REVIEW

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Dysregulated tumor-associated macrophages in carcinogenesis, progression and targeted therapy of gynecological and breast cancers

Tianhan Xu[1†], Sihui Yu[1†], Jiawen Zhang[1,2*] and Sufang Wu[1*]

Abstract

Gynecological and breast cancers are a group of heterogeneous malignant tumors. Although existing treatment strategies have ameliorated the clinical outcomes of patients, the overall survival rate of advanced diseases remains unsatisfactory. Increasing evidence has indicated that the development and prognosis of tumors are closely related to the tumor microenvironment (TME), which restricts the immune response and provokes malignant progression. Tumor-associated macrophages (TAMs) are the main component of TME and act as a key regulator in tumor metastasis, immunosuppression and therapeutic resistance. Several preclinical trials have studied potential drugs that target TAMs to achieve potent anticancer therapy. This review focuses on the various functions of TAMs and how they influence the carcinogenesis of gynecological and breast cancers through regulating cancer cell proliferation, tumor angiogenesis and tumor-related immunosuppression. Besides, we also discuss the potential application of disabling TAMs signaling as a part of cancer therapeutic strategies, as well as CAR macrophages, TAMs-based vaccines and TAMs nanobiotechnology. These research advances support that targeting TAMs combined with conventional therapy might be used as effective therapeutics for gynecological and breast cancers in the future.

Keywords: Tumor microenvironment, Tumor-associated macrophage, Gynecological cancers, Breast cancer, Targeted therapy

Introduction

According to the global cancer statistics in 2020, the total number of gynecological tumors, including cervical, vulvar, corpus uteri, ovarian and vaginal cancers, accounts for up to 15% overall new morbidity in women worldwide. Additionally, breast cancer also accounts for about a quarter of all new cancer cases and one in six cancer death cases in women [1]. Although combined surgery with or without chemoradiotherapy, immunotherapy and targeted therapy have greatly ameliorated the clinical outcomes of patients with gynecological and breast cancers, the overall survival rate of advanced diseases is still low.

In recent years, a new concept and field about tumor microenvironment (TME) has become a hot topic in cancer researches. Tumor cells are surrounding by a dynamic environment which includes macrophages, lymphocytes, mesenchymal stem cells, fibroblasts as well as other immune, inflammatory and stromal cells and a variety of biochemical molecules. Among these components of TME, the tumor-associated macrophages (TAMs) are the main actors, accounting for 30% to 50% of TME cells [2],

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Table 1 TAMs differentiation under the influence of tumor microenvironment

Tumor type	Pathway	Differentiation	References
Breast cancer	Lactate/Gpr132	Pro-M2 polarization	[16]
	Lactate/ERK/STAT3	Pro-M2 polarization	[17]
	Emodin/STAT6/C/EBPβ	Anti-M2 polarization	[18]
	MCT-1/miR-34a/IL-6/IL-6R	Pro-M2 polarization	[19]
	miR-200c/PAI-2	Pro-M2 polarization	[20]
Ovarian cancer	CTHRC1/STAT6	Pro-M2 polarization	[21]
	PPARγ/NF-κB	Pro-M2 polarization	[22]
Endometrial cancer	miRNA-21	Pro-M2 polarization	[48]
	lncRNA NIFK-AS1	Anti-M2 polarization	[23]
	rCTHRC1/CX3CR1	Pro-M2 polarization	[24]
Cervical cancer	Interleukin-17/COX-2/PGE2	Pro-M2 polarization	[25]
Lung cancer	Succinate/SUCNR1/PI3K-HIF-1α	Pro-M2 polarization	[26]
Colorectal cancer	PKN2/DUSP6-Erk1/2	Anti-M2 polarization	[27]
	PKCα/MKK3/6-P38 MAPK	Pro-M1 polarization	[28]
	EGFR/PI3K/AKT/mTOR	Pro-M2 polarization	[29]
	SPON2/integrin β1/PYK2	Pro-M2 polarization	[30]
Gastric cancer	TLR4/PI3K/Akt	Pro-M2 polarization	[31]

which play a crucial role in angiogenesis, tumor metastasis, immunosuppression and therapeutic resistance [3]. Interestingly, gynecological tumors have different cross talk with TAMs due to their characteristics. For example, persistent infection with high-risk human papillomavirus (HPV) is one of the main causes of cervical cancer. HPV E6/E7 oncoproteins not only change cell proliferation and interferon response by targeting cytokine expression [4, 5], but also have multiple associations with TAMs together in furtherance of tumor development [2]. Besides, estrogen receptors, which are highly expressed in endometrial, ovarian and breast cancers, interact with TAMs, contributing to migration and invasion of cancer cells [6, 7]. In our previous studies, we also found the correlation between TAMs infiltration and gynecological cancers [8–10].

Therefore, in this review, we will focus on the TAMs in gynecological and breast cancers with the emphasis on their origin, function, and regulation of tumor progression and metastasis. We also review the promising TAMs target therapies to inhibit pro-tumor TAMs, and novel TAMs-based immunotherapies including CAR macrophages, vaccination and nanobiotechnology which are in full flourish.

Origin and development of TAMs

As a vital component of innate immune system, macrophages belong to mononuclear phagocytic system which can engulf pathogens, inhibit inflammation and coordinate tissue repair [11, 12]. The macrophages in tissues are composed of two parts: yolk sac-derived tissue-resident macrophages (TRMs) and blood monocytes from bone marrow [13]. TAMs are the macrophages gathered in TME [14], and the majority of TAMs are bone marrow-derived macrophages (BMDMs) recruited by chemotactic and cytokines such as monocyte chemotactic protein 1 (MCP-1/CCL2) and colony-stimulating factor 1 (CSF-1) [3]. In general, hematopoietic stem cells (HSC) differentiate into bone marrow progenitor cells (CMP), then go through granulocyte/macrophage-restricted progenitor cells (GMP) and macrophage/dendritic progenitors (MDP), and have the ability to differentiate into monocytes and mononuclear myeloid suppressor cells (M-MDSC) [15]. Once these cells enter the TME, local inducers gradually regulate the differentiation of monocytes into pro-tumor- or anti-tumor-type macrophages (Table 1) [16–31]. TAMs with different origin can be distinguished by the expression of surface markers (such as CX3CR1, CD45, CCR2, MERTK and FcRγ1/CD64), gene expression profile and lineage trackers (Fig. 1) [13]. Besides, different functions of TAMs have been found, for example,TRMs are related to cell proliferation and fibrosis, while BMDMs are related to antigen presentation [32], which affects the growth and metastasis of tumor cells to some extent and provides research directions for possible cancer therapeutic strategies [33, 35, 36].

The polarization of TAMs

According to different polarization factors and immune functions, macrophages can be divided into two types, namely classically activated M1 and alternatively

