OncoTargets and Therapy

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REVIEW

Tumor-associated macrophage-derived cytokines enhance cancer stem-like characteristics through epithelial–mesenchymal transition

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: Cancer stem cells are a small population of cells with the potential for self-renewal and multi-directional differentiation and are an important source of cancer initiation, treatment resistance, and recurrence. Epithelial–mesenchymal transition (EMT) is a process in which epithelial cells lose their epithelial phenotype and convert to mesenchymal cells. Recent studies have shown that cancer cells undergoing EMT can become stem-like cells. Many kinds of tumors are associated with chronic inflammation, which plays a role in tumor progression. Among the various immune cells mediating chronic inflammation, macrophages account for ~30%–50% of the tumor mass. Macrophages are highly infiltrative in the tumor microenvironment and secrete a series of inflammatory factors and cytokines, such as transforming growth factor (TGF)-β, IL-6, IL-10, and tumor necrosis factor (TNF)-α, which promote EMT and enhance the stemness of cancer cells. This review summarizes and discusses recent research findings on some specific mechanisms of tumor-associated macrophage-derived cytokines in EMT and cancer stemness transition, which are emerging targets of cancer treatment.

Keywords: macrophage, cancer stem cell, tumor immunology, inflammatory cytokine, tumor microenvironment

Introduction

Cancer is a malignant disease with a high mortality that causes a significant burden to the society. Data have shown that up to 14.1 million people are likely to develop cancer annually starting in 2014, which has increased from ~10 million in the year 2003. In both developed and developing countries, cancer ranks second in mortality behind cardiovascular diseases.[1,2] Although substantial progress has been made in cancer treatments, major challenges remain, such as tumor recurrence, metastasis, and resistance after conventional treatment. Recent development of cancer stem cell (CSC) theory implies that CSCs within the tumor ultimately lead to cancer recurrence and metastasis causing patient mortality.[3] Traditional therapies can only eliminate treatment-sensitive cancer cells; however, CSCs survive due to treatment resistance and divide into offspring cells, resulting in rapid cancer recurrence. It is known that cancer progression is involved with chronic inflammation, a complex process due to interactions between various immune cells and inflammatory factors. Macrophages are one of the main infiltrating immune cells in chronic inflammation, secreting inflammatory factors and cytokines and influencing tumor angiogenesis and metastasis, particularly in CSCs.

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http://dx.doi.org/10.2147/OTT.S168317

Tumor inflammatory microenvironment

Tumor cells and their peripheral microenvironment have been likened to the relationship between "seeds and soil", a proposition first proposed by Stephen Paget in 1889.[4] The components that constitute the "soil", which in total are called the tumor microenvironment (TME), are extremely complex, and only some of them are understood, despite extensive research. The known elements include tumor cells, fibroblasts, inflammatory mediators, immune cells, reactive oxygen species, and tumor-associated cytokines, among others.[5,6] In addition, most cancer patients have a history of specific virus or bacterial infection; therefore, TMEs contain microorganism-related proteins, such as HBX protein in hepatocellular carcinoma (HCC) and the highly abundant tumorigenic proteins cagA and VacA toxins expressed by *Helicobacter pylori* in gastric cancer.[7,8]

As previously demonstrated, gene mutations and epigenetic alterations fundamentally trigger tumor initiation and progression. However, scientists have found that the TME plays a non-negligible role in tumor invasion, angiogenesis, and epithelial–mesenchymal transition (EMT; Table 1).

Tumor-associated macrophages

The macrophages that infiltrate the TME are defined as tumor-associated macrophages (TAMs). TAMs are one of the most important immune cells in the TME, which act as a bridge connecting the inflammatory microenvironment and the malignant phenotype of tumor cells. Certain cytokines derived from tumor cells and the TME such as CSF-1, chemokine (C-X-C motif) ligand 12, and CCL2/MCP-1 recruit mononuclear cells into the TME and activate them to become TAMs.[21,22]

Macrophages are highly plastic and can be activated into two polarized states through two pathways stimulated by different cytokines and chemokines from the TME. The Th1 cytokines such as LPS, IFN-γ, and tumor necrosis factor (TNF)-α induce macrophages into the M1 polarized state, which plays a role in promoting inflammation and antitumor activity, while M2-TAMs polarized by IL-4 and IL-13 function opposite to the M1 type in immunosuppression and anti-inflammation response.[23–26] Macrophages are abundant in multiple cancers compared with adjacent tissues, and their number positively correlates with cancer stage and poor prognosis, so M2-TAMs can be regarded as cancer-promoting cells.[27–29] TAMs play an indispensable role in the TME by secreting inflammatory factors that mediate the inflammatory microenvironment to regulate proliferation, metastasis, angiogenesis, immunosuppression, and EMT of various cancers (Table 2).

