mn²⁺) is an important intracellular ion that activates cGAS-STING signaling. Cell membrane-derived hybrid nanovesicles (Mn²⁺/Dox loaded-hybrid vesicles) have been constructed and applied in antitumor therapy. Cell-membrane vesicles were derived from M1-like macrophages and fused with liposomes carrying Mn²⁺ and Dox. Finally, the fused vesicles were modified with CXCR4-binding peptide to

target macrophages highly expressing CXCR4. Furthermore, Mn²⁺-mediated activation of cGAS leading to an increased production of cyclic GMP-AMP and activation of STING resulted in the upregulation of IRF3 transcription. i-type interferon and cytokines for antitumor immunity were controlled by STING, upregulating the expression levels of CD80 and CD86, leading to M1 phenotypic polarization (196). CSF2-derived macrophages preferentially produce IL-6, IL-12 and TNF α in response to lipopolysaccharide, whereas CSF1-derived macrophages produce IL-10 and CCL2 but not IL-12. CSF-1R signaling promotes a tumor-promoting macrophage phenotype, whereas its inhibition polarizes TAMs to an antitumor phenotype. The inhibition of CSF1/CSF-1R signaling depletes M2 TAMs to reduce tumor cell infiltration and reprogram the TME (197). CCAAT-enhancer-binding protein α (C/EBP α) is known for its ability to inhibit the tumor polarization of M2 macrophages; however, its role in regulating immunosuppressive myeloid cells is unclear. Application of therapeutic agents associated with C/EBP α mediated by small activating RNA represents a good immunotherapeutic option. The transcription of the CEBPA gene is specifically regulated by CEBPA-51. The encapsulation of CEBPA-51 in SMARTICLES liposomal nanoparticles composed of MTL-CEBPA results in the promotion of C/EBP α expression. In addition, the upregulation of CEBPA expression in monocytes after the action of MTL-CEBPA leads to an increase in the synthesis of PGE2, which is a potent immunosuppressive mediator, resulting in the rapid downregulation of genes and proteins involved in MDSC inhibitory activity, as well as the activation of classical monocytes and granulocytes. Furthermore, MTL-CEBPA and sorafenib induce the transition from M2-type polarized TAMs to M1-type polarized TAMs (198).

Focal adhesion kinase (FAK) is a non-receptor protein tyrosine kinase that promotes M2 polarization of macrophages through the regulation of multiple signaling pathways, including the PI3K/Akt/JAK/STAT3 and p38/JNK/ERK signaling pathways. *Phellinus linteus* is an anticancer herbal medicine. Upon binding to FAK, the combination of DBL and hispolon blocks the action of FAK and inhibits cell proliferation (199).

PLX3397 is a competitive inhibitor targeting CSF-1R and the affinity for CSF-1R tyrosine kinase is higher than that of CSF-1R. Bone marrow-derived monocytes are stimulated to polarize toward an M2-like or M1-like phenotype by either CSF1 or CSF2, the latter protecting macrophages from PLX3397 treatment; thus, TAMs from PLX3397-treated tumors show an M1-like phenotype, and PLX3397 inhibits tumor growth without depleting TAM infiltration *in vivo* (200).

Blocking the change of already polarized M1 TAMs to M2 TAMs is a novel line of research. CSF-1 regulates the repolarization process from M1 macrophages to M2 macrophages through MAPK/ERK/AP-1 signaling pathway activation. CSF-1 mediates the high expression of c-Jun, which belongs to the AP-1 family proteins and is involved in the repolarization process of M1 macrophages with the assistance of NF- κ B (201). The triggering receptor expressed on myeloid cell (TREM) family mainly exerts effects in the regulation of the inflammatory response through the receptor form. TREM2 regulates macrophage polarization, and its inhibition leads to the activation of the PI3K/Akt/NF- κ B axis and the increase of