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Fig. 1 Surface markers of TRMs and BMDMs
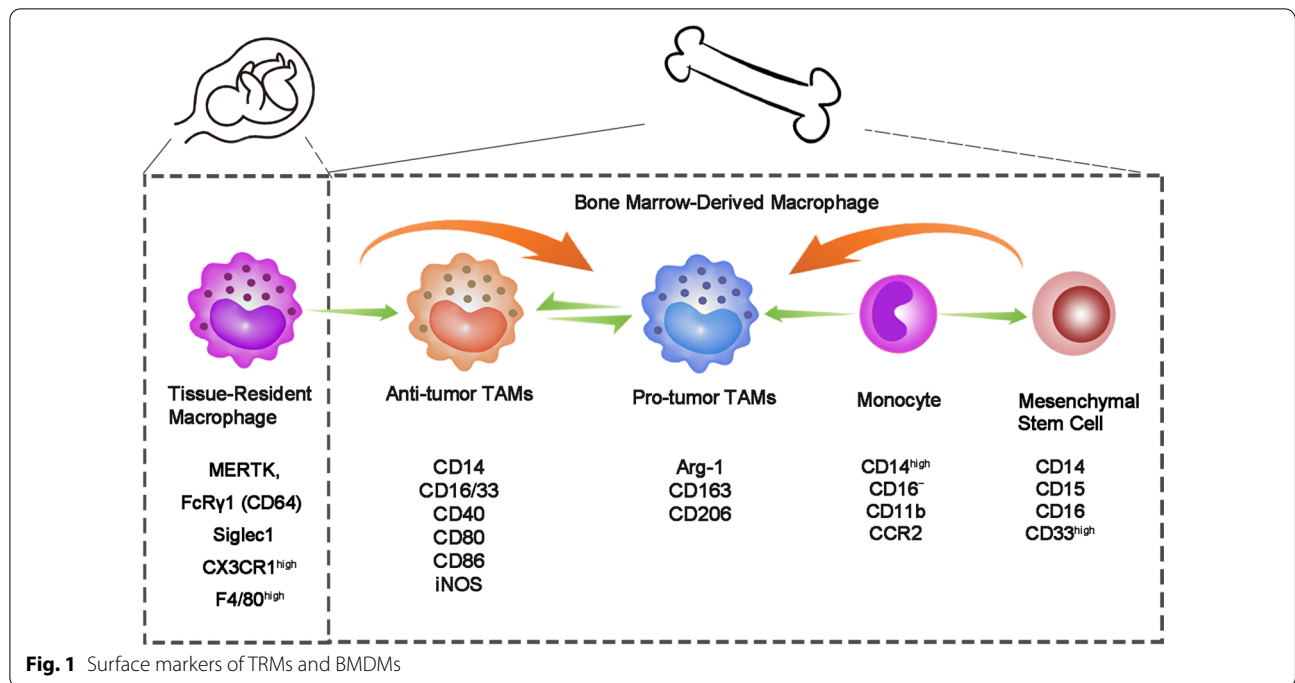
activated M2 macrophages [37]. M1 macrophages are mainly induced by interferon γ (IFNγ), lipopolysaccharide (LPS) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and have cytotoxic effects on cancer cells. On the contrary, M2 macrophages can provide a nutritional advantage to cancer cells when stimulated by IL-4, IL-6, IL-10, IL-13, transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF) and other M2-specific cytokines [34, 38, 39]. It is generally assumed that TAMs are largely polarized into M2 macrophages, promoting tumor progression and restraining anti-tumor immune response.

This polarization trend can be attributed to various inducible factors secreted by constituent cells in TME (Table 1). For example, Pedraza-Brindis et al. reported that the supernatant of cervical cancer cells down-regulated the phosphorylation of NF-κB-p65 and STAT1 in M1 macrophages and induced a stable M2 phenotype, accompanied by increased expression of IL-10, IL-6, CCL2, IL-8, GM-CSF, G-CSF, platelet-derived growth factor (PDGF) AA and PDGF-BB [40, 41]. Experiments have shown that cervical cancer cells secreted prostaglandin (PG) E2 and IL-6 to induce M2 phenotype and produce CCL2 to promote the recruitment of monocytes at the tumor site [34]. Moreover, CSF-1 can induce M2 polarization in ovarian cancer cells with the progression of histological malignancy [42]. In addition, blocking CSF-1 receptor (CSF-1R) can prevent macrophage infiltration and endometrial cancer cell proliferation [43].

What's more, paclitaxel treatment of breast cancer cells enhances the secretion of CSF-1, recruiting TAMs so as to limit the therapeutic effect [44].

Effects of anoxic microenvironment on TAMs

Rapid proliferation of tumor cell results in insufficiency of blood flow, lactic acid accumulation and hypoxia in TME, which leads to more angiogenesis and catalyzes tumor growth [49]. In the TME with low oxygen concentration, tumor cells can recruit TAMs by secreting more chemokines such as CCL2, CCL5, or CSF1 [3]. In the TME of cervical cancer, the hypoxic condition was confirmed to activate M2-like TAMs in vivo [45]. One previous study revealed that macrophages were induced to hypoxic tumor areas and gained a M2-polarized phenotype via hypoxic cancer cell-derived cytokines Oncostatin M (OSM), an inflammatory cytokine belonging to the IL-6 superfamily. Recently, this phenomenon has been proven to be mediated by mTOR signaling complex 2 (mTORC2) [46, 47]. In addition, studies on exosomes have discovered that endometrial cancer with hypoxia mediated the polarization of monocyte into M2 macrophages through exuding exocrine miRNA-21 [48]. Meanwhile, hypoxic TME also leads to decreased extracellular matrix mobility and slower TAMs movement, which enhances the interaction between TAMs and cancer cells [50].

Experiments were also carried out to demonstrate whether hypoxia-induced ZEB1, a key regulator of

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Table 2 TAMs markers

TAM marker	Tumor type	Function	References
CD68	Breast cancer	The expression of CD68 was negatively correlated with ERα or progesterone receptor	[7]
CD14, CD163	Cervical cancer	CD14$^+$CD163$^+$macrophages have poor ability to stimulate T cell proliferation and produce INF-γ	[34]
CD163, CD204	Ovarian cancer	Tumor-derived CSF-1 may induce CD163$^+$CD204$^+$M2 differentiation	[42]
Arg-1, CD206, iNOS, CD86	Endometrial cancer	Endometrial cancer cells induced high expression of Arg-1 and CD206 and low expression of iNOS and CD86 on TAMs	[43]
CD163	Cervical cancer	Hypoxia is positively associated with CD163$^+$TAM infiltration and cervical cancer progression	[45]
CD163, CD206	Breast cancer	mTORC2 mediated CD163$^+$CD206$^+$M2 polarization of macrophages in hypoxic TME	[47]
CD206	Endometrial cancer	Endometrial cancer cells promoted CD206$^+$M2-like macrophage polarization	[48]

epithelial–mesenchymal transformation (EMT), plays a part in TAMs recruitment in the hypoxic cervical cancer TME. The results showed that ZEB1 up-regulated CCL8 which combined with CCL8 receptor (CCR2) and further recruited TAMs though NF-κB signaling phosphorylation [51].

TAM biomarkers

Cell surface markers are a class of substances, usually proteins, that are expressed on the surface of cells to identify cell types or properties. There are many kinds of receptors on the surface of macrophages, among which Tyro3, Axl and MerTK receptor tyrosine kinases were studied far and wide [52]. When these receptors are paired with ligands such as growth inhibition specificity 6 (Gas6) and S protein, macrophages are encouraged to polarize to M2 through the conduction of specific pathways, among which the PI3K/Akt signaling is the most studied pathway [53–55].

Except from receptors on macrophage, these cells also express MHC-II and CD on cytomembrane to participate in the immune response. In general, M1 macrophages express CD14, CD16/33, CD40, CD80 and CD86, produce IL-6, IL-12p70 and IL-23, and play pro-inflammatory, cytotoxic and tumoricidal roles. As for M2 macrophages, arginase 1 (Arg-1), CD163, CD169, CD206, IL-10 and chemokines CCL17 and CCL22 have been identified as markers [57, 58]. Pan-macrophage markers have also been involved in the detection of macrophage cells, such as CD68, CD14, CD45, CD105 and CD204 [14, 40]. Many years ago, some publications simply included TAMs in M2-like macrophage [56], which is no longer applicable today. TAMs tend to polarize to M2 in TME, and their surface receptors and cytokines secreted are si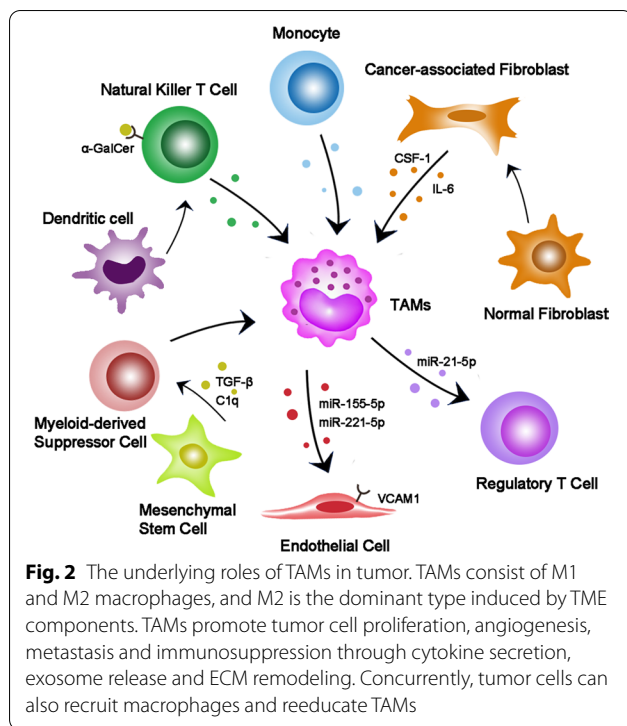milar to M2-like macrophages. Meanwhile, TAMs also express some M1-like macrophage markers. For example, iNOS (+) TAMs were detected to be more beneficial to the prognosis of cancer patients [59]. Besides, the effect of TAMs in stimulating T cell activity with high expression of M2-like markers in ovarian ascites was similar to that of M1-like TAMs [60]. Therefore, we cannot simply classify TAMs as M1- or M2-like macrophages and recognized their function based solely on the expression of surface markers.

