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REVIEW

Role of tumor-associated macrophages in common digestive system malignant tumors

Yue Shen, Jia-Xi Chen, Ming Li, Ze Xiang, Jian Wu, Yi-Jin Wang

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Abstract

Many digestive system malignant tumors are characterized by high incidence and mortality rate. Increasing evidence has revealed that the tumor microenvironment (TME) is involved in cancer initiation and tumor progression. Tumor-associated macrophages (TAMs) are a predominant constituent of the TME, and participate in the regulation of various biological behaviors and influence the prognosis of digestive system cancer. TAMs can be mainly classified into the antitumor M1 phenotype and protumor M2 phenotype. The latter especially are crucial drivers of tumor invasion, growth, angiogenesis, metastasis, immunosuppression, and resistance to therapy. TAMs are of importance in the occurrence, development, diagnosis, prognosis, and treatment of common digestive system malignant tumors. In this review, we summarize the role of TAMs in common digestive system malignant tumors, including esophageal, gastric, colorectal, pancreatic and liver cancers. How TAMs promote the development of tumors, and how they act as potential therapeutic targets and their clinical applications are also described.

Key Words: Tumor-associated macrophages; Digestive system malignant tumors; Tumor development; Therapeutic targets; Clinical applications

Core Tip: This review summarizes the role of tumor-associated macrophages (TAMs) in common digestive system malignant tumors, including esophageal, gastric, colorectal, pancreatic and liver cancers. How TAMs promote the development of tumors, and how they act as potential therapeutic targets and their clinical applications are also described.

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INTRODUCTION

Many digestive system malignant tumors have high incidence and mortality rate, including esophageal cancer (EC), gastric cancer (GC), colorectal cancer (CRC), pancreatic cancer (PC), and liver cancer (LC). There is increasing evidence that the tumor microenvironment (TME), which encompasses the tumor tissue structure comprising stromal cells, is involved in cancer initiation and tumor progression[1-4]. Tumor-associated macrophages (TAMs) as a predominant constituent of the TME, are a special type of macrophages generated by circulating monocytes and recruited into the TME[5]. TAMs are categorized into two functionally contrasting subtypes: Classically activated M1 macrophages and alternatively activated M2 macrophages. TAMs are extensively present in various tumors[6,7], which can participate in the regulation of various biological behaviors and influence the prognosis of digestive system cancers. In this review, we summarize the role of TAMs in EC, GC, CRC, PC and LC. More specifically, we also described how TAMs promote the development of tumors (Figure 1), and how they act as potential therapeutic targets (Figure 2) and their clinical applications.

CHARACTERISTICS OF TAMS

Origin of TAMs

It was originally believed that macrophages in the TME originated from circulating monocyte precursors in the bone marrow (BM), under the influence of tissue microenvironmental signals. However, other studies suggested a minor splenic[8] and early embryonic[9] contribution to the main proportion of TAMs derived from the BM, validating the coexistence of macrophages with different origins.

TAM polarization

In accordance with the commonly accepted theory[10], TAMs can be primarily categorized into the antitumor M1 phenotype (classically activated state) and the protumor M2 phenotype (alternatively activated state), which have contrasting functions. The former has the capacity to remove tumor cells [11] and facilitate tumor cell destruction *via* initiating cytokine[12] production within the TME and recruitment of immunostimulating leukocytes and tumor cells phagocytosis. On the contrary, M2 macrophages have a central role in propagating tumorigenesis. The function of M2 macrophages includes the removal of debris, promotion of angiogenesis, tissue reconstruction, and injury repair, as well as facilitation of tumorigenesis and progression[6].

TAM plasticity

Upon recruited to the TME by tumor-secreted stimuli, TAMs undergo M1- or M2-like activation in response[13]. However, as a result of their remarkable plasticity, TAMs can reversibly respond to specific stimuli in the TME and switch from one phenotype to another[14], transition between antitumor M1-like and protumor M2-like phenotypes amidst the immune response. Colegio *et al*[15] have reported that the hypoxic TME can induce M2-type polarization through the production of tumor-derived lactic acid and hypoxia-inducible factor (HIF)-1α[15]. Many other cytokines can govern M2 polarization, including interleukin (IL)-21[16] and IL-33[17]. TAM plasticity highlights that the reprogramming of TAMs is an attractive potential therapeutic target to inhibit tumor progression.