CXCL3 secretion in macrophages. High TREM2 expression is a hallmark of the repolarizing metabolic reprogramming of M1 macrophages to M2 macrophages (202,203). Echinacoside is a phenyl ethanol glycoside involved in hepatoprotection, anti-inflammation, neuroprotection and tumor therapy. A study found that it reduced TREM2 expression in HCC, while activating PI3K/Akt signaling, acting as an antitumor agent (204). Oxaliplatin is a commonly used clinical anticancer drug. TREM2-IN-1 (OPA), a platinum (IV) complex made from oxaliplatin and artesunate, is a potent TREM2 inhibitor. OPA is also involved in the cytotoxicity induced by oxidative damage to nuclear DNA. It serves an antitumor role in both chemotherapy and immune activation (205). The use of Fc structural domain effector-enhanced antibodies against TREM2 demonstrated that the pro-tumor function of TAMs was reversed in the TME after treatment (206-208). Furthermore, the humanized anti-TREM2 monoclonal antibody PY314 is already used in a clinical trial (209).

Reprogramming of TAM polarization. The use of cellular autophagy to block the immunoregulation of HCC involving TAMs has received unanimous confirmation from experts and scholars (163-165,172,173,180). Baicalin inhibits *in situ* HCC growth through the reprogramming of macrophages. This process requires the involvement of RelB and p52, which are highly expressed in M1-like macrophages compared with M2 TAMs. Baicalin is an activator of the autophagic degradation of TNF receptor associated factor (TRAF)2 in TAMs, and TRAF2/TRAF3 has a limiting effect on intracellular IKK α /RelB/p52 signaling. The indirect activation of the RelB/p52 signaling pathway by baicalin causes the expression of the RelB/p52-specific target genes CXCL12 and CCL9, leading to higher expression of macrophage-secreted IL-6 and TNF- α , which are cytokines with typical pro-inflammatory effects, and causes transformation of M1 TAMs to M2 TAMs (210). Activation of the NF- κ B signaling pathway for macrophage autophagy therapy is widely recognized since it is involved in M1 macrophage polarization. A study has also identified the role of the tumor vaccine Lmdd-MPFG in targeting TAMs. The activation of the NF- κ B signaling pathway by the Lmdd-MPFG vaccine induces M1 polarization through macrophage autophagy (211). Sirtuin 1 (SIRT1) is a deacetylase that regulates transcriptional silencing and cell viability. Overexpression of SIRT1 in macrophages enhances the phosphorylation of p65 and IKK, and promotes M1 macrophage polarization. IKK β inhibition increases tumor suppressor polarization of macrophages (212).

lncRNA COX-2 expression is higher in M1 macrophages than in M2 macrophages. Its inhibition in turn inhibits macrophage polarization to the M1 type, decreases the ability of M1 macrophages to inhibit HCC cell proliferation and increases the ability of M2 macrophages to promote proliferation (213).

Targeting multiple receptors is an essential part of the treatment of HCC, and relevant therapeutic regimens around TAMs take this into account. Use of TLR inhibitors for the treatment of HCC has been widely emphasized (210,212,214). The role of TLR in the activation of the non-specific immunity of the body cannot be ignored. The non-specific immune system promotes the inflammatory response by recruiting immune cells such as macrophages and mast cells to secrete inflammatory factors (215). The most important protein for

