Review

Targeting tumor-associated macrophages to reverse antitumor drug resistance

Sheng Li[1,*], Jiyao Sheng[2,*], Dan Zhang[2], Hanjiao Qin[3]

[1]The Second Hospital of Jilin University, Changchun, China
[2]Department of Hepatobiliary and Pancreatic Surgery, Second Hospital of Jilin University, Changchun, China
[3]Department of Radiotherapy, The Second Hospital of Jilin University, Changchun, China
[*]Equal contribution

Correspondence to: Hanjiao Qin; **email:** qinhanjiao@jlu.edu.cn

ABSTRACT

Currently, antitumor drugs show limited clinical outcomes, mainly due to adaptive resistance. Clinical evidence has highlighted the importance of the tumor microenvironment (TME) and tumor-associated macrophages (TAMs) in tumor response to conventional antitumor drugs. Preclinical studies show that TAMs following antitumor agent can be reprogrammed to an immunosuppressive phenotype and proangiogenic activities through different mechanisms, mediating drug resistance and poor prognosis. Potential extrinsic inhibitors targeting TAMs repolarize to an M1-like phenotype or downregulate proangiogenic function, enhancing therapeutic efficacy of anti-tumor therapy. Moreover, pharmacological modulation of macrophages that restore the immune stimulatory characteristics is useful to reshaping the tumor microenvironment, thus further limiting tumor growth. This review aims to introduce macrophage response in tumor therapy and provide a potential therapeutic combination strategy of TAM-targeting immunomodulation with conventional antitumor drugs.

INTRODUCTION

Chemotherapy, immunotherapy, and targeted therapy are currently widely applied in the clinical treatment of cancer. However, a large number of clinical trials have demonstrated that the long-term application of these drugs makes it difficult to avoid resistance. Moreover, the treatment effect of a single drug application is poor, with few lasting treatment responses and survival benefits. A large number of clinical studies have demonstrated that the development of drug resistance is closely associated with the tumor microenvironment (TME) and tumor-associated macrophages (TAMs).

The TME comprises an extracellular matrix (ECM), stromal cells, and immune cells (including T and B lymphocytes, natural killer cells, and TAMs) [1]. With the gradual advancement of research on the TME in recent years, its vital role in the development and evolution of tumors is becoming increasingly important. TAMs are important components of the TME. Two main sources are involved: one is derived from monocytes in the blood recruited to the tumor site under the effect of chemokines, while the other is derived from tissue-resident macrophages inherent to the corresponding tumor site, which originate during embryonic development. Macrophages demonstrate remarkable plasticity and exhibit two extreme phenotypes when exposed to various stimuli, which are broadly classified as pro-inflammatory M1 (classically activated macrophages) and anti-inflammatory M2 (alternatively activated macrophages) [2]. Inflammation in tumors leads to cell composition change in the TME. Hypoxia and lactic acid accumulation in TME change the TAM populations and phenotype. Increased TAMs offer a good environment for the invasion and metastasis of tumors [3]. Therefore, nearly all drug resistance is closely related to the complex interaction of the TME and TAMs.

This study investigates the interaction between the TME and TAMs and the role of TAMs in tumor progression. We also reviewed the clinical evidence of reprogramming and drug resistance induced by TAMs during tumor treatment. We summarized the recent studies as well as the mechanism of TAM reprogramming and induced drug resistance during treatment. Finally, we discussed the combination of drugs targeting TAM and traditional antitumor drug therapy as an emerging cancer treatment strategy.