In a word, TAMs biomarkers help to detect the presence and function of macrophages in tumor tissues (Table 2), which may facilitate the identification, diagnosis and treatment of diseases. The search and discovery of valuable TAMs biomarkers have become an important research hot spot.

The interaction of TAMs and other immune and stromal cells in TME

TAMs interact widely with other microenvironment cells in TME (Fig. 2). Cancer-associated fibroblasts (CAFs), which mainly originate from normal fibroblasts in the interstitial tissue around the tumor, are closely related to TAMs [61]. It was found that macrophages co-cultured with CAFs increased the ability to differentiate into M2-like macrophages via IL-6 and CSF-1 secreted by CAFs [62]. In the experiment of three-way cross talk among cancer cells, CAFs and monocytes, the group with cancer cell conditioned medium (CM) showed the highest level of M2-like differentiation [62]. At the same time, CAFs and TAMs activate each other, which play a synergistic role in promoting tumor cell invasion and angiogenesis [63].

For endothelial cells, the exosomes derived from macrophages can promote their proliferation and increase the vascular density of tumor [64]. On the other hand,

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Fig. 2 The underlying roles of TAMs in tumor. TAMs consist of M1 and M2 macrophages, and M2 is the dominant type induced by TME components. TAMs promote tumor cell proliferation, angiogenesis, metastasis and immunosuppression through cytokine secretion, exosome release and ECM remodeling. Concurrently, tumor cells can also recruit macrophages and reeducate TAMs

Fig. 3 The interaction of TAMs and other immune and stromal cells in TME

studies have shown that M2-like macrophages in ovarian cancer directly contact with endothelial cells to enhance vascular barrier and reduce vascular permeability to restrict ascites formation [65].

For T cells, TAMs not only up-regulated the expression of PD-L1, but also decreased the proportion of activation and proliferation of CD8^{+}T cells [66]. Some studies have shown T cell elimination in liver metastasis, which was mediated by macrophages [67]. Regulatory T (Treg) and T helper 17 (Th17) cells are two subsets of CD4^{+} T cells. The imbalance of Treg/Th17 cells is one of the characteristics of tumors [68]. In ovarian cancer, the exosomes from M2 macrophages which contain hsa-miR-21-5p increase the Treg/Th17 ratio and promote tumor progression and metastasis to the peritoneum [68]. On the other hand, Treg cells can preferentially promote M2-like TAMs by inhibiting the secretion of IFN-γ by CD8^{+} T cells [69]. In addition, activation of natural killer T cells increases iNOS^{+}CD206^{−} M1 macrophages and controls the growth of solid tumors [70].

Myeloid-derived suppressor cells (MDSCs) are immature bone marrow cells with the morphological and phenotypic characteristics of neutrophils and monocytes [71]. Blocking TAMs can contribute compensatory infiltration of G-MDSC, thus counteracting the reduction in tumor load by inhibiting TAMs [72]. Additionally, exosomes released by tumor-induced mesenchymal stem cells (MSC) accelerated the progression of breast
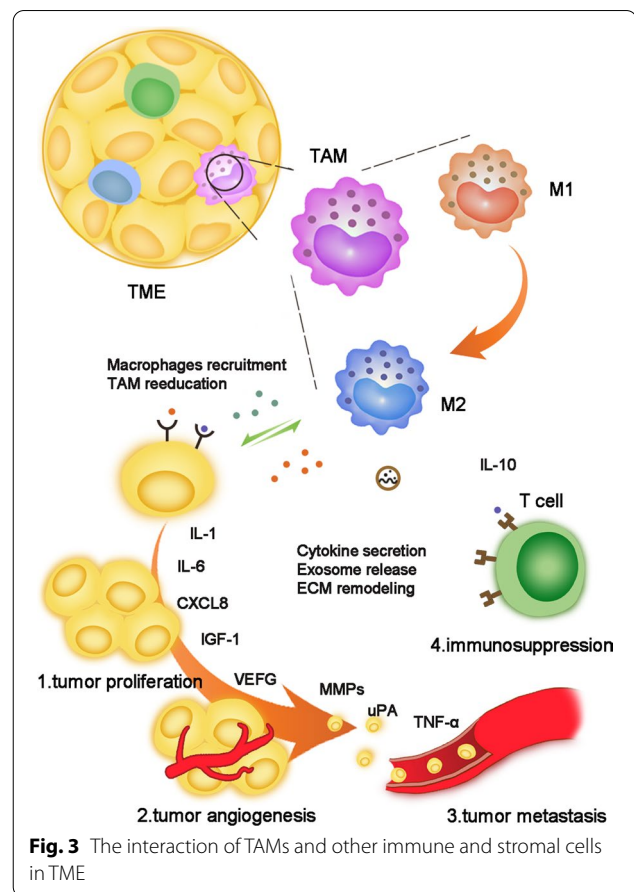
cancer by inducing M-MDSC to differentiate into M2 macrophages in TME [73]. Moreover, evidence also suggests that tumor exosomes can differentiate MDSC into M2 macrophages as well [74].

The relationship of TAMs with gynecological and breast cancers

The emerging new evidences suggest that TAMs participate in different stages and aspects of tumor development by secreting diverse factors. These molecules, such as IL-1/6/8/10, IGF-I, VEGF, EGF, MMP-7/9, uPA, TNF-α and TGF-β, are related to tumors to some extent (Fig. 3, Table 3) [75–77]. Here, we try to identify the influence of TAMs toward the tumor progression through the following aspects (Table 3).

Promoting tumor cell proliferation
Cancer cells are thought to divide out of control and proliferate indefinitely, making them difficult to be removed and destroying the surrounding normal tissues. Different studies have shown that TAMs secrete IL-6 [78, 79], which is a cytokine belonging to the

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Table 3 Roles of TAM-derived cytokines in gynecological and breast cancers

Cytokines	Tumor type	Interacting molecules	Function	References
IL-6	Cervical cancer	IL-6/JAK/STAT3	HPV E6 oncoprotein participates in the phosphorylation activation of the STAT pathway by IL-6 and promotes cancer cell proliferation	[84]
	ER-positive breast cancer		The IL6/STAT3 pathway independent of ER pathway promotes the proliferation of cancer cells	[86]
IL-1	Breast cancer	sCD44	A novel positive feedback loop between IL1β and CD44 promotes TNBC malignant progression	[75]
IGF-1	Breast cancer	Akt	Serum IGF-1 concentrations and IGF-I/IGFBP3 ratio correlated with Akt phosphorylation which promote breast cancer progression and poor disease outcome	[77]
CXCL8/IL-8	Endometrial carcinoma	HOXB13	Down-regulation of ERα expression in endometrial carcinoma, leading to tumor invasion and poor prognosis	[88]
	ER-positive breast cancer	HOXB13, mTOR	Up-regulation of HOXB13 can promote cell proliferation and metastasis in vitro and in vivo by directly inhibiting ERα, while ERα can be inhibited by decreasing the expression of mTOR	[89]
	Epithelial ovarian cancer	Estrogen, IL-6	Estrogen, IL-6 and CXCL8 interact to regulate epithelial ovarian cancer growth through a cascade of amplification effects of ERα pathway	[91, 92]
VEGF-C/D	Endometrial cancer and cervical cancer	VEGFR-3	VEGF-C, VEGF-D and receptor VEGFR-3 are correlated with different stages of tumor progression	[95, 96]
EGF	Ovarian cancer	VEGF	EGFR activation and up-regulation of VEGF/VEGFR signaling pathway in surrounding tumor cells supported tumor cell proliferation and migration. EGF up-regulated αMβ2 integrin and ICAM-1 and promoted the adhesion of tumor cells to TAMs	[99]
MMP-9	ER-positive breast cancer	ER	TAMs secretion of MMP-9 is associated with reduced overall survival via ER	[104]
MMP-7	Ovarian cancer	p38	MMP-7 promoted macrophage infiltration to further form tumor microenvironment	[105]
uPA	Breast ductal carcinoma in situ	uPAR	uPA reshaped the extracellular matrix by degrading the components involved, which in turn led to the removal of tumor cells from the primary site	[110]
TNF-α	Breast cancer	Estrogen	TNF-α involved in EMT and metastasis of breast cancer cells	[76]
IL-10	Cervical cancer	HPV E2 T cell	HPV E2 protein could bind to IL-10 gene promoter, triggering the increase in IL-10. Increased IL-10 inhibited T cell immunity	[118, 119]
	Breast cancer	CD8^{+} T cell	Macrophage-derived IL-10 overexpression leads to tumor development in response to CD8^{+} T cell-dependent chemotherapy	[121, 122]
TGF-β1	Cervical cancer	HPV E6/E7	As tumors develop, TGF-β induces EMT	[118]
	High-grade serous ovarian cancer	Unknown	High levels of TGF-β1 secretion promote peritoneal metastasis of cancer cells	[112]
GDF15	Cervicalcancer	PI3K/AKT and MAPK/ERK	The PI3K/AKT and MAPK/ERK signaling pathways are phosphorylated by ErbB2 to promote tumor progression	[113]