CSCs

CSCs are a small population of cells within tumors that were first found in human acute leukemia nearly 2 decades ago. They have the potential for self-renewal, differentiation, and unlimited proliferation and may divide into a series of heterogeneous cancer cell types resulting in cancer recurrence and treatment resistance.[43] The CSC theory proposed that CSCs cause tumor treatment failure by acting as progenitor cells that survive conventional treatment, and thus, cancer can be completely cured only by eliminating CSCs.

The origin of CSCs has generated much controversy, and there is still no consensus. Some researchers have argued that CSCs may be derived from normal stem cells or highly differentiated progenitor cells that have dedifferentiated.[44] Another view on the origin of CSCs is called the cell fusion theory. In this scenario, fusion genes such as *CD74-NRG1*, *FOXF1*, and *SYT-SSX* are generated after tumor cells fuse with bone marrow-derived progenitor cells, including hematopoietic stem cells and mesenchymal stem cells or

Table 1 Influence and mechanisms of components in the TME of cancer cells

Components or factors in TME	Effects on cancer or cancer patients	References
Cancer-associated fibroblasts	Radiosensitivity	9
	CXCL12 expression	10
	High autophagic activity	11
	EMT	12
Extracellular matrix	EMT	13
	Type I collagen, likely contributes to bladder cancer progression	14
	MMP-2 and MMP-9 degrading collagen type IV	15
Hypoxia condition	Angiogenesis	16 and 17
Immune cells	Immune escape	18 and 19
	Shorter survival or worse prognosis	20

Abbreviations: TME, tumor microenvironment; CXCL12, chemokine (C-X-C motif) ligand 12; EMT, epithelial–mesenchymal transition.

Table 2 Specific mechanisms of tumor invasion and progression triggered by TAMs

Tumor type	Malignant phenotype	Specific mechanisms	References
Breast cancer	Lymph node metastasis, invasion, poor prognosis, increased adhesion to blood and lymphatic endothelial cells, and angiogenesis	TAMs secret COX-2, inducing MMP-9 expression, promoting EMT, and promoting M2 macrophage polarization	26
		CCL18 released from TAMs promotes angiogenesis	30
HCC	Increased migration and invasion ability and apoptosis inhibition	TAM-derived IL-6 activates the STAT3 pathway, subsequently activating anti-apoptotic genes and cell cycle promoting genes	31
		Macrophage-derived IL-8 induces EMT via activating the JAK2/STAT3/Snail pathway	32–34
Gastric cancer	Immune escape; EMT	Macrophage-derived TGF-β1 impairs NK-cell function	35 and 36
Colon cancer	Lymphatic metastasis, histological types, and TNM stages	TAMs markedly induce HIF-1α and Sema4D expression in colon cancer cells	37
Ovarian cancer	Angiogenesis	Upregulation of IL-8 expression in ovarian cancer cells induced by macrophages	38
Mucoepidermoid carcinoma	Increased migration and invasion ability	TAMs are correlated with microvessel density and VEGF-A expression	39
BCC	Increased depth of invasion, microvessel density, and COX-2 expression	Macrophages induce BCC cells to release MMP-9, VEGF-A, and bFGF	40
Lung cancer	Increased PD-L1 expression	TAM-derived IFN-γ activates JAK/STAT3 and PI3K/AKT signaling pathways	41
	Lymph node metastasis and pleural invasion	TAMs secrete IL-10 and cathepsin B	42

Abbreviations: TAM, tumor-associated macrophage; EMT, epithelial–mesenchymal transition; HCC, hepatocellular carcinoma; TGF, transforming growth factor; NK, natural killer; BCC, basal cell carcinoma.

mononuclear cells from the TME, transforming various kinds of tumor cells into CSCs.[45–50] Cancer cells after cell fusion retain the ability of invasion and metastasis but have also acquired the potential for self-renewal and other stem-like characteristics. What has been confirmed is that CSCs are not like somatic stem cells or embryonic stem cells (ESCs), which exist in the body, but are acquired like tumor cells by tumorigenic factors, implying that the relationship between TME and CSCs is critical. What, if any, molecules from the TME promote the stemness transition?