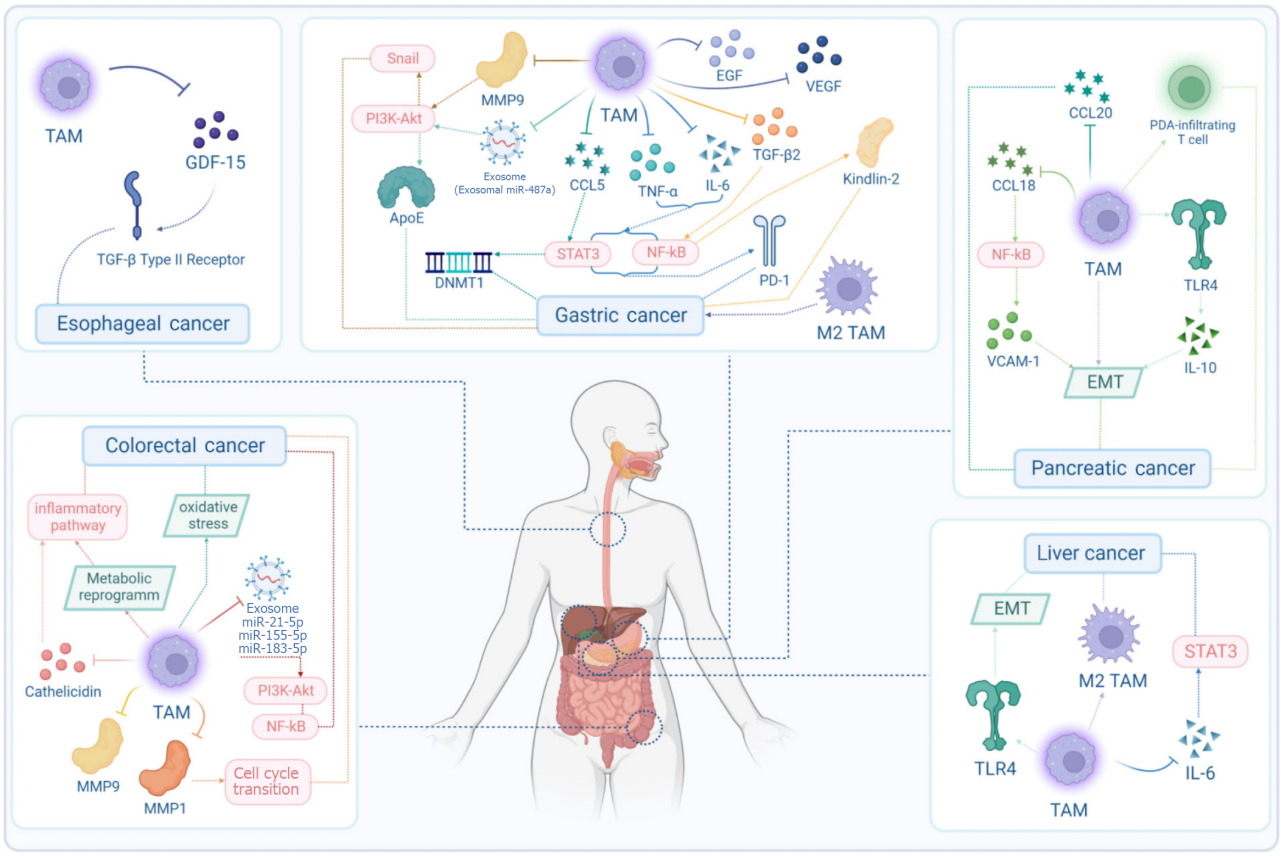

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Figure 1 Tumor-associated macrophages can promote the development of tumors. Tumor-associated macrophages (TAMs) can affect cancer progression through multiple mechanisms, which are varying in esophageal cancer (EC), gastric cancer (GC), colorectal cancer (CRC), pancreatic cancer (PC), liver cancer (LC). Color differences indicate various strategies the TAMs use on their targets, the arrows represent secretory or regulatory behaviors, and braces represent combined action of the factors. Moreover, the pink icons stand for common signaling pathways and the green icons, biological processes. In EC, growth/differentiation factor-15 and transforming growth factor-beta receptor are involved in regulations. In GC, stimulation with anti-inflammatory triggers, growth factors, chemokine, exosomes and enzymes, leads to expression of transcription factors. In CRC, TAMs work with exosomes, matrix metalloproteinases and cathelicidin, concerning signaling pathways, cell cycle transition, metabolic reprogram, inflammatory pathways and oxidative stress. In PC and LC, TAMs regulate their development similarly through interleukins and Toll like receptor 4, leading to activation of transcription factors and epithelial mesenchymal transition of tumors. Thus, TAMs can regulate digestive system malignant tumors by diverse direct and indirect mechanisms. TAM: Tumor-associated macrophages; GDF-15: Growth/differentiation factor-15; TGF-β: Transforming growth factor-β; PI3K: Phosphoinositide 3-kinase; MMP9: Matrix metalloproteinases 9; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor; CCL5: CC ligand 5; TNF-α: Tumor necrosis factor-α; IL: Interleukin; STAT3: Signal transducers and activator of transcription 3; NF-kB: Nuclear factor kB; PD-1: Programmed death 1; PDA: Pancreatic ductal adenocarcinoma; TLR4: Toll like receptor 4; VCAM: Vascular cellular adhesion molecule-1; EMT: Epithelial mesenchymal transition; DNMT1: DNA methyltransferase 1.

TAM STATUS IN TUMORS

TAMs can influence tumor progression

M2 TAMs are crucial drivers of tumor invasion, growth, angiogenesis, metastasis, immunosuppression, and resistance to therapy[18]. TAMs can propagate tumor progression through upregulation of proteolytic enzymes[19] and in a manner dependent on tumor necrosis factor (TNF)-α and matrix metalloproteinases (MMPs)[20]. TAMs can also express a number of soluble factors[13] and major inflammatory mediators[21], stimulating tumor cell proliferation and survival.

TAMs act in various microenvironments, such as invasive regions where they facilitate cancer cell movement, stromal and perivascular regions where they promote metastasis, and avascular and perivascular regions where hypoxic TAMs induce angiogenesis[18].

Clinical implication of TAMs

Research advances in cancer immunology have led to multifarious strategies for modulation of TAMs for therapeutic applications[22], including strategies to deplete TAMs, inhibit TAM recruitment, influence TAM polarization, and target TAM receptors. M2 TAMs can also contribute to evaluating prognosis, which has been proven to be correlated with poorer outcomes in almost all digestive system malignant tumors[23]. On the contrary, increasing levels of M1 TAMs indicate better prognosis[24], resulting in emerging therapeutic strategies to remove M2 TAMs or alter TAM phenotypes, which can facilitate promising therapeutic benefits.