TME and TAMs

In the TME, inflammation leads to changes to TAMs, including the recruitment from monocytes in the blood and the proliferation of tissue-resident macrophages. This cancer-related inflammation always promotes the development and progression of tumors. In acute inflammation, the expression of pro-inflammatory cytokines and chemokines increases, including IL-1, IL-6, C-C motif ligand 2 (CCL2), CCL5, C-X-C motif chemokine ligand 8 (CXCL8), CD40, and TNFα. These cytokines or chemokines recruit monocytic macrophages into tumors and have a crucial role in the TME [4, 5]. In addition to the chemotaxis and recruitment of monocytes in blood circulation, tissue-resident macrophages have an important role in the formation of the TME [6]. Evidence has shown that IL-4, a cytokine secreted by Th2 cells, drives the proliferation and expansion of tissue-resident macrophages in inflammation led by Th2 cells [7]. The tissue-resident macrophages are among the first cells to interact with transformed cells in tumors, and they may play a vital role in tumorigenesis [6]. Different from acute inflammation, chronic inflammation has a long-term effect on TME formation and is always closely associated with tumors in chronic inflammation. Chronic inflammation is a major risk factor for colorectal cancer. The p38αMAPK/ MAKAP Kinse2 (MK2) axis is an important component of cell stress. In response to the stimulatory signals of chronic inflammation, it promotes the polarization of TAMs to pro-angiogenic M2-like macrophages in colorectal cancer and then stimulates the progression of chronic inflammation to colorectal cancer [8]. In breast cancer, obesity causes the CCL2 signal to initiate chronic inflammation, thus leading to the recruitment to the TME of many macrophages and fibroblasts, thus resulting in collagen deposition and tumor fibrosis in the TME and significantly promoting tumor progression [9]. Chronic inflammation also causes an increase in reactive oxygen, resulting in DNA damage, cell death, and loss of repair programs. This reduces the antitumor ability of cytotoxic T cells and promotes immune escape of tumors [4]. In conclusion, these studies suggest that acute and chronic inflammation in the TME could impact the components of TAMs through numerous mechanisms, and TAMs promote tumor growth, invasion, angiogenesis, metastasis and immunosuppression through several mechanisms [10].

In mice, tissue-resident macrophages in the lung interstitium have been shown to offer nutritional support to tumor cells and promote tumor growth. Additionally, macrophages recruited by CCL2 primarily promote tumor invasion and spread in the lungs [10]. In breast tumors, macrophages are attracted by colony-stimulating factor-1 (CSF-1) released by cancer cells. The released epidermal growth factor (EGF), in response, stimulates cancer proliferation. This paracrine cycle between macrophages and cancer cells is mediated by EGF, and CSF-1 promotes tumor invasion [11, 12]. In terms of angiogenesis promotion, TAMs primarily expressing angiopoietin receptor Tie2 have been reported to accumulate in the perivascular region of tumors and promote tumor angiogenesis. This function can be further upregulated by exposure to tumor-derived factors such as angiopoietin-2 (ANGPT2) [13, 14]. TAMs also have an important part in promoting distant tumor dissemination and metastasis. The experimental results demonstrate that circulating tumor cells reside in the area with rich tissue-resident macrophages. These cells may thus contribute to the establishment of the pre-metastatic niche by maintaining an optimal "soil" for the eventual seeding of disseminated tumor cells [6]. Along with tissue-resident macrophages, TAMs, which primarily express Tie2, promote the increase in vascular permeability and the infiltration of tumor cells via vascular endothelial growth factor A (VEGF-A) signaling and then promote the distant spread of tumor cells [15]. Along with the above-mentioned mechanisms, TAMs mediate immune suppression in tumor treatment, help tumors to escape from immune response, and have a therapeutic effect. Both recruited macrophages and tissue-resident macrophages express inhibitory checkpoint molecules, namely programmed cell-death-ligand 1 (PD-L1), PD-L2, and PD-1, which inhibit the antitumor activity of T cells and affect immune checkpoint blockade (ICB) therapy. In conclusion, macrophages in the TME can impact all aspects of tumor growth and invasion through several mechanisms, and the TME is a complex system, the characteristics of which affect macrophages.

The accumulation of a large amount of lactic acid caused by hypoxia is the primary cause of TAM differentiation into the pro-tumor phenotype. Hypoxia in the TME is primarily classified into two types, namely chronic hypoxia and cycling hypoxia [16]. Chronic hypoxia is caused by the large distance