Markers of CSCs

CSCs share some common surface markers with normal stem cells, such as CD133, CD44, and CD99.[51,52] ESC nuclear transcription factors such as SOX-2, Oct3/4, Klf-4, Nanog, and c-Myc are also regarded as CSC markers.[53–55] One study showed that even Nestin, a specific marker of neural stem cells, can be used to identify CSCs.[56] These markers can be utilized not only to identify and isolate CSCs but also to predict treatment efficacy in the clinic, shedding light on how CSCs contribute to poor survival and tumor progression.[55] The markers shared between CSCs and normal stem cells imply that there are some similar biological characteristics between them, such as self-renewal and endless proliferation, under the suitable conditions.

TAM-induced EMT of cancers

EMT is a process by which epithelial cells lose the tight junctions between cells and gain an elongated, fibroblast-like morphology similar to mesenchymal cells, along with downregulation of epithelial markers (E-cadherin, occludins, and claudins) and upregulation of mesenchymal markers (vimentin, fibronectin, and N-cadherin).[57,58] It is widely associated with human embryonic development,[59] wound healing or tissue repair,[60] and angiogenesis.[61,62]

Evidence shows the ability for metastasis and invasion of cancer cells after EMT is remarkably enhanced, and these mesenchymal-like cells are strongly resistant to targeted drugs or radio- or chemotherapy.[63–65] Tumor cells after EMT express high levels of stem surface markers, indicating that these cells have become stem-like cells.[66–68] One interesting study revealed that breast CSCs originate from the fusion of M2-TAMs and breast cancer cells; these hybrid cells overexpress mesenchymal-associated genes and stemness