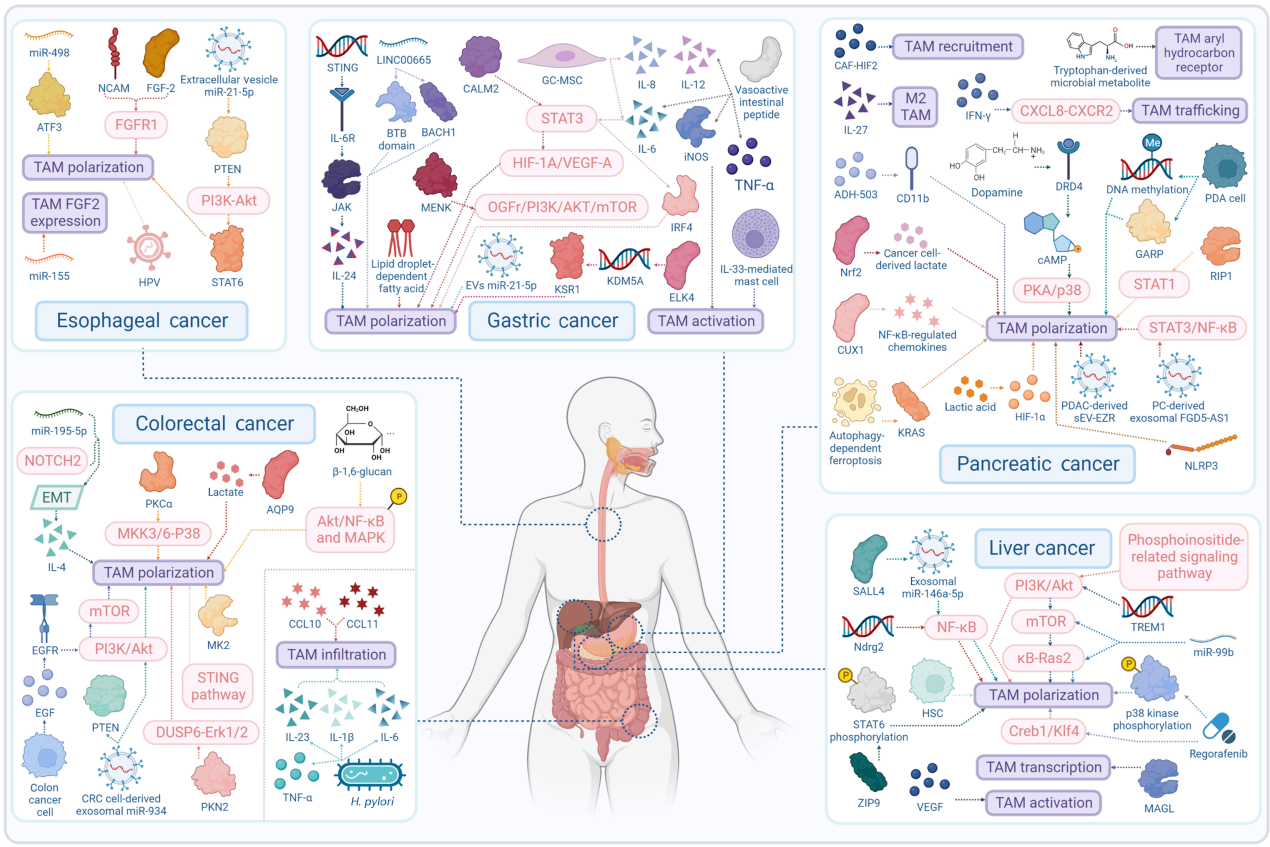

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Figure 2 Tumor-associated macrophages act as potential therapeutic targets for tumors. Multifarious strategies for modulation of tumor-associated macrophages (TAMs) are unveiled for therapeutic applications, which are varying in different digestive system malignant tumors. Color differences indicate various approaches to regulate TAMs' behaviors, the arrows represent secretory or regulatory behaviors, and braces represent combined action of the factors. Moreover, the pink icons stand for common signaling pathways, the green icons stand for biological processes, and the purple icons stand for different reactions of TAMs, including TAMs' polarization, activation, recruitment, trafficking, infiltration, transcription, and so on. Tumor and immune cells secrete growth factors, cytokines, chemokines, metabolites and extracellular vesicles that promote TAM protumor polarization. Besides, RNA, virus and specific cells also exert influence on TAM plasticity and activation. Several key signaling pathways are involved in these regulation processes, including phosphoinositide 3-kinase-Akt-mammalian target of rapamycin, nuclear factor kB, stimulator of interferon genes, and so on. Thus, TAMs can act as a promising potential therapeutic target for digestive system malignant tumors. NCAM: Neural cell adhesion molecule; FGF-2: Fibroblast growth factor 2; ATF3: Activation transcription factor 3; TAM: Tumor-associated macrophages; PI3K: Phosphoinositide 3-kinase; HPV: Human papillomavirus; STAT3: Signal transducers and activator of transcription 3; STING: Stimulator of interferon genes; IL: Interleukin; TNF-α: Tumor necrosis factor-α; VEGF: Vascular endothelial growth factor; mTOR: Mammalian target of rapamycin; iNOS: Inducible nitric oxide synthase; NF-kB: Nuclear factor kB; MAGL: Monoacylglycerol lipase; TREM: Triggering receptors expressed on myeloid cells; EMT: Epithelial mesenchymal transition; EGF: Epidermal growth factor; HSC: Hematopoietic stem cell; GARP: Glycoprotein A repetitions predominant; IFN-γ: Interferon-γ; EVs: Extracellular vesicles; CCL: CC ligand; PTEN: Phosphatase and tensin homolog.

Interaction of TAMs and T cells

Numerous studies have shown that TAMs can directly and indirectly dampen the antitumor activity of cytotoxic T lymphocytes (CTLs)[25] and tumor-infiltrating T cells[26] in various tumors[27,28]. Underlying this functional role are molecular mechanisms that initially involve immune checkpoint engagement, which is initially mediated through the expression of molecules like programmed cell death 1 (PD-1) ligand 1 (PD-L1)[29]. In addition, the production of inhibitory cytokines and transcription factors are also implicated in the suppression progress, which mainly include IL-10[28], interferon (IFN)-γ[30], transforming growth factor (TGF)-β[31,32] and HIF-1α[26]. Metabolic activities of TAMs, concerning the consumption of metabolites such as L-arginine[33] and generation of reactive oxygen species, also contribute to suppression of T-cell responses that is either specific to or independent of antigens. Finally, TAMs inhibit T-cell responses indirectly by controlling the immune microenvironment, including regulation of the vascular structure, extracellular matrix[34] and the chemokine milieu, such as TAM-derived chemokine CXC ligand (CXCL)9 and CXCL10[35]. Conversely, T regulatory (Treg) cells maintain metabolic adaptability, mitochondrial integrity, and survival rate of M2-like TAMs in an indirect but selective manner. This is achieved through the inhibition of IFN-γ secretion by CD8+ T cells, which subsequently hinders the activation of fatty acid synthesis intervened by sterol regulatory element binding protein 1 in immunosuppressive M2-like TAMs[36].

Specifically in digestive system cancers, TAMs are similarly thought to have mutual modulation with T cells, including but not limited to blocking the recruitment and priming of T cells and resulting in T-cell exclusion within the TME. In GC, TAMs and LAMP3$^+$ dendritic cells (DCs) are involved in mediating T-cell activity and form intercellular interaction hubs with tumor-associated stromal cells [37]. IL-10$^+$ TAM infiltration yielded an immunoevasive TME featured by Treg cell infiltration and CD8$^+$ T-cell dysfunction[38]. In CRC, C1q$^+$ TAMs modulate tumor-infiltrating CD8$^+$ T cells by expressing multiple immunomodulatory ligands in an RNA N6-methyladenosine (m6A)-dependent manner. There is evidence that compensation between TAMs and Forkhead box (Fox)p3$^+$ Treg cells promote tumor progression by limiting antitumor immunity. Decreasing colony-stimulating factor (CSF)1-dependent TAMs led to heightened CD8$^+$ T-cell against tumors, although the impact on tumor growth was restricted by a compensatory rise in Foxp3$^+$ Treg cells[39]. In pancreatic ductal adenocarcinoma (PDAC), receptor-interacting serine/threonine protein kinase (RIP)1 inhibition in TAMs resulted in CTL activation and T helper (Th) cell differentiation toward a mixed Th1/Th17 phenotype[40]. By targeting proliferating tumor-infiltrating macrophages, the infiltration of CD8$^+$ CTL and the spatial redistribution of CD8$^+$ T cells within tumors could be escalated[41]. TAMs are critical regulators in orchestrating epigenetic profile of PDAC-infiltrating T cells towards a protumoral phenotype[42]. In hepatocellular carcinoma (HCC), HCC-derived exosomes instigate macrophages to heighten IFN-γ and TNF-α expression in T cells, while upregulating the expression of inhibitory receptors PD-1 and cytotoxic T-lymphocyte-associated antigen-4[43]. These findings collectively demonstrate that TAMs are central drivers of immunosuppressive TME within digestive system tumors by suppressing T cell mobilization and performance.

TAMS AND TARGETED THERAPIES OF DIGESTIVE SYSTEM MALIGNANT TUMORS

EC

TAMs can promote development of EC: TAMs can facilitate a variety of protumorigenic mechanisms in EC (Figure 1 and Table 1). In esophageal squamous cell carcinoma (ESCC), growth differentiation factor 15 derived from TAMs promoted cancer progression *via* TGF-β type II receptor activation[44].

TAMs act as potential therapeutic targets for EC: TAMs might be potential therapeutic targets to prevent EC progression (Table 2). There is evidence supporting that miR-498 inhibits autophagy and M2-like polarization of TAMs in EC *via* inhibiting murine double minute 2-mediated degradation of activated transcription factor-3[45]. miR-155-regulated fibroblast growth factor (FGF)-2 expression from TAMs inhibited EC cell invasion, migration and proliferation, and blocked vasculature formation[46]. EC-derived extracellular vesicle miR-21-5p upregulated ESCC-derived EVs-miR-21-5p through the phosphatase and tensin homolog (PTEN)/AKT/signal transducers and activator of transcription (STAT)6 pathway, thus disorganizing macrophage polarization through, and contributing to epithelial mesenchymal transition (EMT) of ESCC cells *via* TGF-β/Smad2 signaling[47]. PTEN induced M2 TAM polarization through the phosphoinositide 3-kinase (PI3K)/AKT cascade, thus enhancing the malignant behavior of tumor-associated vascular endothelial cells and promoting ESCC angiogenesis[48]. Neural-cell-adhesion-molecule- and FGF2-mediated FGFR1 signaling in the TME of EC regulated the survival and migration of TAMs and cancer cells[49]. Human papillomavirus 16 infection can promote an M2 macrophage phenotype, contributing to the invasion and metastasis of ESCC[50].