mitochondrial fission, dynamin-related protein 1, is involved in HCC progression by regulating cell survival and metastasis. The dynamics of mitochondrial fusion and fission are necessary for mitochondrial DNA (mtDNA) distribution and mitochondrial homeostasis. Increased mitochondrial fission induces cytoplasmic mtDNA stress in HCC cells, which in turn promotes CCL2 secretion via the TLR9-mediated NF- κ B signaling pathway, leading to TAM infiltration in HCC tissues (216). In HCC treatment, motolimod (TLR7 agonist), GS9620 (TLR8 agonist) and R848 (resiquimod; dual TLR7/8 agonist) produce an M1 increase. Certain dextran nanoparticles have natural macrophage affinity and are effective carriers for targeting TAMs with drugs. Among them, β -cyclodextrin has a similar chemical composition to linear dextran, and easily activates the phagocytic effect of macrophages to exert drug effects (214,217-221). Cyclodextrin nanoparticles (CDNPs) have a high macrophage affinity and a high drug-carrying dose. After combining with CDNPs, the so-called nano R848 inhibitor enhances the reprogramming ability of TAMs (217). In addition, PI3K γ is a classical therapeutic target for reprogramming TAMs and is a key signaling molecule required for macrophage accumulation in inflammation. PI3K γ blocks pro-inflammatory responses of stimulating macrophages. Macrophages deficient in PI3K γ exhibit a reduced ability to respond to immunotropism through G protein coupling (222), upregulation of M1 polarization-associated genes and proteins, and downregulation of M2 polarization-associated cytokine expression. PI3K γ promotes immunosuppression through the activation of mTOR/S6K α /C/EBP β signaling and the inhibition of NF- κ B (223). Indirect promotion of Th1 cells and cytotoxicity reduce immune responses (224). A pan-PI3K inhibitor has recently been identified as an enhancer of pro-inflammatory cytokine transcription in TAMs (3). The metabolism of substances in TAMs serves an integral role in the polarization of cellular phenotypes, and the inhibition of certain pathways of macrophage substance metabolism activates the reprogramming of M2 TAMs (225). Macrophages are a relevant source of active insulin-like growth factor (IGF-1). IGF-1 is a key growth factor for macrophages to drive the growth of HCC cells from macrophages. Sorafenib inhibits the release of IGF-1 (226). IGF-binding protein 4 (IGBP-4) binds IGF-1 to inhibit its activity (227). Low expression of IGBP-4 in polarized macrophages leads to active secretion of IGF-1, which ultimately promotes the proliferation of HCC cells. Targeted inhibition of the IGF/IGF-1R signaling axis is a promising approach to modulate the HCC environment (228). Receptor interacting serine/threonine kinase 3 (RIPK3) is downregulated in HCC-associated TAMs. The extent of the distribution of lipid droplet deposition is increased in TAMs after RIPK3 knockdown. Reactive oxygen species/caspase 1 signaling mediates the inhibition of PPAR expression by RIPK3. The lack of RIPK3 in TAMs results in an increase in the expression levels of PPAR α and PPAR γ , which regulate fatty acid metabolism, promote TAM infiltration and M2 polarization, and facilitate the development of HCC. The upregulation of RIPK3 reverses TAM polarization and attenuates HCC. The RIPK3 inhibitor GSK872 and fatty acid oxidation blockers are two factors mediating reprogramming of M2 TAMs (229).

Regulation of TAM products. TAM products are protein molecules in TAMs that can act in the tumor microenvironment to regulate tumor development, such as TGF- β and Wnt1. TAMs accelerate tumor progression by releasing tumor growth factors. LPS-induced activation of PI3K/Akt increases the levels of miR-101, which in turn binds to dual specificity phosphatase 1 (DUSP1) mRNA and directly represses its expression (230). DUSP1 is a negative regulator of the activity of MAPKs. MAPKs are highly conserved serine/threonine protein kinases that include ERK, JNK/stress-activated protein kinases and p38 (231). Sorafenib inhibits PI3K/Akt activation and decreases miR-101 expression, and subsequently inactivates MAPK via the induction of DUSP1 expression in HCC. Sorafenib inhibits the release of TGF- β and CD206 in M2 macrophages (232). TGF- β is a key growth factor for macrophage-driven HCC cell proliferation and metastasis (217). Wnt/ β -catenin signaling is a classically conserved signaling pathway, and its activation is associated with the degree of HCC. M2 macrophages specifically release Wnt1, which stimulates the activation of β -catenin signaling in tumor cells, leading to HCC cell proliferation and malignant transformation in a Wnt1-dependent manner. Bufferin targets M2 macrophages and inhibits HCC growth by specifically blocking Wnt1/ β -catenin signaling (222). Isoproterenol stimulates the secretion of microvesicles by TAMs, which deliver miR-142-3p from macrophages to HCC cells. miR-142-3p is taken up by HCC cells and directly inhibits their viability, proliferation and invasiveness *in vitro* by downregulating Rac family small GTPase 1 (224). Compound kosher injection (CKI; also known as Yanshu injection) is used in clinical practice in the treatment of a variety of solid tumors, including HCC, gastric carcinoma, breast carcinoma, lung carcinoma and colorectal carcinoma. CKI increases the therapeutic effect of low-dose sorafenib. It also reduces the M2 TAM levels in the TME and increases the ratio of M1 TAMs to CD8 T cells by targeting TNF receptor superfamily member 1A and its downstream NF- κ B p65 and MAPK p38 signaling cascades, reducing tumor recurrence and triggering an effective antitumor memory response against HCC (3).