interleukin family associated with tumorigenesis. It has been proved that IL-6 played a vital role through IL-6-JAK-STAT signal transduction [80–82], and activation of STAT3 was an important factor affecting cell proliferation, differentiation and survival [83]. STAT3 protein level and phosphorylation state were significantly induced in HPV-positive cervical cancer cells compared with HPV-negative ones, which has been demonstrated to be mediated by HPV E6 oncoprotein [84]. Meanwhile, Luan et al. observed a synchronous increase in IL-6R expression of cervical cancer cells, which appears to be detrimental to patients' prognosis [85]. This suggests that IL-6 secreted by TAMs may affect tumor proliferation, migration and adhesion through up-regulated IL-6R. However, the activation of IL6/STAT3 pathway which was found in a brand-new

study promoted the metastasis of ER$^+$ intraductal breast cancer in vivo, and it strikingly constituted another oncogenic pathway which was relatively independent of ER pathway [86].

Another member of interleukin family, CXCL8 (also known as IL-8), has been widely concerned in tumorigenesis due to its pluripotency including angiogenesis and mitogenic effects [87]. CXCL8 is mainly secreted by mononuclear macrophages. It has been reported that TAMs down-regulated the expression of ERα in endometrial carcinoma tissues by over-secretion of CXCL8 via homeodomain transcription factor HOXB13, which is associated with tumor invasion and poor prognosis [88]. The parallel results were found in ERα$^+$ breast cancer. Up-regulated HOXB13 accelerated cell proliferation and metastasis both in vitro and in vivo through direct suppression of ERα, which could be inhibited by reducing the expression of mTOR [89]. In the meantime, one research found that the expression of ERα in cervical cancer decreased by more than 15 times as cervical cancer progressed from normal to cancer [90]. However, the relationship between ERα reduction and TAMs in cervical cancer cells has not been reported.

Moreover, it has been demonstrated that estrogen, IL-6 and CXCL8 are capable of interacting with each other to regulate the growth of epithelial ovarian cancer through cascade amplification effect via an ERα pathway [91, 92].

Dysregulating angiogenesis and lymphangiogenesis

The increasing division and growth of cancer cells indicate that they need more nutrients from the blood. Therefore, tumor angiogenesis plays a pivotal role in solid tumor growth, invasion and metastasis. Recently, TAMs have been shown to tight tie with angiogenesis and lymphangiogenesis through the secretion of VEGF-A, VEGF-C, VEGF-D, EGF, placental growth factor (PlGF), TGF-β, TNF-α, IL-1β, IL-8, CCL2, CXCL8 and CXCL12 [93]. In breast cancer, TAM infiltration is closely associated with VEGF expression and microvascular density (MVD), which jointly affects the prognosis of patients [94]. In addition, previous studies have confirmed that VEGF-C, VEGF-D and their receptor VEGFR-3 were positively correlated with different stages of cervical lesions, allowing the development of lymphangion [95, 96]. Interestingly, the expression of VEGF-C and VEGF-D increased significantly after the disease progressed to CIN3 stage [96]. However, the opposite conclusion has been drawn in endometrial cancer [95]. One study reported that lower level of VEGF-C was detected in endometrial cancer samples [95]. We suspect tha t the char acteristics of different tumors and the limited sample size may account for the controversy.

On the other hand, TAMs expressed HIF-1α to active angiogenesis [97]. In breast cancer, HIF-1α-stabilizing long noncoding RNA (HISLA) was proved to prevent the inactivation of HIF-1α from hydroxylation by prolyl hydroxylase domain 2 (PHD2) [98]. Moreover, HISLA produced by extracellular vesicles released by TAMs can inhibit the interaction between HIF-1 α and PHD2 and promote the stability of HIF-1α in TME [97].

In the study of transcoelomic metastasis of ovarian cancer, TAMs in tumor clusters (spheroids) motivated EGF expression at early stage of metastasis which was integrated with activated tumor EGFR, further supporting tumor cell proliferation and migration by up-regulating VEGF/VEGFR signaling in surrounding tumor cells [99]. EGF was also observed to increase αMβ2 integrin on TAMs and ICAM-1 on tumor cells, promoting the adhesion between TAMs and tumor cells [99]. Ishihara et al. discovered that Wiskott–Aldrich syndrome protein (WASp) allowed TAMs to secrete EGF and approach CSF-1-expressing breast cancer cells chemotactically to regulate tumor metastasis [100].

Facilitating EMT and tumor metastasis

EMT and extracellular matrix remodeling constitute remarkable links in promoting tumor metastasis. Jing et al. revealed that under the action of ERα agonists, ERα$^+$ M2 macrophages significantly up-regulated CCL18 and activated the mTOR/KIF5B signaling pathway in endometrial cancer cells to promote EMT [101].

Matrix metalloproteinases (MMPs), which are widely presented in TME, can not only facilitate EMT, but also promote lymphangiogenesis in conjunction with the VEGF [93]. Recently, one study demonstrated that M2-like macrophages have been found to secrete large amounts of MMP-9 that promoted tumor progression both in breast cancer and in colon cancer, which was considered as prognostic markers and therapeutic targets [102, 103]. In ER$^+$ breast cancer, MMP-9 secreted by TAMs was associated with worse overall survival, but not in ER-negative breast cancer or triple-negative breast cancer (TNBC) [104]. Wen et al. reported that MMP-7 elevation in macrophages which was co-cultured with ovarian cancer cells occurred through the p38 pathway and promoted the infiltration of macrophages to form TME [105]. At the same time, the majority of the studies supported the view that increased MMP-9 can also promote the development of cervical cancer [106, 107], although a few articles have suggested that MMP-9 was helpful for cervical cancer prognosis [103]. Therefore, taking into account the differences in researches, the effect of MMP on cervical cancer needs to be further optimized.

Moreover, TAMs also exert an enormous function in promoting tumor cell metastasis by releasing urokinase-type plasminogen activator (uPA) and up-regulating the expression of uPA receptor (uPAR), which belongs to the fibrinolysis system [108]. The combination of uPA and uPAR initiates the reactions to reshape the extracellular matrix by degrading the relative components and thereafter leads to the distant migration of tumor cells from the primary site [109]. Additionally, increased uPAR can also induce macrophage aggregation to tumor tissue, forming a positive feedback [110]. In breast ductal carcinoma in situ and invasive breast carcinomas, blood monocytes with higher uPAR levels might be selectively recruited into cancer tissues, which induced elevated uPAR levels in TAMs through paracrine action as well [110].

As a member of transforming growth factors, TGF-β is a multifunctional cytokine. It acts as a potent tumor suppressor in the early stage of cancers, while later these cytostatic effects become resistant and TGF-β is involved in inducing EMT [111]. With regard to high-grade serous ovarian cancer, ascites with high levels of TAMs and TGF-β1 facilitated cancer cell migration [112]. In cervical cancer, GDF15 which belongs to TGF-β superfamily phosphorylated PI3K/AKT and MAPK/ERK signaling pathways via ErbB2, a member of EGFR family, to achieve the purpose of promoting tumor progression [113].