Clinical significance of TAMs in EC: Clinically, TAMs are associated with the response of EC to chemotherapy. In patients undergoing neoadjuvant chemotherapy, high infiltration of CD68$^+$/CD163$^-$ macrophages can serve as an adverse prognostic factor in esophageal and gastric adenocarcinoma[51, 52].

GC

TAMs can promote development of GC: In GC, peritoneal dissemination transpires through an invasive mechanism in which cancer cells directly penetrate the gastric wall and exfoliate into the peritoneal cavity (Table 1). Stimulation with anti-inflammatory triggers (such as TNF-α and IL-6), growth factors [such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and TGF-β2], chemokines [such as chemokine CC ligand (CCL)5], exosomes and enzymes (such as MMP and PI3K/Akt), leads to expression of transcription factors [such as STAT6, nuclear factor (NF)-κB and Snail) (Figure 1). Intraperitoneal TAMs are involved in promoting peritoneal dissemination of GC *via* secreted IL-6[53] and polarization to the M2 phenotype[54].

Numerous studies have demonstrated that TAMs are capable of express multifarious cytokines and chemokines that promote tumor cell proliferation and viability, including EGF[55], VEGF[55], TNF-α [56], TGF-β2[57], IL-6[56], and CCL5[58]. TAMs can facilitate the development of GC through multiple signal pathways, such as cyclooxygenase-2/prostaglandin E2/TGF-β/VEGF[59], and CCL5/chemokine CC receptor 5/STAT3[60].

Table 1 Tumor-associated macrophages can promote the development of tumors

Diseases	Factors	Functions	Mechanism	Ref.
EC	GDF-15 derived from TAMs	Promoting progression of ESCC	Activating TGF-β type II receptor	[44]
GC	TAMs	Promoting peritoneal dissemination of GC	Secreting IL-6	[53]
	TAMs	Promoting progression in GC	Polarizing to the M2 phenotype	[54]
	TAMs	Supporting peritoneal metastasis	Producing EGF and VEGF	[55]
	TNF-alpha and IL-6 secreted by TAMs	Promoting proliferation of GC cells	Activating the NF-κB and STAT3 signaling pathway to regulate PD-L1 expression	[56]
	TGFβ2 secreted by TAMs	Promoting the invasion of GC cells	Regulating Kindlin-2 through NF-κB	[57]
	CCL5 secreted by TAMs	Promoting the proliferation, invasion and metastasis of GC cells	Stat3 signaling pathway	[58]
	TAMs	Influencing omental milky spots and lymph nodes micrometastasis	COX-2/PGE-2/TGF-β/VEGF signal pathways	[59]
	TAMs	Promoting epigenetic silencing of tumor suppressor gelsolin, and silence GSN	Upregulation of DNMT1 by CCL5/CCR5/STAT3 signaling	[60]
	TAMs	Inducing invasion and poor prognosis in GC	Promoting MMP9 expression	[63]
	MMP-9 secreted by TAMs	Suppressing distant metastasis in GC	PI3K/AKT/Snail dependent pathway	[64]
	Exosomal miR-487a derived from TAMs	Promoting the proliferation and tumorigenesis in GC	-	[65]
	M2 macrophage-derived exosomes	Remodeling the cytoskeleton-supporting migration in recipient GC cells	Mediating an intercellular transfer of ApoE-activating PI3K-Akt signaling pathway	[66]
CRC	TAMs	Potentiating the angiogenic capacity of the TME	Oxidative stress-dependent manner	[91]
	Metabolic reprogramming in TAMs	Building a bridge between metabolic dysfunction and the onset and progression of CRC	Inflammatory pathways	[92]
	M2 macrophage-derived exosomes	Promoting CRC cells' migration and invasion	MiR-21-5p and miR-155-5p	[93]
	Exosomal miR-183-5p Shuttled by M2 TAMs	Promoting the development of colon cancer	THEM4 mediated PI3K/AKT and NF-κB pathways	[94]
	MMP1 derived from TAMs	Facilitating colon cancer cell proliferation	Accelerating cell cycle transition from G0/G1 to S and G2/M phase	[95]
	M2 TAMs	Inducing colon cancer cell invasion	MMP-9	[96]
	Cathelicidin secreted by TAMs	Promoting the growth of CRC	Recruiting inflammatory cells	[97]
PC	Intraperitoneal TAMs	Promoting peritoneal dissemination and chemoresistance	Inducing EMT	[123]
	M2 TAMs	Promoting EMT	TLR4/IL-10 signaling	[124]
	TAMs	Promoting progression and the Warburg effect	CCL18/NF-Kb/VCAM-1 pathway	[125]
	CCL20 secreted by M2 TAMs	Promoting the migration, epithelial-mesenchymal transition, and invasion of pancreatic cancer cells	-	[126]
	TAMs	Orchestrating functions PDA-infiltrating T cells	Odulating PDA-infiltrating T cells epigenetic profile towards a pro-tumoral phenotype	[42]
LC	TAMs	Promoting LCSLC self-renewal capability and carcinogenicity	M2 polarization	[151]

TAMs	Promoting EMT of Hep3B hepatoma cells	TLR4	[153]
IL-6 secreted by TAMs	Promoting expansion of these CSCs and tumorigenesis	STAT3 signaling	[154]

Tumor-associated macrophages (TAMs) contribute to the development of esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer and liver cancer. The effective factors are TAMs and their derivants or secretions. The function indicates that how these factors exert influence on tumor progression, concerning proliferation, invasion, metastasis, migration and so on. In addition, the mechanism indicates the corresponding signaling pathways or regulatory intermediates, through which TAMs and their derivants promote or suppress development of the cancers. The last column indicates the corresponding reference of the entry. EC: Esophageal cancer; GC: Gastric cancer; CRC: Colorectal cancer; PC: Pancreatic cancer; LC: Liver cancer; GDF-15: Growth/differentiation factor-15; TAM: Tumor-associated macrophages; ESCC: Esophageal squamous cell carcinoma; TGF-β: Transforming growth factor-β; IL: Interleukin; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor-α; NF-kB: Nuclear factor kB; STAT3: Signal transducers and activator of transcription 3; PD-L1: Programmed Cell Death Ligand 1; PGE-2: Prostaglandin E2; PI3K: Phosphoinositide 3-kinase; MMP9: Matrix metalloproteinases 9; CCL5: CC ligand 5; TLR4: Toll like receptor 4; LCSLC: Liver cancer stem-like cell; CSC: Cancer stem cell.

It is also reported that TAMs may promote the invasion, metastasis and poor prognosis of GC cells by increasing expression of MMP9 and MMP2[61-63], mechanistically involving the PI3K/AKT/Snail-dependent pathway[64].

As for exosomes like exosomal miR-487a[65] derived from M2 macrophages, they can promote the proliferation and tumorigenesis, and remodel cytoskeleton-supporting migration in GC, through the ApoE-activating PI3K/Akt signaling pathway[66].