Inhibition of immune escape in HCC. HCC avoids phagocytosis by TAMs mainly through the ‘do not eat me’ signaling pathway. Signal-regulated proteins (SIRPs) have extracellular immunoglobulin-like domains, and SIRP α and SIRP γ bind to the widely expressed cell-surface transmembrane glycoprotein CD47 (also known as integrin-associated protein). The binding of SIRP α to macrophages reduces the production of the pro-inflammatory cytokine TNF and reduces polarization in the M1 direction. The binding of CD47-SIRP α to macrophages leads to the inhibition of the ‘do not eat me’ signaling, negatively regulating the activation of macrophages and phagocytosis (233). Activation of SIRP α activates the phosphorylation of tyrosine-based inhibitory motifs of the immune receptor, preventing the recruitment of Src homologous phosphatase (SHP)-1 and SHP-2 phosphatases in cells. Two phosphatases are recruited to prevent myosin-IIa accumulation at phagocytic synapses in macrophages. The disruption of the CD47-SIRP α axis in preclinical models leads to enhanced phagocytosis and tumor reduction, and it

is a means of cross-presenting tumor antigens to T cells (234). Two therapeutic options are available based on CD47-SIRP α axis inhibition, anti-CD47 therapy and anti-SIRP α therapy. At present, scholars generally choose anti-CD47 therapy as the main therapy to restore macrophage capacity through the use of surface-engineered exosomes equipped with membrane-bound proteins. Researchers have used exosome models containing SIRP α variants specifically competing for SIRP α binding sites on CD47 on the surface of tumor cells. Newly developed SIRP α variants have an improved affinity for human CD47 compared with wild-type SIRP α . SIRP α exosomes block CD47-SIRP α interactions, inducing increased phagocytosis of various cancer cells by bone marrow-derived macrophages (235). Treatment of macrophages with B6H12 or CD47 monoclonal antibody 400 antibodies, which are two specific CD47 blocking antibodies, enhances phagocytosis of HCC cells and reduces tumor size in mice with ectopic tumors. Furthermore, CD47 inhibition leads to an increase in the migration of macrophages to HCC *in vivo*, which is more conducive to the phagocytosis of macrophages. CD47 blocking antibodies have great advantages in maintaining the normal physiological functions of the liver, and the use of the antibodies does not cause direct *in vivo* damage to the liver and normal hepatocyte viability (236). In a recent study, a high affinity CD47 blocker (modified SIRP α D1 structural domain) was added to the inactive IgG Fc region, resulting in the engineered protein evorpaccept (also known as ALX148). ALX148 is recognized by macrophages through the active Fc structural domain and binds to its Fc γ receptor, and the resulting CD47 inhibitor targets the CD47/SIRP α signaling pathway, increasing autoimmune processes in the TME. Evorpaccept had a good safety profile both when administered alone and in combination with the standard regimen of pembrolizumab and trastuzumab (237). In addition, CD47 expression in tumor cells is positively regulated by STAT3 phosphorylation levels. IL-6 reverses the suppressed CD47 expression in HCC cells after blocking STAT3 and enhances the ability of tumor cells to evade phagocytosis. Tocilizumab, a humanized monoclonal antibody directed against the IL-6 receptor, is used to inhibit the inflammation in rheumatoid arthritis, but it also blocks TAM-mediated anti-phagocytosis, making it a potential drug for HCC treatment (238). Histone deacetylase 6 (HDAC6) is involved in autophagy signaling and degradation of ubiquitinated proteins. It directly inhibits the expression of let-7i-5p, which regulates the expression of thrombospondin-1 (TSP1), which competes with SIRP α . Activation of the HDAC6/let-7i-5p-TSP1 regulatory axis converts CD47-SIRP α to CD47-TSP1 interactions between HCC and macrophages, thereby altering the ‘do not eat me’ self-protection mechanism of tumors. Therefore, targeting of the HDAC6/let-7i-5p/TSP1 axis could represent a novel immunotherapeutic strategy to treat human HCC in the future (239). B6H12.2 is a CD47 blocking antibody that enhances CD47-SIRP α expression in CCA, thus enhancing the phagocytosis of CCA cells highly expressing CD47 (238). Glypican-3 (GPC3) is one of the most well-characterized HCC-associated antigens. Bispecific antibodies co-acting with GPC3 and CD47 have excellent antitumor effects with minimal toxicity. GPC3/CD47 bispecific antibody readily binds preferentially to bi-antigen-expressing tumor cells, and