Forming immunosuppression

Tumor cells escape from recognition and attack by the body's immune system through multitudinous mechanisms. IL-10 is a multicellular cytokine with immunosuppressive effects and can inhibit antigen delivery by the mononuclear phagocyte system [114, 115]. One previous study found that IL-10 promoted the transformation of macrophages into M2-like macrophages in TME, and polarized M2-like macrophages in turn highly secrete IL-10 [116]. In cervical lesions, it has been reported that the amount of IL-10 in TME was associated with the type of HPV infection and the degree of progression from lesions to cervical cancer. Moreover, with the significantly increase in IL-10, the expression of HPV E6 and E7 was detected to augment [117]. Besides, IL-10 has been proven to play a role in anti-tumor T cells [119, 120]. In breast cancer, macrophage-derived IL-10 overexpression resulted in tumor development via inefficiency of CD8^{+} T cell-dependent responses to chemotherapy [121]. As Chu et al. reported, IL-10 was also an independent factor for adverse prognosis in patients with ER-negative breast cancer [122].

In ovarian cancer tissues, Qu et al. discovered the increased expression of PD-L1 on the surface of TAMs, which stimulated apoptosis of T cells to suppress immunity [123]. Up-to-date study has found that overexpression of human epididymis protein 4 (HE4) in ovarian cancer cells may be one of the reasons for the elevated PD-L1 by macrophages [124]. In the meantime, TAMs as well as IFN-γ, TNF-α, IL-10 and especially IL-6 secreted by TAMs induced the expression of PD-L1 both in the cell membrane and in the cytoplasm of ovarian cancer cells, which inhibited the function of CD8^{+} T cells and promoted tumor growth [125]. The same inhibitory effect on T cells was also detected in HPV16-associated cervical cancer through M2 macrophages [119]. Recently, in studies of progression of stromal tumors, the inhibition of CD8^{+} T cells by PD-1/PD-L1 may be realized through the PI3K/Akt/mTOR signaling pathway [126]. Additionally, hypoxic macrophages promote the release of exosomes containing miR-223. It can be transferred to co-cultured epithelial ovarian cancer cells to enhance drug resistance through the PTENPI3K/AKT pathway both in vivo and in vitro [127]. As mentioned above, accompanied by TME hypoxia, VEGF is overexpressed in macrophages. It not only drives angiogenesis, but also suppresses immune cells from playing their normal role [128]. For T cells, VEGF blocks the differentiation of T progenitor cells into CD4^{+} and CD8^{+} lymphocytes, weakens the immune function of T cells. On the other hand, VEGF increases the infiltration of TAMs into tumor sites which forms a positive feedback from VEGF to TAMs [129].

Taken together, TAMs are involved in the secretion of cytokines and growth factors to influence tumor growth, metastasis and progression. Different types of gynecological and breast cancers have similar or specific characteristics of TAMs (Fig. 4). Comprehensive studies need to be carried out to find more factors secreted by TAMs which take part in tumor regulation, providing more insight into targeted treatments toward TAMs.
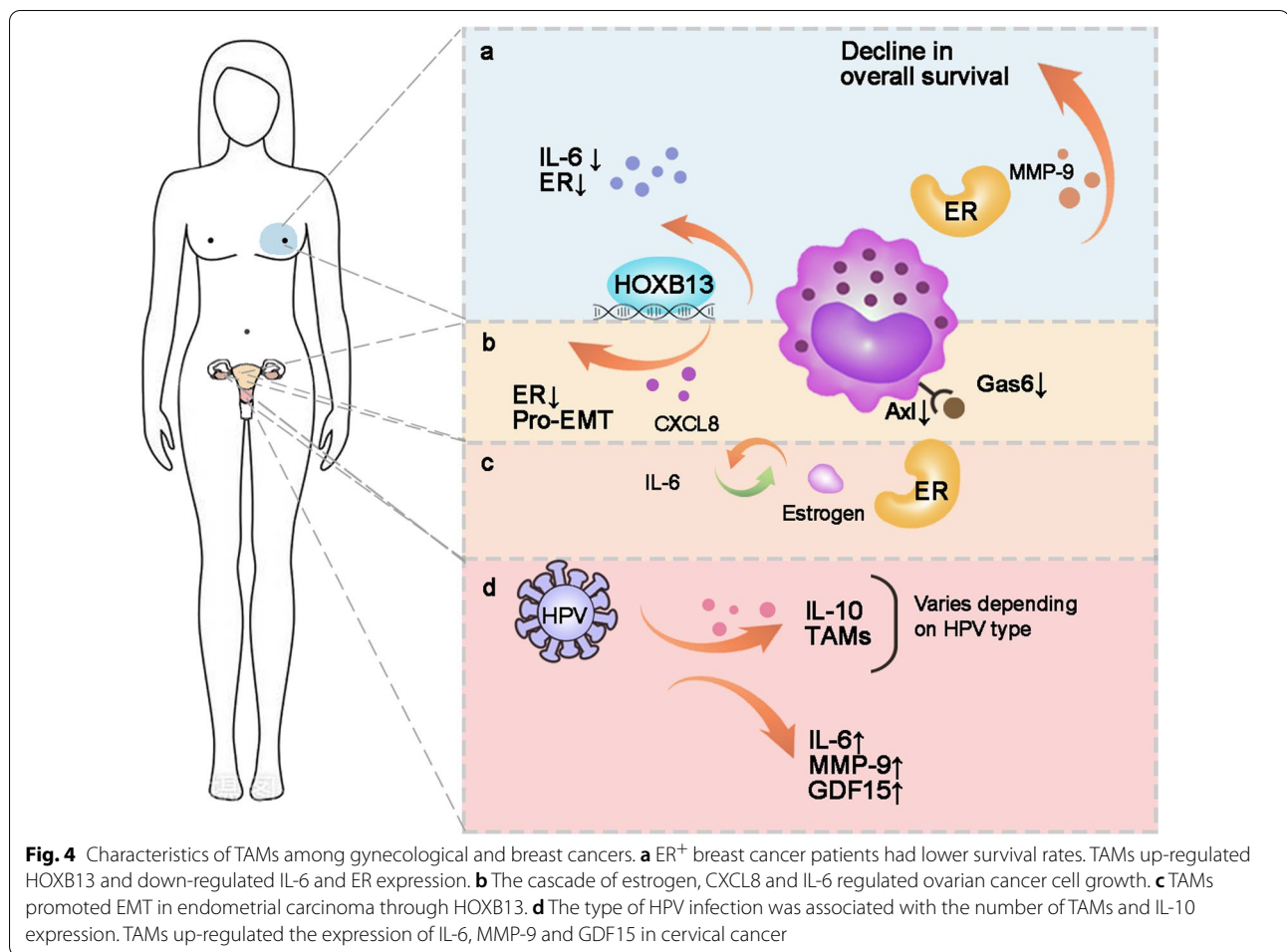
TAM-targeted therapy in gynecological and breast cancers

Macrophages are a kind of immune cells that can be stimulated by TME to display different characteristics and have plentiful functions in cancer proliferation, metastasis and immune resistance. Nowadays, various clinical trials on TAM-targeted therapy have been carried out in gynecological and breast cancers (https://clinicaltrials.gov/, Table 4). After the above discussion on the roles of TAMs, we are deeply aware that the intervention of TAMs including depleting macrophages, inhibiting pro-TAMs or activating anti-TAMs, might be a promising therapeutic approach (Fig. 5, Table 5).

Reducing TAMs generation

The polarization of TAMs is regulated by a variety of microenvironmental cytokines, growth factors and signals from both tumor and stromal cells, which is a

Fig. 4 Characteristics of TAMs among gynecological and breast cancers. **a** ER+ breast cancer patients had lower survival rates. TAMs up-regulated HOXB13 and down-regulated IL-6 and ER expression. **b** The cascade of estrogen, CXCL8 and IL-6 regulated ovarian cancer cell growth. **c** TAMs promoted EMT in endometrial carcinoma through HOXB13. **d** The type of HPV infection was associated with the number of TAMs and IL-10 expression. TAMs up-regulated the expression of IL-6, MMP-9 and GDF15 in cervical cancer

process of mutual conversion between M1 and M2 [14]. Considering the extensive role of TAMs in TME, controlling the number of TAMs, in other words, suppressing the polarization of M2 macrophages or guiding macrophages to differentiate into M1-like have wide interest as a new treatment strategy.