TAMs act as potential therapeutic targets for GC: As a potential therapeutic target in GC, TAMs can be reprogrammed into a proinflammatory subtype by targeting many pathways (Table 2), such as the stimulator of interferon genes (STING) pathway[67]. At the RNA level, LINC00665 interfaces with transcription factor BTB domain and CNC homology 1 to activate Wnt1 and mediates M2 polarization of TAMs in GC[68]. Many proteins can also mediate TAM polarization (calmodulin 2[69], methionine enkephalin[70], ETS-like transcription factor 4[71], IL-6[72], and IL-8[73]) and repress TAM activation (vasoactive intestinal peptide[74]), *via* signaling pathways such as STAT3/HIF-1A/VEGF-A axis[69], opioid growth factor receptor/PI3K/AKT/mammalian target of rapamycin (mTOR) axis[70], and IL-6/STAT3/interferon regulatory factor 4 axis[72], and so on. Lipid-droplet-dependent fatty acid metabolism[75] and miR-151-3p derived from GC exosomes[76] can also control the immunosuppressive phenotype of TAMs.

TAMs can be regulated by other cells, such as tumor-promoting GC-derived mesenchymal stromal cells[74] and IL-33-mediated mast cells[77].

Clinical significance of TAMs in GC: More clinically, TAMs can be used to potentiate localized immunotherapy of GC. For instance, researchers created an injectable hydrogel that can shear-thin and is loaded with polyphyllin II and resiquimod, which can help potentiate localized immunotherapy of GC by repolarizing TAMs[78]. Polyclonal antibody stimulator monotherapy or combined with PD-1 antibody[79], as well as using a natural alkaloid product isolated from sophora alopecuroides. L, sophoridine[80], may decrease the number of immunosuppressive M2-polarized TAMs.

When it comes to chemotherapy, exosomes and other factors could represses the chemosensitivity of gastric tumor cells in a TAM-dependent manner. Exosomal transfer of TAM-derived miR-21 confers cisplatin resistance in GC cells[81]. Yu *et al*[82] discovered that macrophages can be stimulated into a tumor-protective M2-like phenotype by tumor-derived leukemia inhibitory factor through activation of the STAT3 signaling pathway[82]. 5-Fluorouracil (5-FU) treatment activates HIF-1α in GC cells, leading to the accumulation of M2 TAMs that shield tumor cells from the effects of chemotherapeutic agents [83]. By generating growth differentiation factor 15 to exacerbate fatty acid β-oxidation in tumor cells, the recruited TAMs display the tumor-supporting M2 phenotype and enhance the chemoresistance of GC cells. And inversely polarized M2 macrophages can potentiate 5-FU resistance in tumors *via* CCL8 and phosphorylation of the Janus kinase 1/STAT3 signaling pathway[84].

The positive correlation between high level of TAMs in tumors and low overall survival of patients has been demonstrated. High density of M2 TAMs was associated with larger tumor size, diffuse Lauren type, poor histological differentiation, deeper tumor invasion, lymph node metastasis, and advanced TNM stage[85]. Abundance of CD163-positive TAMs in early GC[86] as well as $CD206^+$ myeloid-derived TAMs[87] predict te recurrence after curative resection. $CD8^+$ tumor-infiltrating lymphocytes and $CD68^+$ TAMs[88], and high expression of HIF-1α combined with TAM infiltration[89] and coexistence of osteopontin and infiltrating M2 TAMs[90] can serve as a prognostic marker in GC.

CRC

TAMs can promote the development of CRC: The protumor role of TAMs in the development of colon carcinoma has been confirmed (Table 1). TAMs work with exosomes, MMP and cathelicidin, concerning signaling pathways (such as PI3K/Akt and NF-κB), cell cycle transition, metabolic reprogramming, inflammatory pathways, and oxidative stress (Figure 1). TAMs potentiate the angiogenic capacity of the

Table 2 Tumor-associated macrophages act as potential therapeutic targets for tumors

Diseases	Factors	Types	Targets	Functions	Mechanism	Ref.
EC	MiR-498	MiRNA	Inhibiting autophagy and M2-like polarization of TAMs in esophageal cancer	-	Inhibiting MDM2-mediated ATF3 degradation	[45]
	MiR-155	MiRNA	Regulating TAMs FGF2 expression	Suppressing EC cell proliferation, migration, invasion and inhibiting vasculature formation	-	[46]
	EC-Derived Extracellular Vesicle miR-21-5p	MiRNA	Disorganizing macrophages polarization	Contributing to EMT of ESCC cells *via* TGF-β/Smad2 signaling	PTEN/AKT/STAT6 pathway	[47]
	PTEN	Protein	Inducing M2 TAMs polarization	Enhancing the malignant behavior of TECs, promoting ESCC angiogenesis	Activating the PI3K/AKT signaling pathway	[48]
	NCAM- and FGF-2-mediated FGFR1 signaling	Signaling	Regulating the survival and migration of TAMs and cancer cells	-	NCAM knockdown *via* a suppression of PI3K-Akt and FGFR1 signaling, and rhFGF-2 -through FGFR1 signaling	[49]
	HR-HPV; HPV16 infection	Virus	Promoting M2 macrophages phenotype	Promoting the invasion and metastasis of esophageal squamous cell carcinoma	-	[50]
GC	STING	Gene	Promoting TAMs polarizing into pro-inflammatory subtype	Inducing apoptosis of GC cells	IL6R-JAK-L24pathway	[67]
	LINC00665	LncRNA	Activating Wnt1 and mediating TAMs M2 polarization	-	Interacting with BTB domain and BACH1	[68]
	CALM2	Protein	Polarizing TAMs	Facilitating angiogenesis and metastasis of GC	STAT3/HIF-1A/VEGF-A	[69]
	MENK	Protein	Skewing macrophages toward M2 phenotype from M1 phenotype	Inducing cells apoptosis	OGFr/PI3K/AKT/Mtor signaling pathway	[70]
	ELK4	Transcription factor	Promoting M2 polarization	Promoting the development of GC	Reducing the PJA2-dependent inhibition of KSR1 by transcriptional activation of KDM5A	[71]
	IL-6	Cytokine	Polarizing the Mφs	Promoting tumor invasion	IL-6/STAT3/IRF4 signaling pathway	[72]
	GC-MSCs	Cell	Promoting M2 polarization	Promoting metastasis and EMT in GC	Secreting IL-6 and IL-8	[73]
	Vasoactive intestinal peptide	Protein	Repressing activation of TAMs	-	Regulating TNFα, IL-6, IL-12 and Inos	[74]
	Lipid droplet-dependent fatty acid	Fatty acid	Controlling the immune suppressive phenotype of TAMs	-	-	[75]
	MiR-151-3p derived from GC exosomes	Exosome	Inducing M2-phenotype polarization	Promoting tumor growth	-	[76]
	IL-33-mediated mast cell	Cell	Mobilizing macrophages	Promoting GC	-	[77]
CRC	PKN2	Protein	Inhibiting M2 phenotype polarization	-	DUSP6-Erk1/2 pathway	[98]
	AQP9	Protein	Stimulating M2-like polarization	Promoting colon cancer progression	Transporting lactate	[99]
	PKCα	Tumor suppressor	Promoting M1 macrophages polarization	-	MKK3/6-P38 signaling pathway	[100]
	MK2	Protein	Promoting polarization	-	-	[101]