efficiently blocks SIRP α /CD47 (240). Anti-SIRP α treatment regimens have progressed more slowly compared with CD47 antibody therapy (241). CRISPRed macrophages can be used for cell-based cancer immunotherapy. The CRISPR-CRISPR associated protein 9 (Cas9) nuclease system is commonly used to target modifications of the genome in cells to block gene expression (242). Cationic arginine-coated gold nanoparticles (ArgNPs) bind Cas9 proteins, and CRISPR-Cas9 encapsulated with ArgNPs can knock down SIRP α in RAW264.7 cells, activating phagocytosis and eliminating cancer cells (243). In contrast to therapeutic measures targeting CD47, therapeutic regimens targeting SIRP α are still missing (244).

Drug resistance, efficacy and potential risks. In response to a study of tumor-targeted macrophage therapeutic regimens, current studies have found that the use of CSF-1R may lead to the development of drug resistance (97,150,197,200). The activation of PI3K is involved in the resistance of HCC after treatment with the CSF-1R inhibitor BLZ945. After the treatment with BLZ945, IGF-1 drives the activation of PI3K signaling (245). Therefore, IGF-1R and PI3K may serve as biomarkers for predicting drug resistance. Combined inhibition of IGF-1R and PI3K enhances the efficacy of CSF-1R in treating tumors by reducing drug resistance. Novel advances in CSF-1R antagonistic therapy in combination with other receptor tyrosine kinase inhibitors have been reported (246). The generation of numerous tumors is inextricably linked to the neogenesis of blood vessels in their tissues (247). The complications associated with treatments in patients in whom the angiogenic pathway is blocked are a difficult problem to resolve. Monocytes/macrophages expressing the Ang receptor TIE-2 regulate interstitial angiogenesis in tumors after receiving CXCL12/CXCR4 recruitment messages in combination with Ang (248-250). Targeted therapies are often applied with TIE-2-expressing monocytes/macrophages (TEMs) as a therapeutic focus to avoid the development of complications while determining efficacy. By blocking TEM depletion, targeted therapies, by avoiding angiogenic mechanisms in tumors, avoid issues in human physiological functions triggered by extensive angiogenic inhibition (251). There are potential risks associated with the regulation of angiogenesis in tumors, as hypoxia due to TEM inhibition may activate strong vascular remodeling and maturation in the periphery of the tumor, leading to a failure of the tumor-suppressive effect of the drug (252).