between cells and blood vessels, the growth of which cannot cope with the rapid growth of tumors, resulting in a continuous decline in oxygen levels [16], while circulatory hypoxia is a local intermittent hypoxia caused by an abnormal vascular structure [17]. Hypoxia can promote the further recruitment of TAMs and enable the function of TAMs to be more oriented towards the M2 phenotype, thus promoting tumor progression. Chronic hypoxia increases the expression of CXCL4 in uveal melanoma cells [18], CXCL9 and CXCL10 in liver cancer cells [19, 20], and CXCL1 and CXCL2 in TAMs [21]. Circulating hypoxia increases the expression of CXCL8 in TAMs [21]. The majority of these chemokines of the CXC family have the function of promoting TAM recruitment to the TME [16]. Chronic hypoxia is continuously accompanied by the activation of the NF-κB signaling pathway, which improves the response of TAMs to the above cytokines and further promotes their recruitment [22]. Additionally, a study on hypoxia in lung cancer reports that hypoxia reduces the secretion of proinflammatory factors of M1-like TAMs and promotes the polarization to M2-like TAMs [23]. Along with the effect of hypoxia on TAMs, hypoxia could produce a large amount of lactic acid through anaerobic glycolysis to promote tumor progression. Hypoxia inducible factor-1α (HIF-1α) is an essential transcription factor for vascular endothelial growth factor (VEGF), and lactic acid can stabilize HIF-1α, make it enter the nucleus, and induce TAMs to secrete VEGF [24]. HIF-1α entering the nucleus under the effect of lactic acid induces TAMs to express arginase, which can catalyze the conversion of arginine to ornithine. Ornithine is conducive to the production of polyamines, which have a crucial role in cell proliferation and are conducive to tumor growth and invasion [24]. Additionally, experiments have indicated that TAMs express higher levels of M2-like genes Arg1 and Mrc1 under the influence of lactic acid, which promotes TAMs to differentiate into M2-like phenotypes [24]. Therefore, lactic acid is among the "signals" for communication between tumors and macrophages. Macrophages monitor tumors via lactic acid and "maintain homeostasis" to preserve tumor growth [24].

Clinical evidence for TAMs in tumor response to therapies

Changes to the TME have an impact on the number and subtype of TAMs. In the clinical treatment of tumors, the majority of drugs change the TME and then change the number and phenotype of macrophages via recruitment and polarization. These recruited and tissue-resident macrophages contribute to tumor growth and metastasis, thus affecting the prognosis of tumor patients. In several recent clinical trials of tumor therapy, TAMs have been the focus of researchers. In several studies, macrophages were used as markers to indicate the therapeutic impact of tumors or the prognosis of patients. Evidence of macrophage recruitment and polarization can be found in clinical trials of multiple mainstream cancer therapies (including chemotherapy, immunotherapy, and vascular targeted therapy) (Table 1).

Chemotherapy

Chemotherapy drugs are currently the most broadly applied drugs in clinical cancer treatment. Even though targeted therapy and immunotherapy have emerged in the past few years, they still cannot replace the salient position of chemotherapy drugs. Recent clinical trials have demonstrated changes in the number of TAMs or M1/M2 phenotypes in tumors post-chemotherapy. These changes are always suggestive of tumor response to chemotherapy drugs, and some are closely associated with poor prognosis of tumor patients. A clinical trial of a chemotherapy regimen for advanced classical Hodgkin's lymphoma demonstrated that an increase in CD68+ macrophages in the TME post-treatment was closely associated with poor prognosis, and CD68 could even be applied as a poor prognostic marker [25]. Along with chemotherapy alone, TAMs are equally important in the combination of chemotherapy and immunotherapy. In a study of durvalumab combined with paclitaxel, doxorubicin, cyclophosphamide, as well as other chemotherapeutic agents in triple-negative breast cancer, RNA and DNA sequencing technology indicated that patients with residual disease (RD) exhibited upregulated CCL-3 and CCL-5 compared with patients with complete response (CR). This promotes the recruitment and infiltration of macrophages to the tumor site and indicates that the increased number of macrophages is related to the poor prognosis of patients [26]. Along with the poor prognostic significance of TAMs in chemotherapy, several studies have shown that an increase in TAMs may represent the impact of the drug in treatment. In a clinical trial on cabazitaxel in the treatment of gastroesophageal cancer, the enrichment of M2-like macrophages in tumors suggested a response to treatment [27]. In breast cancer, TAMs and their marker CD68 were increased in tumors treated with taxane and carboplatin, which can be used as markers of response to chemotherapy [28]. Notably, in a study on the combination of chemotherapy and targeted therapy in diffuse large B-cell lymphoma (DLBCL), an increase in CD68+TAMs post-chemotherapy alone indicated a poor prognosis, while an increase in CD68+TAMs content post-rituximab treatment had a positive effect on the prognosis of patients [29].