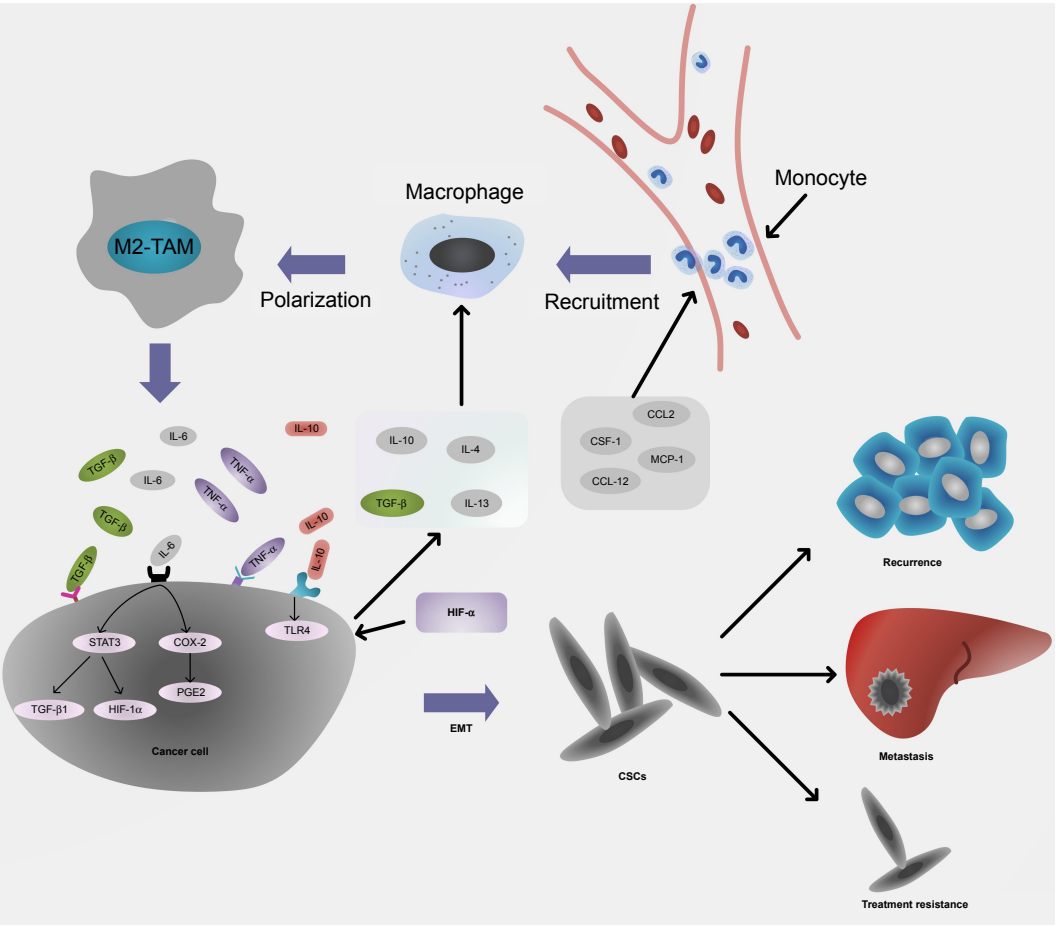

Figure 1 The interaction between TAM-derived cytokines and cancer cells promotes EMT and stemness.
Notes: CCL2, CSF-1, MCP-1, and CCL-12 derived from tumor inflammatory microenvironment recruit monocytes to form macrophages. Then, IL-10, IL-4, TGF-β, and IL-13 polarize macrophages into M2 type secreting TGF-β, IL-6, TNF-α, as well as IL-10 that promote EMT and enhance the stemness of cancer cells, resulting in cancer recurrence, organ metastasis, and treatment resistance.
Abbreviations: TAM, tumor-associated macrophage; EMT, epithelial–mesenchymal transition; TGF, transforming growth factor; TNF, tumor necrosis factor; CSC, cancer stem cell.

markers.[48] Therefore, it can be said that tumor cells after EMT are likely becoming CSCs to some extent.

Factors that induce EMT come from the TME. These signals include aberrant expression of microRNAs, abnormal expression of hormone receptors, and factors secreted by cancer-associated stromal cells and fibroblasts, which are all involved with stem-like transition triggered by EMT.[69–72] Macrophages secrete various soluble cytokines and inflammatory mediators that are not only involved in tumor angiogenesis, matrix degradation, and invasion but also promote conversion of cancer cells into stem-like cells, resulting in tumor recurrence and metastasis (Figure 1).[12]

Major cytokines derived from TAMs in EMT and CSCs

Transforming growth factor (TGF)-β

The TGF-β family is a group of extracellular growth factors that includes TGF-βs, activins, and bone morphogenetic proteins (BMPs) that regulate growth, migration, angiogenesis, and immune responses of cancer.[73] TGF-β has a dual effect on tumor behavior. It plays an anticancer role by suppressing tumor proliferation, inducing apoptosis, and promoting cancer cell differentiation into normal cells but changes its role to become a "catalyst" of cancer progression in the later stages.[74] However, the body produces compensatory TGF-β that stimulates angiogenesis and immunosuppression and enhances cell mobilization once cancer cell resistance to the suppressive effects of TGF-β occurs.

TGF-β is the main inflammatory mediator in TME and participates in cell EMT and cancer stemness transition. Treatment of Hep3B or PLC/PRF/5 HCC cells by recombinant TGF-β promotes EMT along with expression of stemness-related markers CD44, EpCAM, and CD133.[75–77] In HCC tumor specimens, the density of CD68+ TAMs is positively correlated with EpCAM+ tumor cell distribution; TGF-β1 secreted by M2-TAMs promotes EMT of

Hepa1-6 cells to become stem-like cells.[78] In brain tumors, heat shock protein-47 enhances high-level TGF-β expression, which induces the TGF-β pathway to promote EMT and stemness in glioblastoma.[79] Ye et al[80] found that the invasive front of glioma contains abundantly infiltrating TAMs and CD133+ glioma cells in both surgical resections and animal xenografts. These TAMs secrete immunosuppressive factors such as IL-10, and TGF-β1 in turn polarizes macrophages into the M2 type. The hypoxic microenvironment in the center of a tumor could induce stemness-associated transcription factors by enhancing TGF-β1 expression, resulting in regulatory T-cell and macrophage infiltration into the TME.[81]

IL-6

IL-6 is a multifunctional proinflammatory cytokine in serum and tissues and plays a key role in both acute and chronic inflammatory responses in autoimmune diseases,[82] cardiovascular diseases,[83] and cancers.[84,85] IL-6 in the TME may originate from bone marrow-derived myofibroblasts,[86] mesenchymal stem cells,[87] mesenchymal stromal cells,[88] and/or CD4+ T cells.[89] However, the main source of IL-6 is TAMs, and it is closely connected with tumor progression and invasion by inducing lymphangiogenesis and EMT.[90–92] The concentration of IL-6 in patient serum is related to advanced tumor stage and overall survival time, and it has potential as a biomarker to evaluate prognosis before surgery.[93]