			of protumorigenic TAMs			
	MiR-195-5p/NOTCH2-mediated EMT	-	Affecting M2-like TAMs polarization	-	Modulating IL-4 secretion	[102]
	CRC cell-derived exosomal miR-934	Exosome	Inducing M2 macrophages polarization	-	Downregulating PTEN expression and activate the PI3K/AKT signaling pathway	[103]
	Stimulator of STING pathway	Signaling pathway	Activating reprogramed TAMs toward the M1 phenotype	-	-	[104]
	Colon cancer cell	Cell	Promoting M2 polarization of TAMs	-	Secreting EGF; EGFR/PI3K/AKT/Mtor pathway	[105]
	CXCL10 and CXCL11	Chemokine	Inducing the infiltration of TAMs	Leading to the poor prognosis of CRC	-	[106]
	β-1, 6-glucan	Organic compound	Reseting TAMs from M2-like to M1-like phenotype	Inhibiting the viability of colon cancer cells	Increasing the phosphorylation of Akt/NF-κB and MAPK	[107]
	H. pylori infection	Becteria	Reducing the infiltration of M2-like TAMs	-	Downregulating TNF-α, IL-1β, IL-6 and IL-23	[108]
PC	Autophagy-dependent ferroptosis	-	Driving TAMs polarization	-	Releasing and uptaking of oncogenic KRAS protein	[127]
	RIP1	Kinase	Reprogramming TAMs	-	STAT1-dependent manner	[40]
	Deletion of CAF-HIF2	Protein	Decreasing the intratumoral recruitment of immunosuppressive M2 macrophages	-	-	[128]
	ADH-503	Small-molecule agonist	Leading to the repolarization of TAMs	-	Partial activation of CD11b	[129]
	NLRP3	Inflammasome	Regulating TAMs polarization	Enhancing lung metastasis of PDAC	-	[130]
	IL-27	Cytokine	Targeting M2 TAMs	Dampening the proliferation, migration and metastasis of PC cells	-	[131]
	IFN-γ	Chemokines	Preventing trafficking of TAMs	Improving the efficacy of PD1 blockade therapy in PC	Blocking the CXCL8-CXCR2 axis	[132]
	PC-derived exosomal FGD5-AS1	Exosome	Stimulating M2 macrophages polarization	Promoting proliferation and migration of PC cell	Activating STAT3/NF-κB pathway	[133]
	PDAC-derived Sev-EZR	Exosome	Modulating TAMs polarization	Promoting PDAC metastasis	-	[134]
	CUX1	Transcription factor	Mediating M1 polarization	Inhibiting angiogenesis and tumor progression	Downregulating several NF-κB -regulated chemokines	[135]
	Tryptophan-derived microbial metabolite	Metabolite	Activating the aryl hydrocarbon receptor in TAMs	Suppressing anti-tumor immunity	-	[136]
	Nrf2	Transcription factor	Stimulating M2 macrophages polarization	Promoting EMT	Activating cancer cell-derived lactate	[137]
	Lactic acid	Organic compound	Redistributing M2TAMs subsets	Upregulating PDL1 to assist tumor immune escape	HIF1α signaling pathway	[138]
	Activation of DRD4 by DA	Protein	Suppressing the tumor-promoting inflammation of TAMs	-	Decreasing Camp; inhibit the activation of PKA/p38 signal pathway	[139]
	PDA cells	Cell	Reprogramming M1-like macrophages	-	GARP-dependent and DNA methylation-mediated mechanism	[140]

LC	Ndrg2	Gene	Influencing TAMs polarization	-	NF-κB pathway	[155]
	TREM1knockdown	Gene	Shifting M2 macrophages towards a M1 phenotype	-	Inhibiting PI3K/AKT/Mtor activation	[156]
	MiR-99b	MiRNA	Promoting M1 while suppressing M2 macrophages polarization	-	Targeting κB -Ras2 and/or mTOR	[157]
	MAGL	Kinase	Promoting the transcription and secretion of inflammatory factors in TAMs	-	-	[158]
	-	-	Blocking triggering receptor expressed on myeloid cells-1-positive TAMs	Reversing immunosuppression and anti-PD-L1 resistance in LC	-	[159]
	Regorafenib	Multikinase inhibitors	Reversing M2 polarization	-	Suppressing p38 kinase phosphorylation and downregulating Creb1/Klf4 activity in BMDMs	[160]
	ZIP9	Protein	Promoting M2 macrophages polarization	-	Enhancing phosphorylated STAT6	[161]
	Phosphoinositide-related signaling pathway	Signaling pathway	Reprogramming TAMs	-	Enhancing activation of the PI3K/Akt pathway	[162]
	Inhibite VEGF signaling pathway	Signaling pathway	Attenuating TAMs activity in liver cancer	-	-	[163]
	SALL4-mediated upregulation of exosomal miR-146a-5p	Exosome	Leading to M2-polarized TAMs	-	Activating NF-κB signaling and inducing pro-inflammatory factors	[43]
	Activated HSCs	Cell	Converting macrophages to TAMs	-	-	[164]

In esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer and liver cancer, there are multifarious approaches to regulate tumor-associated macrophages (TAMs), the effective factors of which, and corresponding types, are presented in the second and third column. The targets indicate which behaviors of TAMs that are modulated. In addition, the functions, mechanism and reference section are similar as Table 1. EC: Esophageal cancer; GC: Gastric cancer; CRC: Colorectal cancer; PC: Pancreatic cancer; LC: Liver cancer; TAM: Tumor-associated macrophages; PTEN: Phosphatase and tensin homolog; TEC: Tumor endothelial cells; STAT3: Signal transducers and activator of transcription 3; ESCC: Esophageal squamous cell carcinoma; NCAM: Neural cell adhesion molecule; FGF-2: Fibroblast growth factor 2; HPV: Human papillomavirus; VEGF: Vascular endothelial growth factor; STING: Stimulator of interferon genes; MSC: Mesenchymal stem cell; TNF-α: Tumor necrosis factor-α; IL: Interleukin; PI3K: Phosphoinositide 3-kinase; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; STAT1: Signal transducers and activator of transcription 1; IFN-γ: Interferon-γ; GARP: Glycoprotein A repetitions predominant; HIF-1α: Hypoxia-inducible factor-1α; PD-L1: Programmed Cell Death Ligand 1; EMT: Epithelial mesenchymal transition; mTOR: Mammalian target of rapamycin; HSC: Hematopoietic stem cell; OGFR: Opioid growth factor receptor; Nrf2: Nuclear factor erythroid 2-related factor 2.

TME in an oxidative-stress-dependent manner[91] or by metabolic reprogramming[92].

M2-macrophage-mediated regulation of CRC cell migration and invasion relies on M2-macrophage-derived exosomes, such as miR-21-5p and miR-155-5p[93], which may take effect through downregulating expression of *BRG1*. Exosomal miR-183-5p transferred by M2 polarized TAMs facilitate colon cancer through targeting thioesterase superfamily member 4-mediated PI3K/AKT and NF-kB pathways [94].