In terms of reducing the number of TAMs, clodronate has emerged as the primary choice for drugs to deplete macrophages [130]. In cervical cancer, Lepique et al. injected clodronate-containing liposomes (CL) in a mouse model to consume macrophages by accumulating methylene-containing ATP analogues in the cytoplasm. Although CL did not directly regulate the cytoactive of cancer cells, the reduced number of macrophages inhibited tumor growth in vivo and contribute to the infiltration of tumors by HPV16 E7(49–57)-specific CD8 lymphocytes [119]. However, the therapy still needs further optimization to meet the clinical needs, for example, how to focus on TAMs without interfering with other macrophages in normal body tissues.
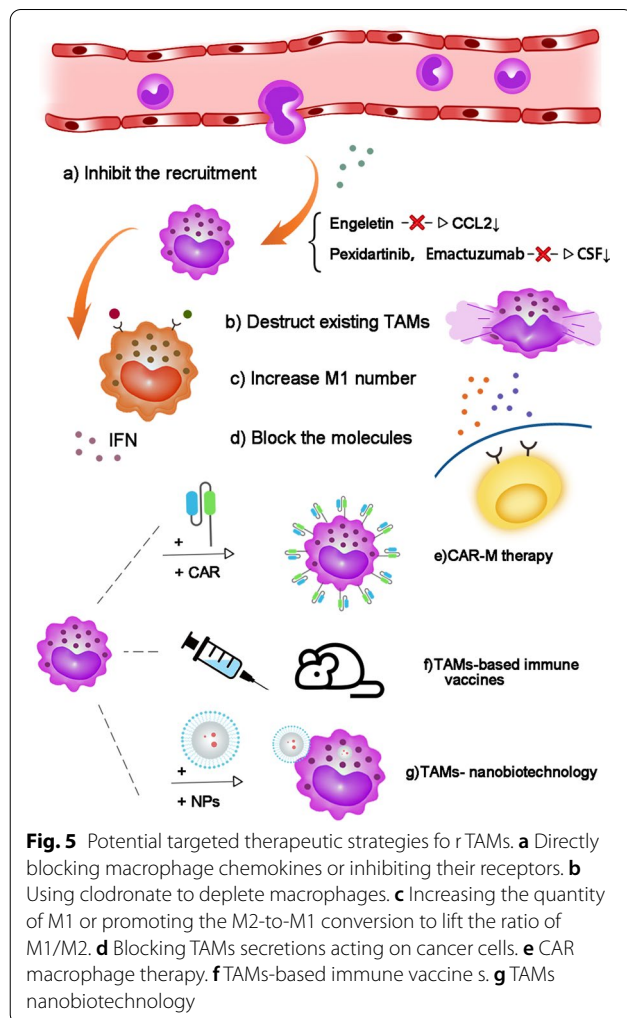
In another way, impeding the recruitment of TAMs into tumor tissue has broad application prospects in the future by preventing TAMs recruitment through cytokines. Engeletin (ENG, dihydrokaempferol 3-rhamnoside) is a substance which has anti-inflammatory properties [131, 132]. In cervical cancer, one research found that ENG significantly reduced the secretion of CCL2 via blocking NF-κB signaling pathway, which could be considered as an inhibitor of NF-κB [133]. Due to the help of ENG, monocytes in peripheral blood were less recruited to TME. CSF1/CSF1R inhibitors such as MCS110, Pexidartinib (PLX3397, PLX108-01) and Emactuzumab (RG7155) are being studied in clinical trials in solid tumors including ovarian and endometrial cancers [43, 134]. Heusinkveld et al. reported that a certain concentration of PGE2 and IL-6 could induce CD14+ macrophages to differentiate into CD163+ M2 macrophages [34]. Fortunately, the effect of PGE and IL-6 was completely blocked by the cox-oxidase inhibitor and IL-6 antibodies [34]. Similarly, the use of inhibitors of various pro-factors such as IL-4, IL-10, TGF-β and IL-13 may

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Table 4 Registered clinical trials involving targeting TAMs in gynecological and breast cancers

TAM target	NCT Number	Study results	Conditions	Interventions	Phases	Year of registration
CAR-M	NCT04660929	NA	Breast cancer Ovarian epithelial cancer	Biological: CT-0508	Phase 1	2020
CD47	NCT04881045	NA	Ovarian cancer	Biological: PF-07257876	Phase 1	2021
	NCT03957096	NA	Breast cancer Ovarian cancer	Drug: SGN-CD47M	Phase 1	2019
	NCT02890368	NA	Breast cancer HPV-related malignant neoplasm	Drug: TTI-621 monotherapy Drug: TTI-621 + PD-1/PD-L1 Inhibitor Drug: TTI-621 + pegylated interferon-α2a Other: TTI-621 + T-Vec Other: TTI-621 + radiation	Phase 1	2016
	NCT02125344	NA	Breast cancer	Drug: non-pegylated liposomal doxorubicin Drug: Carboplatin Drug: Paclitaxel Drug: Epirubicin Drug: Cyclophosphamide Drug: Pertuzumab Drug: Trastuzumab Drug: Ferric carboxymaltose	Phase 3	2014
TLR	NCT04278144	NA	HER2-positive solid tumors	Drug: BDC-1001 Drug: Pembrolizumab	Phase 1/2	2020
	NCT04116320	NA	Breast cancer Cervical cancer Ovarian cancer	Device: Echopulse Drug: Imiquimod Drug: Standard of care PD-1 therapy	Phase 1	2019
	NCT01421017	NA	Breast cancer Metastatic breast cancer Recurrent breast cancer	Radiation: Radiation Drug: Imiquimod Drug: Cyclophosphamide	Phase 1/2	2011
	NCT00899574	2 patients achieved a partial response (20%; 95% CI, 3%-56%)	Breast cancer Breast neoplasms	Drug: Imiquimod	Phase 2	2009
	NCT00319748	0 complete response, 0 partial response, 1 stable disease, 2 progressive disease	Breast cancer Ovarian cancer Endometrial cancer Cervical cancer	Drug: 852A	Phase 2	2006
CSF	NCT04542356	NA	Cervical cancer	Drug: PEG-rhG-CSF Drug: rhG-CSF	Phase 2	2020
	NCT04514692	NA	Cervix cancer Endometrial cancer	Diagnostic Test: FDG PET/CT Drug: GCSF	Phase 1/2	2020
	NCT04418219	NA	Breast cancer	Drug: Cyclophosphamide Biological: Allogeneic GM-CSF-secreting Breast Cancer Vaccine SV-BR-1-GM Biological: Pembrolizumab Biological: Recombinant Interferon Alpha 2b-likeProtein Other: Questionnaire Administration Other: Quality of Life Assessment	Phase 1/2	2020
	NCT04144023	NA	Breast ductal carcinoma in situ	Biological: Granulocyte-macrophage colony-stimulating factor Biological: Multi-epitope HER2 peptide vaccine H2NVAC Procedure: Therapeutic conventional surgery	Phase 1	2019

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Table 4 (continued)

TAM target	NCT Number	Study results	Conditions	Interventions	Phases	Year of registration
	NCT03858166	NA	Ovarian neoplasms Ovarian cancer	Drug: PEG-rhG-CSF	Phase 4	2019
	NCT03206684	NA	Cervical cancer	Drug: PEG-rhG-CSF Drug: rhG-CSF	Phase 4	2017
	NCT02978222	NA	Platinum-sensitive ovarian cancer Ovarian cancer	Biological: FRα peptide plus Adjuvant (GM-CSF) Drug: Adjuvant (GM-CSF) Alone	Phase 2	2016
	NCT02469116	16 complete response, 1 partial response, 0 stable disease, 1 progressive disease	Ovarian cancer	Drug: Docetaxel Drug: Carboplatin Drug: Pegylated G-CSF	Phase 2	2016
	NCT02017678	NA	Ovarian cancer	Biological: JX-594	Phase 2	2013
	NCT01570036	DFS was improved for NeuVax versus control (HR, 0.26; 95% CI, 0.08–0.81, $P = 0.01$)	Breast cancer	Drug: Herceptin Drug: NeuVax vaccine Drug: GM-CSF (control)	Phase 2	2012

Fig. 5 Potential targeted therapeutic strategies fo r TAMs. **a** Directly blocking macrophage chemokines or inhibiting their receptors. **b** Using clodronate to deplete macrophages. **c** Increasing the quantity of M1 or promoting the M2-to-M1 conversion to lift the ratio of M1/M2. **d** Blocking TAMs secretions acting on cancer cells. **e** CAR macrophage therapy. **f** TAMs-based immune vaccine s. **g** TAMs nanobiotechnology

reduce the migration of TAMs toward the tumor microenvironment to a certain extent [135–137].