IL-6 and CSCs mutually influence each other. Macrophage-derived IL-6 activates the STAT3 signaling pathway, increasing CD44+ HCC cells and enhancing sphere formation when HCC cells are cocultured with macrophages.[94] In breast cancer, IL-6 activates the STAT3 pathway and its target genes, such as TGF-β1 and HIF-1α, to increase the proportion of CD44+/CD24– cancer stem-like cells during chemotherapy-induced apoptosis.[95] There is a positive feedback loop between IL-6 and CSCs; CD133+ glioma stem cells but not bulk glioma cells induce microglial IL-6 secretion through MyD88-TLR4 signaling in macrophages, which in turn promotes glioma stem cell enlargement.[96]

Lung cell malignancies triggered by chronic inflammation caused by toxic cigarette extract have elevated IL-6 expression that promotes EMT and CSC formation through the STAT3 pathway.[97] Moreover, increased IL-6 induces EMT through the COX-2/PGE2 pathway and promotes tumor cell invasion by activating β-catenin during interactions between macrophages and lung cancer cells.[94]

IL-10

IL-10 is derived from not only leukocytes but also normal and malignant epithelial cells in hypoxic conditions.[98] However, concentration of macrophage-derived IL-10 is almost 10-fold greater than that from leukocytes within the tumor,[99] playing a role in immunosuppression in tumors, which is related to tumor drug resistance,[100] cellular growth, and proliferation.[42,101] IL-10 inhibits both CC and CXC chemokines that are indispensable for activation or recruitment of monocytes, dendritic cells, and neutrophils. In addition, IL-10 directly inhibits cytokine production, CD4+ T-cell proliferation, and T-cell cloning.[102]

EMT is also triggered by IL-10. Tumor cells cocultured with macrophages go through EMT in an IL-10-dependent manner.[103,104] IL-10 expression is elevated when M2-TAMs are cocultured with pancreatic cancer cell lines such as PANC-1 and BxPC-3, causing the EMT of cell lines through the TLR4/IL-10 signaling pathway combined with enhancing of CD133 and CD44, which suggests that IL-10 is the key element in these changes.[105]

In HCC, hypoxic stress induces the cells to release Netrin-1, resulting in EMT and a high-level of IL-10 expression,[106] which may synergistically participate in the promotion of CSCs. HIF-1α in a hypoxic environment in the HCC mouse model drives hepatocytes to secrete IL-10, which activates tissue-resident macrophages to polarize toward the M2-TAM phenotype, a positive feedback enhancing tumor evolution.[107] These studies together demonstrate that in an inflammatory microenvironment, IL-10 derived from TAMs or tumor cells plays a role in mediating EMT directly or indirectly, which may enhance tumor cell stemness transition.

TNF-α

TNF is a superfamily of proinflammatory cytokines involved in various inflammation responses, including rheumatoid arthritis and cardiovascular disease, in part through activation of the nuclear factor-kappa B (NF-κB) pathway.[108] TNF-α is chiefly released by host innate immune cells, including activated macrophages, T lymphocytes, and natural killer (NK) cells in tumors. Other cells including fibroblasts, smooth muscle cells, and tumor cells also secrete a small quantity of TNF-α.[109,110] TNF-α is a critical inflammation mediator in the TME and exerts its antitumor activity by promoting inflammation and immune response, host defense, tumor cell apoptosis, and tumor vasculature destruction.[111,112] However, some recent studies have found that TNF-α plays a completely reversed role in tumor progression and is involved in tumor migration,[113] metastasis,[114] angiogenesis,[115] and negative regulation of immune homeostasis.[116] The mechanism of these double-edged effects has not been fully elucidated, and they depend on the distribution of TNF-α receptors, the tumor stage, and the tumor type.[117–120]

Table 3 Recent studies on drugs or chemical substances that suppress EMT-induced cancer stem-like cell initiation