Multiple studies indicated that MMPs, such as MMP1 and MMP9, derived from TAMs may induce colon cancer cell invasion and proliferation[95,96]. It has been demonstrated that cathelicidin secreted by TAMs can promote the growth of CRC in mice by recruiting inflammatory cells such as macrophages into the TME[97].

TAMs act as potential therapeutic targets for CRC: In colon carcinoma, TAM M2 phenotype polarization can be regulated by diverse proteins (Table 2), such as protein kinase N2[98], aquaporin 9 [99], tumor suppressor protein kinase (PK)Cα[100], and MAPKAP kinase 2[101]. miR-195-5p/NOTCH2-mediated EMT also affects M2-like TAM polarization by modulating IL-4 secretion in CRC[102], as does CRC-cell-derived exosomal miR-934 by downregulating PTEN expression and activating the PI3K/AKT signaling pathway[103].

The activation of pathways like the STING[104] and EGFR/PI3K/AKT/mTOR axis[105] has some of this same functionality. As chemokines, neuroendocrine-like-cell-derived CXCL10 and CXCL11 expand the infiltration of TAMs, accounting of the poor prognosis of CRC[106].

From the metabolic perspective, β-1,6-glucan resets tumor-supporting M2-like macrophages to tumor-inhibiting M1-like phenotype by activating the phosphorylation of Akt/NF-kB) and mitogen-activated protein kinase[107]. In mice with colitis-associated colorectal tumors, *Helicobacter pylori* infection quenched infiltration of TAMs, especially M2-like TAMs, while downregulating proinflammatory and protumorigenic factors TNF-α, IL-1β, IL-6, and IL-23[108].

Clinical significance of TAMs in CRC: TAMs with an M2-like phenotype have been associated with immunosuppression and resistance to chemotherapy of CRC. CD206/CD68 ratio[109] functions as a potent prognostic biomarker for predicting postoperative adjuvant chemotherapy in stage II colon cancer. In CRC, high infiltration of $CD68^+$ TAMs[110], as well as type and number of intratumoral macrophages and clever-$1^{(+)}$ vessel density[111] could both function as a favorable prognostic marker.

Several TAM-targeting immunotherapies have been shown to promote antitumor immunity in CRC. A ketogenic diet restrains colon tumors *via* inducing intratumor oxidative stress through downregulation of MMP9 expression, and facilitating the polarization of TAM towards an M1-like proinflammatory phenotype[112]. By re-educating TAMs in CRC, piceatannol is an effective TGF-β1/TGF-Br1 pathway inhibitor and TME modulator that inhibits tumor progression and metastasis[113]. Licorne-mediated immunogenic photodynamic therapy synergizes with myeloid-derived suppressor cell (MDSC)-targeting immunotherapy[114], Bte-Pd-Au-R-combined radiophotothermal therapy[115], as well as combination of foretinib and anti-PD-1 antibody immunotherapy[116] significantly inhibited tumor growth *via* decreasing tumor infiltration or the percentage of M2-like TAMs. Numerous studies have demonstrated that triptolide decreased TAM infiltration and M2 polarization[117] to remodel the colon cancer immune microenvironment through suppressing the sphingosine kinase–sphingosine-1-phosphate signaling pathway[118], or inhibiting tumor-derived CXCL12 *via* NF-kB and the extracellular signal-regulated protein kinases 1 and 2 axis[119]. Plinabulin[120], a distinct microtubule-targeting chemotherapy, as well as short-course radiotherapy[121], promoted a shift in M2 to M1 TAM polarization.

PC

TAMs can promote development of PC: Pancreatic tumors are characterized by a desmoplastic stroma consisting of fibroblasts, immune cells, and a dense network of collagen fibers. Within this stroma, TAMs are among the most numerous immune cell populations[122]. Their protumorigenic function is predominantly attributed to their capacity to facilitate immune evasion and metastasis (Figure 1 and Table 1).

In PC, intraperitoneal TAMs potentially play a crucial role in promoting peritoneal dissemination and chemoresistance by inducing EMT[123]. Similarly, M2-polarized TAMs enhanced EMT in PC cells partially *via* Toll like receptor (TLR)-4/IL-10 signaling[124]. TAMs promote progression and the Warburg effect *via* CCL18/NF-kB/vascular cellular adhesion molecule 1 pathway in PDAC[125]. In addition, CCL20 secreted by M2 macrophages promoted the migration, EMT, and invasion of PC cells [126]. The study indicated a decisive role of TAMs in orchestrating functions of PDAC-infiltrating T cells by modifying their epigenetic profile towards a pro-tumoral phenotype[42].

TAMs act as potential therapeutic targets for PC: TAMs can also act as potential therapeutic targets for PC (Table 2). Autophagy-dependent ferroptosis accelerates TAM polarization *via* secretion and absorption of oncogenic KRAS protein[127]. Researchers discovered upregulation of RIP-1 in TAMs in PDAC[40]. Deletion of cancer-associated fibroblast HIF-2 significantly decreased the intratumoral recruitment of immunosuppressive M2 macrophages[128]. Fractional activation of CD11b by a small-molecule agonist contributes to TAM repolarization[129]. NLRP3 activation in TAMs enhanced lung metastasis of PDAC through regulation of TAM polarization[130].

By targeting M2-like TAMs, IL-27 dampened the proliferation, migration and metastasis of PC cells and boosted the potency of gemcitabine[131]. IFN-γ is a potential translational strategy to optimize performance of PD-1 blockade therapy in PC by preventing migration of $CXCR2^+CD68^+$ macrophages by blocking the CXCL8/CXCR2 axis[132]. PC-derived exosomal FGD5-AS1 induced M2 macrophage polarization *via* STAT3/NF-κB pathway[133]. The PDAC-derived small extracellular vesicle Ezrin can modulate macrophage polarization and promote PDAC metastasis[134]. Cut like homeobox 1 suppresses handful NF-κB-regulated chemokines like CXCL10, which are linked with M1 polarization and hindrance of angiogenesis and tumor development[135].

In addition, tryptophan-derived microbial metabolites stimulate the aryl hydrocarbon receptor in TAMs to inhibit antitumor immunity[136]. Cancer-cell-derived lactate activates macrophage nuclear factor erythroid 2-related factor 2 (Nrf2), skewing macrophages polarization towards an M2-like phenotype. These educated macrophages then trigger Nrf2 activation in cancer cells, ultimately promoting EMT[137]. Modulation of lactic acid level can redistribute M2 TAMs and upregulate PD-L1 to assist tumor immune escape, possibly through the HIF-1α signaling pathway[138]. Activation of dopamine receptor D4 by dopamine is instrumental in a depletion of cAMP, thereby hindering the

activation of the PKA/p38 signaling pathway, ultimately leading to the suppression of tumor-promoting inflammation of TAMs[139].

For PC cells themselves, they render TAMs metabolically reprogrammed through a glycoprotein A repetitions predominant (GARP)-dependent and DNA-methylation-mediated mechanism to adopt a precancerous fate[140].

Clinical significance of TAMs in PC: The association between TAMs and immune response has primarily been observed as a reduction in the immunostimulatory function of TAMs.