In cervical cancer, compared with HPV preventive vaccine which has been already universally in use as a countermeasure of HPV-associated cervical cancer [138], the therapeutic HPV vaccine is still in development. In a vaccine trial involving the HPV16 E7 43–77 peptide, a decrease was observed in the number of M2 macrophages and the expression of M2 macrophage-related cytokines, such as IL10, TGF-β, MMP-2, MMP-9 and VEGF in the vaccine group [139], while M1 macrophage-related chemokines (such as CXCL-9 and CXCL-10) were up-regulated [139].

Reactivating M1 TAMs phagocytosis

As mentioned above, low M1/M2 rate often predicts poor patients' prognosis [140]. Therefore, trying to increase the number of M1 or improve the ratio of M1/M2 is a feasible way for possible treatment [141]. Indoleamine-2,3-dioxygenase (IDO1) is a key enzyme to degrade amino acid tryptophan through the kynurenine pathway [142], which can regulate macrophages and inhibit the immune function of T cells in a variety of diseases and cancers [142–145]. In cervical cancer, existing studies have shown that IFN-γ activated autophagy of cervical cancer cells and macrophage phagocytosis reactivation through IDO1 overexpression and kynurenine metabolism [146, 147]. In addition to cervical cancer, Feng et al. confirmed that high expression of IDO1 showed better survival prognosis in breast and ovarian cancer [148]. Although these studies revealed that up-regulation of IDO1 was beneficial to the suppression of cancer to some degree, more studies indicated that overexpressed IDO1

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Table 5 Strategies of targeted therapy for TAMs

Strategy	Method	Function	References
To reduce TAMs generation	Clodronate-containing liposomes (CL) Engeletin, CSF1/CSF1R inhibitors (MCS110, Pexidartinib and Emactuzumab), cox-oxidase inhibitors	CL can deplete macrophages in vivo and inhibitors of chemokines can reduce TAMs recruitment	[39, 43, 119, 131, 132]
To reactivate M1 TAMs phagocytosis	IFN-γ/IDO1 Anti-CD47 antibodies (Hu5F9-G4, HX009, AK117) HMGB1 inhibitors (A Box, RAP and EP), TGF-β receptor I inhibitors (SB4x), DNMTi 5-Azacytidine (5AZA-C) and ornithine decarboxylase inhibitor α-difluoromethylchlorine (DFMO) TAM receptors inhibitors (BMS-777607, BGB324 and AVB-S6-500)	Targeting IFN-γ/IDO1 pathway, blocking CD47-SIRPα axis and using several valid drugs can reactivate macrophage phagocytosis and convert M2 into M1 macrophages Blocking TAM receptors can inhibit TAM activation and polarization	[142, 143–145, 160, 170–172]
To inhibit macrophage-derived molecules	Broad-spectrum MMP inhibitor (CP-471,474) Selective MMP-12 inhibitors (CGA, CGA-1 and AGA) uPA inhibitor B-428 IL-6 inhibitor Siltuximab, Tocilizumab and Cetuximab TGF-β inhibitor Fresolimumab (GC1008), LY3022859, LY2109761 and 1D11 IL-10 receptor-blocking mAb (aIL-10R; clone 1B1.3A)	Inhibitors of TAMs-derived molecules (MMPs, uPA, IL-6, TGF-β, IL-10) were used to block the occurrence and development of tumor cells	[121, 177–184, 186, 189, 190]
CAR macrophage therapy	Edited specific chimeric antigen receptor on macrophages to target antigen (such as CD19, HER2)	CAR-M therapy can reverse M2 into M1 macrophages and activate phagocytosis	[169, 192, 193]
TAMs-based immune vaccines	Fused macrophage–tumor cytomembrane with vaccine adjuvant (CpG ODNs) Therapeutic vaccine with TAMs receptor inhibitor	TAMs-based immune vaccines can increase M1 macrophages and enhance immune response of immune cells. Combining therapeutic vaccine with TAMs receptor inhibitor obtains synergistic therapeutic effects	[191, 194]
TAMs nanobiotechnology	Macrolide-Au nanorod aCD47@CaCO3 NPs R848-loaded NPs Supramolecular NPs	Nanobiotechnology can target TAMs to boost anti-tumor effect, release CD47, or active TLR-7/TLR-8 to amplify M1 repolarization and phagocytosis	[196, 200]

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was related to immunosuppression and played an adverse role in the process of tumor development [149, 150].

Cancer cells express CD47 to protect cells from phagocytosis by binding and activating the receptor SIRPα on macrophages to inhibit macrophage phagocytosis. Targeting CD47-SIRPα axis has become a potential therapeutic mechanism in various preclinical models by stimulating the phagocytosis of cancer cells in vitro and in vivo [151, 152]. Up-regulated expression of CD47 was found in almost all types of tumor cells, which was associated with poor survival and prognosis [153–155]. Huang et al. constructed a novel oncolytic adenovirus carrying a signal regulatory protein-α (SIRPα)-IgG1 Fc fusion gene (termed SG635-SF), which significantly inhibited the growth of ovarian cancer cells in vivo [156]. Samanta et al. reported that treatment of TNBC cells with carboplatin, doxorubicin, gemcitabine or paclitaxel promoted the enrichment of CD47$^+$CD73$^+$PDL1$^+$ TNBC cells and promoted tumor immune evasion, which could be eliminated by inhibiting HIF [157]. Based on the crucial role of CD47-SIRPα axis in tumor immune escape, clinical trials of anti-CD47 antibodies are under way, involving drugs such as Hu5F9-G4, HX009 and AK117. A breast cancer study found that CD47 and HER2 activated each other at the transcriptional level [158]. Double antibody blocking CD47 and HER2 not only inhibited tumor clone formation, but also enhanced macrophage-mediated attack [158]. In TNBC, anti-CD47 antibody inhibited the differentiation of cancer stem cells (CSC) and down-regulated the expression of EGFR [159]. In addition, immunoliposome (ILips) combined with anti-CD47 and paclitaxel also produced a synergistic anti-tumor effect on converting M2 to M1 and enhancing systemic T cell immune response [160].

High-mobility group box 1 (HMGB1) is a non-histone chromatin-binding protein that exists widely in the nucleus and cytoplasm, which has been proven to up-regulate Treg cells and M2 macrophages in basal-like breast cancer cells [161]. Moreover, this effect could be blocked by HMGB1 inhibitors A Box, RAP, or EP, resulting in a reduced proportion of Treg cells and an up-regulated M1/M2 ratio [161]. Similarly, in the study of traditional Chinese medicine (TCM) treatment for ovarian cancer, astragaloside IV was found to weaken the polarization of M2 macrophages by inhibiting HMGB1-TLR4 signal transduction [162].

Toll-like receptors (TLRs) refer to conserved membrane proteins that recognize pathogens [163]. A study verified that TLR7 bound with TGF-β receptor I inhibitors SB431542 (SB4x) jointly provoked the polarization of M1 and CD4$^+$, CD8$^+$ and CD19$^+$ cells [164]. Travers et al. found that DNMTi 5-azacytidine (5AZA-C) activated type I interferon signaling in ovarian cancer,

catalyzed the number of IFN-γ$^+$ immune cells and lowered the percentage of macrophages in TME [165]. Furthermore, 5AZA-C combined with the ornithine decarboxylase inhibitor α-difluoromethylchlorine (DFMO) significantly reduced the M2 macrophages and increased the M1 macrophages [165]. Zhao et al. discovered that colorectal cancer treated with Cetuximab repolarized TAMs from M2 to M1 macrophages in an IL6- dependent manner [166].

In the above description of biomarkers for TAMs, we mentioned that stimulating macropha ges with different factors can affect the expression of receptors (Tyro3, Axl and MerTK receptor) on the surface of macrophages. Sun et al. proved that the expressions of Axl and its ligands Gas6 were abnormal in highly differentiated endometrial cancer, which may be related to tumor progression and inhibition of apoptosis [168]. However, Goyette et al. found that high AxL protein levels were associated with tumor metastases in HER2$^+$ breast cancer, which was independent of Gas6 [169]. Taking into account that TAMs receptors mediate tumor growth, invasion and metastasis, the researches on receptor inhibitors are booming [167]. Several studies found that pan TAMs kinase inhibitor BMS-777607 could inhibit the activation of TAMs receptor, further block the PD-L1 signaling pathway and suppress tumor progression [170], while selective Axl inhibitor BGB324 appears to induce apoptosis by inhibiting the PI3K pathway [171]. In addition, the function of AVB-S6-500 has been confirmed in clinical trials as an anti-Axl Fc fusion protein in epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer [172].