Drugs or chemical substances	Cancers	Mechanisms	References
Honokiol	Renal cancer	Modulates miR-141/ZEB2 signaling	127
DFOG	Gastric cancer	Downregulation of FoxM1 and Twist1 expression	128
EGFR inhibitors such as erlotinib and cetuximab	Esophageal squamous-cell carcinoma	Suppression of TGF-β and ZEB1-mediated EMT and activation of Notch1 and Notch3 to induce tumor cell differentiation	129
Silibinin	Bladder cancer	Inactivation of β-catenin/ZEB1 signaling	130
γ-Secretase inhibitor IX	Pancreatic ductal adenocarcinoma	Inhibition of the Notch signaling pathway that induces EMT and suppression of the growth of CD44+/EpCAM+ cells	131
Valproic acid	Esophageal squamous-cell carcinoma	Unclear	132
Pomegranate extract P123	Breast cancer	Downregulates genes such as TWIST1 involved in EMT as an agonist of BMP signaling, blocking TGF-β	133 and 134
Dioscin	Melanoma	Polarizes macrophages toward the M1 phenotype	135

Abbreviations: EMT, epithelial–mesenchymal transition; DFOG, 7-difluoromethoxyl-5,4′-di-*n*-octyl genistein; EGFR, epidermal growth factor receptor; FoxM1, forkhead box M1; TGF, transforming growth factor; BMP, bone morphogenetic protein.

TNF-α in the microenvironment promotes EMT of various tumor cells and CSC transition in addition to tumorigenesis as discussed earlier.[121–123] Mikami et al[124] found that in clear cell renal cell carcinomas (ccRCC), TNF-α is significantly correlated with CD44+ cancer cells in late-stage patients, inducing ccRCC progression and sunitinib resistance through EMT. Murine mammary carcinoma cells show EMT along with a high proportion of CD24-/lowCD44+ phenotypes, when they are exposed to TGF-β/TNF-α in vitro.[125] In that study, even the withdrawal of TGF-β/TNF-α from the conditioned medium did not completely reverse the mesenchymal phenotype, indicating that TNF-α promotes stemness at the gene level. This conclusion is in accordance with TNF-α triggering chromosomal instability in liver progenitor cells and contributes to their conversion to liver CSCs.[126]

Conclusion

EMT contributes to drug resistance, tumor invasion, and CSC transition, and thus, it is a potential target for inhibition to suppress CSC generation. However, critical regulatory pathways are still unknown due to the complicated mechanisms by which EMT promotes cancer cell stemness. Drugs and other methods to suppress this process have only recently begun to be investigated in vitro and have thus far achieved only modest results (Table 3).

Eliminating CSCs is a critical approach to suppress tumor recurrence and increase treatment sensitivity. However, targeting CSCs has some difficulties due to the limitations of culturing, identifying, and isolating them, which indicates that more attention should be paid to the TME, especially regarding protumor factors. It is reasonable to regard tumor mass and CSCs as parts of a whole, with the physiological functioning of the integrated parts requiring support from the TME. Therefore, it is desirable to destruct the "soil" that is favorable for tumor growth to slow down progression.

In this review, we have summarized TAM-derived cytokines in CSC transition. In addition to secretory pathways and direct contact by cell fusion, some recent studies have found that exosomes may serve as a delivery vehicle and mediate communication between TAMs and cancer cells,[136,137] which emphasizes that the cardinal work is to figure out interplays between TAMs in TME and CSCs.

Targeting TAMs is a promising direction, but additional factors need to be considered. First, TAMs infiltrate the TME in abundance, but there are no highly specific markers of TAMs. One study has shown that cancer cells after coculture with TAMs can even express the macrophage-specific marker CD163.[103] Second, macrophages are the most important immune cells, and they exert their antitumor role by discovering and eliminating mutated cells in the early stages of tumor initiation. So which macrophage phenotype should be targeted and when is the best time to target it? TAMs can paradoxically promote tumor metastasis and angiogenesis once anti-TAM therapy has ceased.[138] Third, some CSCs are in a dormant state where they are arrested in G0/S and have no physiological activity. These CSCs are not regulated by TAMs;[139] whether TAMs break the dormant state of CSCs is unknown. These issues and others should be thoroughly studied before targeting of TAMs can become a clinical reality.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (Nos 81774261 and 81373582), the Natural Science Foundation of Guangdong Province (No S2013010012636), the Administration of Traditional Chinese Medicine of Guangdong (Nos 20171001,

20181008 and 20181002.) and the Foundation of GuangZhou Science Technology and Innovation Commission (Nos 201803010088, 201804010118).

Author contributions

Yongxu Chen and Wei Tan contributed to searching literature, drafting, and editing of the manuscript. Changjun Wang participated in the conception of the idea. All authors contributed toward data analysis, drafting, and revising the paper and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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