An exosome-based dual delivery biosystem was created to improve immunotherapy for PDAC and reverse immunosuppression of M2 TAMs upon disruption of the galectin-9/dectin 1 axis[141]. A TME-responsive micellar system co-loaded with gemcitabine and PI3K inhibitor wortmannin was employed to achieve dual targeting of TAMs and tumor cells, aimed at repolarizing TAMs and improving the chemoimmunotherapy efficacy against PC[142].

Hyaluronic acid nanoparticle-encapsulated miRNA-125b reprogrammed TAMs to an antitumor phenotype in PDAC[143]. M2-TAM-targeting nanomicelles were created to simultaneously deliver PI3K-γ inhibitor NVP-BEZ 235 and CSF-1R-siRNA, leading to specific TAM reprogramming and antitumor immune response activation[144]. A customized nanocomplex through the self-assembling synthetic 4-(phosphonooxy)phenyl-2,4-dinitrobenzenesulfonate and Fe^{3+}, subsequently decorated with hyaluronic acid, jointly repolarized TAMs to deactivate stromal cells and therefore weaken stroma[145]. A reduction-responsive RNAi nanoplatform utilized its reduction-responsive characteristic to rapidly release siRNA, inducing depolarization of TAMs into tumor-inhibiting M1-like phenotype[146].

To aid diagnosis, metabolizable near-infrared-II nanoprobes were applied to dynamic imaging of deep-seated TAMs in PC[147]. DN-ICG nanoprobes were qualified to discern dynamic variation of TAMs stimulated by low-dose radiotherapy and zoledronic acid.

By activating M2-like TAM polarization, atorvastatin mitigates the effect of aspirin on PC development and the chemotherapeutic potency of gemcitabine in PC[148]. Combined blockade of TGF-β1 and granulocyte-macrophage CSF improves chemotherapeutic effects in PC by modulating the TME [149]. In tumor-bearing *Klebsiella pneumoniae* carbapenemase mice, pharmacological TAM depletion enhanced therapeutic response to gemcitabine[150].

LC

TAMs can promote development of LC: TAMs have been proved to promote the development of LC (Table 1). M2 polarization of TAMs in the TME promotes LC stem-like cell self-renewal capability and carcinogenicity[151,152]. Since TAMs can hasten EMT of Hep3B hepatoma cells, reduction of TLR4 expression in TAMs may attenuate that[153]. TAMs produce IL-6, which promotes expansion of these cancer stem cells and tumorigenesis. Restraint of TAM-stimulated CD44+ cell activity can be attainable by obstructing IL-6 signaling using tocilizumab, a drug approved by the United States Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis[154].

TAMs act as potential therapeutic targets for LC: TAMs have also been found to serve as potential therapeutic targets for LC (Table 2). Researchers demonstrated that loss of *Ndrg-2* influenced TAM polarization *via* the NF-κB pathway[155]. Knocking down triggering receptors expressed on myeloid cells (TREM1) in macrophages quenched the activation of the PI3K/AKT/mTOR pathway in M2 macrophages polarization[156]. Targeted delivery of miR-99b and/or miR-125a into TAMs substantially decelerated the progression of HCC and Lewis lung cancer, particularly following miR-99b delivery [157].

The mechanistic study illustrated that the high expression of monoacylglycerol lipase promoted the transcription and excretion of inflammatory factors such as IL-1β, IL-6 and TNF-α in M2-type TAMs cells[158]. Blocking TREM1-positive TAMs induced by hypoxia reverses immunosuppression and anti-PD-L1 resistance in LC[159]. Regorafenib, a multikinase inhibitor, reversed M2 polarization by suppressing p38 kinase phosphorylation and downstream Creb1/Klf4 activity in BM-derived macrophages[160]. The zinc-regulated transporters, iron-regulated transporter-like protein 9 upregulates phosphorylated STAT6 to facilitate polarization of M2 macrophages while downregulating the phosphorylation of IκBα/β to hinder M1 macrophage polarization[161].

TNF-α-induced protein 8-like 1 redounded arousal of the PI3K/Akt pathway in macrophages by directly attaching to and modulating the metabolism of phosphatidylinositol 4,5-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate[162]. Inhibiting the VEGF signaling pathway was shown to attenuate TAM activity in LC[163]. Sal-like protein-4-mediated upregulation of exosomal miR-146a-5p remodeled macrophages by triggering NF-κB signaling and proinflammatory factors, contributing to M2-type polarization in TAMs[43].

In the TME, activated hematopoietic stem cells transform macrophages to TAMs and respectively stimulate the differentiation of DCs and monocytes into regulatory DCs and MDSCs[164].

Clinical significance of TAMs in LC: To reverse immunosuppressive process, a BisCCL2/5i mRNA nanoplatform was directly evolved, which appreciably ignited the antitumoral M1-type polarization in TAMs and reduced immunosuppression in the TME[165]. Researchers developed a nanoliposome-loaded C6-ceremide (LipC6) to reduce the number of TAMs and their production of reactive oxygen

species[166]. LipC6 animated TAM differentiation into M1 phenotype, which engendering a decrease in immunosuppression and an increase in CD8+ T cell activity.

By interference with insulin-like growth factor (IGF)-1 secretion, sorafenib altered macrophage polarization, reduced IGF-1-driven cancer growth *in vitro* and partially inhibited macrophage activation *in vivo*[167]. Elevated serum levels of taurocholic acid were associated with reduced sirtuin (SIRT)5 expression and an increase in M2-like TAMs in HCC patient samples. Treatment with cholestyramine, a bile acid sequestrant and FDA-approved medication for hyperlipemia, reversed the implication of SIRT5 deficiency in impelling M2-like polarized TAMs and LC progression[168]. The novel glycyrrhetinic acid-tetramethylpyrazine conjugate TOGA exerted an anti-hepatocarcinogenic effect by attenuating effectiveness of TAMs on tumor cells through a mechanism related to the NF-κB pathway [169].

In the HCC microenvironment, M2 TAMs secreted considerable amounts of IL-17, which suppressed oxaliplatin-induced tumor cell apoptosis by triggering chaperone-mediated autophagy and curtailing cyclin D1 expression[170]. Radiofrequency ablation suppressed protumoral activation of local TAMs [171]. The combination of zwitterionic chito-oligosaccharides (COSs) with a photothermal material impaired the undesirable tumor promotion of TAMs, thus enhancing the outcome of photothermal therapy. Zwitterionic COSs acted as potent immune activators to re-educate TAMs to M1[172].

CONCLUSION

TAMs play a significant role in digestive system malignant tumors; therefore, TAM modulation is an attractive potential therapeutic target to enhance antitumor immune response and inhibit tumor progression. So far, diverse clinical therapies targeting TAMs have proven to be effective, highlighting the clinical significance of TAMs in digestive system malignant tumors. However, there are still many questions about the characteristics and functions of TAMs in digestive system malignant tumors. Continuous basic, transformation and clinical research may reveal some new prospects, such as how to use TAMs to improve cancer outcomes. Therefore, this is a promising field of cancer treatment, which may provide fruitful results.

FOOTNOTES

Author contributions: Wu J and Wang Y designed study, revised the manuscript, reviewed the results and made critical comments on the manuscript; Shen Y, and Chen JX analyzed data and performed manuscript drafting; Li M and Xiang Z searched the literature and collected data; All authors reviewed and approved the final version; Shen Y and Chen JX contributed equally to this work; Wu J and Wang Y contributed equally to this work.

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