Additionally, Zhao et al. demonstrated that promoting the expression of long noncoding RNA (lncRNA)-Xist in M1 macrophages and down-regulating microRNA (miR)-101 expression in M2 macrophages could facilitate M2-to-M1 macrophage-type conversion, which might play a beneficial role in inhibiting the proliferation and migration of breast and ovarian cancers [173].

Inhibiting macrophage-derived cytokines

As previously stated, macrophages promote the growth and metastasis of tumor cells by secreting cytokines and growth factors. Therefore, blocking the corresponding signal transduction to interfere with cytokines is another method to restrict the role of TAMs.

Recent studies have shown that in cervical cancer, Poly(I:C), an adjuvant for cancer vaccine, may act through the NF-κB signaling pathway to promote the expression of M1-type cytokines (such as IL-1β and IL-6) and inhibit the expression of M2-type cytokines (such as IL-10 and CCL22) [174]. Another study showed that TAMs autocrine VEGF also acted through NF-κB pathway [175].

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Blocking the transmission of TAMs internal NF-κB pathway can weaken the pro-angiogenesis effect of VEGF as well. Besides, in MMP-12 knockout macrophages, the expression and phosphorylation of p38 and ERK1/2 were reduced, and the secretions of IL-1β, IL-6, TNF-α, CXCL1 and CXCL3 were down-regulated [176]. Three novel selective inhibitors of hydroxy ester MMP-12 (CGA, CGA-1 and AGA) and two 99mTc radioactive tracers derived from AGA [99mTc]-AGA-1 and [99mTc]-AGA-2 have been reported in recent studies [177]. In addition, a broad-spectrum MMP inhibitor CP-471/474 and a dual MMP-9/MMP-12 inhibitor (AZ11557272) showed well inhibition of MMP [178, 179]. However, further clinical trials are needed for selective MMP inhibitors to reduce drug toxicity. As for uPA, its inhibitor, 4-iodo benzo [b]thiophene-2-carboxamidine (B-428), has been shown to hinder the growth and metastasis of breast cancer in combination with tamoxifen back since the 1990s, which was superior to their separative effects [180].

Based on the important role of TAMs-derived IL-6 in cancer, therapeutic strategies targeting the IL-6 pathway are in active development. Siltuximab pertains to monoclonal antibodies (Mabs) that block IL-6 receptor [181]. In Siltuximab-treated ovarian cancer and ERα-positive breast cancer, cancer cells were found to reduce IL-6 production, which inhibited tumor growth, TAMs invasion and angiogenesis [182–184]. Analogously, Tocilizumab was effective in ovarian cancer, cervical cancer, endometrial cancer and breast cancer [185–188]. Besides, one study discovered that Cetuximab could also enhance the anti-tumor function of macrophages through IL-6 pathway [166].

To deal with up-regulated TGF-β, the researchers used antibodies to block both the receptor and the ligand, such as Fresolimumab (GC1008) and LY3022859 [189]. Altering the structure or composition of the ligand or the receptor to affect their binding is also helpful [189]. TGF-β targeting agents, such as LY2109761 and 1D11, have been proven effective in inhibiting metastasis in metastatic breast cancer [190].

IL-10 is an attractive therapeutic target due to its immunosuppression function and participation in tumorigenesis. One previous experiment showed that IL-10 receptor-blocking mAb (αIL-10R; clone 1B1.3A) increased the therapeutic effect of chemotherapy in breast cancer model in a CD8$^+$ T cell-dependent manner [121]. Additionally, Alotaibi et al. used RNAi to reduce secretion of IL-10, resulting in accelerating the apoptosis of breast cancer cells with a suppression in PI3K/Akt pathway [136].

To sum up, therapy targeting cytokines and growth factors can be performed in the following ways. Firstly, at the gene level, RNA interference technology can influence molecule expression. Besides, the expression of genes can be blocked by interfering the normal signal transducing pathway. In addition, we can also use a variety of methods to block the binding of receptors and ligands and further block the role of ligands.

CAR-macrophage (CAR-M) therapy

In recent years, chimeric antigen receptor (CAR) T cell therapy has developed rapidly in the treatment of hematological tumors. At the same time, human macrophages, which are modified with edited specific CAR to target antigen (such as CD19 and HER2) in order to recognize tumor cells and improve the ability of phagocytosis and antigen presentations, are in development as an immunotherapy [191]. The application of CAR-M therapy in solid tumors was first reported by Klichinsky et al. in 2020 [192]. The study has shown that CAR-M targeting HER2 significantly reduced tumor load, inhibited lung metastasis and prolonged the survival time in ovarian cancer mouse model [192]. Moreover, the expression of CAR structure can also promote TAMs polarization and even reverse M2 macrophages to transform into M1 macrophages [192, 193]. In addition, CAR-expressing macrophage cells (CAR-iMac) based on induced pluripotent stem cells (iPSCs) showed the ability to inhibit tumor cell growth both in hematological and in ovarian cancer model with lift expression of M1 pro-inflammatory cytokines [193].

TAMs-based immune vaccines

As a novel strategy, tumor immune vaccines based on macrophages can reshape the TME and prevent tumor recurrence after operation. Wang et al. designed a biologically fused cytomembrane (FM) which contained both M1 macrophage and 4T1 breast tumor cell cytomembrane [194]. With the assistance of vaccine adjuvant cytosine-phosphate-guanosine oligodeoxynucleotides (CpG ODNs), the vaccine successfully increased the number of pro-inflammatory M1 macrophages, promoted the maturation of dendritic cells and activated memory T cells [194]. On the other hand, the combined vaccine which consists of therapeutic vaccine and TAMs receptor inhibitor provides a new way to treat cancer by inhibiting the up-regulated TAM receptors after vaccine treatment [191].

TAMs-nanobiotechnology

Nanobiotechnology targeting TAMs is another promising immunotherapy. Nanoparticles loaded with TLR agonists, cytokines, monoclonal antibodies and metal oxides have achieved preferable results in cancer therapy [195, 196]. CAR-M combined with nanocarrier has been

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proved to be effective in solid tumors [197]. Kang et al. treated monocytes or macrophages with genes encoding CAR and IFN-γ through polymer nanocarriers, which successfully led to the phenotypic transition from M2 to M1 and the enhancement of macrophage phagocytosis [197]. In breast cancer model, TAMs were modified by iron-based metal organic framework (Fe-MOF) nanoparticles with ferroptosis-inducing agents, which allowed iron ions released in TAMs and further enhanced ferroptosis-associated stress in macrophages to induce effective M1 phenotypic polarization [195]. TAM-membrane-coated nanoparticles with conjugated photosensitizer (NPR@TAMM) and CSFR not only consumed tumor-derived CSF1, but also induced M2 macrophages transform into M1 via photodynamic immunotherapy [198]. Besides, nanoparticles loaded with TLR-7/TLR-8 agonist resiquimod (R848) and doxorubicin (DOX), which induced immunogenic cell death (ICD) or loaded with curcumin (Cur) and baicalin (Bai), had satisfactory tumor cytotoxicity in TME and significantly improved the efficacy of immunotherapy [199, 200].

Conclusions

It is clear that TAMs in gynecological and breast cancers affect tumor proliferation, angiogenesis, metastasis and immunosuppression by secreting cytokines and expressing receptors, which is related to the amount and proportion of anti-tumor M1 and pro-tumor M2 in TME. Since the phenotype of TAMs is elusive, scientists have explored the biomarkers of TAMs in attempt to distinguish TAMs and relevant cytokines, hoping to provide new ways to conquer tumors.

However, TAMs-targeted therapy has not yet achieved total success. To realize its full potential, several issues need to be addressed. First, complex mechanisms of TAMs in TME formation have not been fully clarified. Secondly, the accuracy of target tumor-promoting TAMs is the main problem facing various targeted drugs, and drug resistance and side effects should also be taken into consideration. In addition, the specificity of gynecological and breast cancers may contribute to different cancer-promoting patterns of TAMs via different gene expression and mechanistic pathways.

In conclusion, the relationship between TAMs and gynecological and breast cancers is worth in-depth investigation. Future researches could focus on new tumor-promoting mechanisms and targeted therapies including TAMs-based immunotherapies. There is no doubt that targeting TAMs in combination with existing therapies may improve patient outcomes in the future, which emerges as a novel treatment approach with great potential.

Abbreviations

Acknowledgements

Authors' contributions

Funding

Availability of data and materials

Declarations

Ethics approval and consent to participate

Consent for publication

Competing interests

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