6. Discussion

The present review focuses on the crosstalk between tumor cells and macrophages; however, to the best of our knowledge, there is no in-depth research finding on the mechanism regulating the crosstalk between macrophages and specific immune cells. Furthermore, information on the joint crosstalk between multiple cells is still lacking, and there is no systematic mechanism to regulate the tumor immune microenvironment. The study of the effect of HCC on the polarization direction of macrophages revealed the possibility that some juvenile macrophages may already have shifted their polarization direction when they are not affected by HCC, a factor mostly ignored by other studies (3-6,8,13,15). At present, TAMs are roughly classified into M1 TAMs and M2 TAMs, but more and more

polarized phenotypes of macrophages have been identified, with no clear and distinct boundary between the macrophage subtypes that have been investigated. Furthermore, some TAMs have the characteristics of both the M1 subtype and the M2 subtype of macrophages, suggesting that the balance of the physiological functions of macrophages in HCC should be studied in the future. More and more subtypes of TAMs have been identified, immunotherapy measures targeting macrophages in HCC are too homogeneous at present, and the proportions of macrophage subtypes in tumors of different patients with HCC vary greatly, leading to the conclusion that it is necessary to study the signature biomarkers of multiple subtypes of TAMs, and use these biomarkers for the detection of macrophages in tumors as well as the selection of targeted therapeutic regimens. The TRP ion pathway is a tumor-related signaling pathway that has received increasing attention from experts in tumor targeted therapy (253). The TRP ion pathway is a classical pain target, and high TRP ion pathway activation is present in liver cancer. The specific functions and regulatory factors of the TRP ion pathway have not yet been conclusively determined (254). Thus, the TRP ion pathway in liver cancer should be investigated in the future, potentially representing a novel development direction (255).

7. Conclusion

Chinese and international scientists have investigated the role of TAMs in the microenvironment of HCC and found that TAMs are an important factor in controlling HCC development. The present review is divided into two parts, focusing on the role of TAMs in the HCC microenvironment: Direct control of HCC cells and indirect promotion of HCC development. M2 TAMs positively regulate the migration, invasion and proliferation of tumor cells through the secretion of related cytokines, but inflammatory factors produced by M1 TAMs also contribute to the formation of blood vessels, leading to the development of tumors.

Existing scientific studies tend to analyze the pro-tumor direction of M2 TAMs and study the effect of TAMs on advanced HCC. Since the polarization of TAMs in the early stages of a tumor is biased towards the M1 phenotype, there is still a gap in the study of the pro-tumorigenic role of M1 TAMs and the repolarization process. After early diagnosis, the inhibition of the early polarization orientation by M1 TAMs can predictably target early-stage HCC compared with the treatment of HCC by inhibiting the pro-tumor effect of M2 TAMs. Early relevant diagnosis and treatment by enhanced polarization of TAMs towards M1 TAMs can improve the high lethality of advanced HCC. Most studies macroscopically replace tumor characteristics with only the tumor cell characteristics, ignoring the characteristics of the immune cells in HCC. Therefore, more studies on signaling crosstalk between TAMs and HCC cells should be carried out to investigate the differences between HCC and other tumor types.

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Authors' contributions

MinY and HY contributed to the preparation, creation and description of the work for publication, in particular writing a first draft (including substantive translation). MinY, HY and HW contributed to presentation of research ideas and the development and formation of overall research objectives. CL, XZ and ZS contributed to the development and design of methods, and created models. WC and HY contributed to the application of statistical, mathematical, computer and other forms of techniques to analyze and integrate research data. XZ, MJ and XX contributed to implementing research and data/evidence collection. MJ, CL and XZ provided research materials, reagents, patients, experimental samples, animals, instruments, computational resources or other analytical tools. MiaY and MJ carried out metadata management, data cleansing and data maintenance (including software code needed to interpret the data) for initial use and subsequent reuse. HW revised the manuscript. MJ carried out review and revision (both pre- and post-publication phases). MinY and HW revised the manuscript. CL and MJ oversaw and led the planning and execution of research activities. CL and XZ assumed responsibility for the management and coordination of the planning and execution of research activities. CL and XZ obtained financial support for this publication project. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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