Table 1. Clinical evidence for the role of TAMs in tumor responses to therapies.

Treatment	Drug	Tumor	TAM Reeducation	Significance	References
Chemotherapy	Doxorubicin, bleomycin, vinblastine	Classical Hodgkin's lymphoma	CD68+ macrophages are significantly increased	The increase in CD68+ macrophages is associated with poor prognosis and could be a single prognostic biomarker	David W. Scott 2013
	Durvalumab, nab-paclitaxel	Breast cancer	Compared with pCR, the cancers with RD had higher expression of macrophage markers such as CCL-3, CCL-5, CXCL-1, CXCL-6, IL-1, IL-34 and more TAM infiltration	Increased TAMs and upregulated expression of TAM-related genes are associated with poor prognosis	Kim R. M. Blenman 2022
	Cabazitaxel	Gastroesophageal cancer	M2-like TAMs are enriched in tumors	The enrichment of macrophages suggests that the tumor is responsive to treatment	Manish A. Shah 2020
	NAC	Invasive breast cancer	Increased TAMs and CD68+ phenotype in the tumor bulk and infiltrative areas and increased TAMs after neoadjuvant chemotherapy (NAC) is associated with response to NAC in invasive breast cancer	TAMs and CD68 could be used as an immune predictive signature for response to NAC in invasive breast cancer	Lauren E. McLemore 2018
	Chemotherapy and rituximab	Diffuse large B-cell lymphoma	CD68+ macrophages are increased significantly after chemotherapy	The prognosis of patients with increased CD68+ macrophages after chemotherapy was poor, while the prognosis of patients with increased CD68+ macrophages after immunotherapy was good	Sari Riihijärvi 2015
Immunotherapy	Anti-PD-1 blockade	Intrahepatic cholangiocarcinoma	The number of TAMs increased, and the expression of SPP1 gene was upregulated. The MIF signaling pathway between tumor cells and TAMs or T cells is increased	Upregulation of SPP1 gene and increase in MIF signaling pathway promote tumor progression	Bao-Ye Sun 2022
	Keytruda, cyclophosphamide	Sarcoma	The infiltration of CD163+ macrophages increases after treatment. Meanwhile, the expression of indoleamine 2, 3-dioxygenase 1 (IDO1) in macrophages increases	Indoleamine 2, 3-dioxygenase 1 (IDO1) expressed by macrophages can produce kynurenine. Activation of the IDO1/kynurenine pathway may be an important mechanism leading to resistance to anti-PD-1 therapy	Maud Toulmonde 2018
	Atezolizumab, carboplatin, paclitaxel	Non-small-cell carcinoma (NSCLC)	Both the number and volume of CAMLs increase	Increased numbers of CAMLs are associated with tumor progression and poor survival	Alexander Augustyn 2021
	Toripalimab, carboplatin, pemetrexed	Non-small-cell carcinoma (NSCLC)	The infiltration of M2-like macrophages decreases, and M1/M2 ratio increases significantly	The reduction in M2-like macrophage infiltration is associated with longer survival and better prognosis	Tao Jiang 2021
	Camrelizumab, radiation and chemotherapy	Esophageal carcinoma	The proportion of PD-L1-negative macrophages in tumor is increased after treatment	Patients with a higher proportion of PD-L1-negative macrophages have a longer survival time, and the closer tumor cells are to PD-L1-negative macrophages, the better the prognosis	Xiaoxue Ma 2022
	Bevacizumab and ipilimumab	Metastatic melanoma	Extensive macrophage infiltration after treatment	The infiltration of macrophages affects the prognosis of patients	F Stephen Hodi 2014
	Anti-CD19 chimeric antigen receptor T cells	B-cell non-Hodgkin's lymphoma	TAM infiltration increases after treatment, and CD68 + and CD163 + cells increased	Increased TAM infiltration is negatively correlated with remission status, which can	Zi-Xun Yan 2019

		(CAR-T)	more significantly in the PR group than in the CR group	affect the efficacy of CAR-T	
Vascular targeted therapy	Bevacizumab	Rectal cancer	Upregulated gene expression of SDF1α and its receptor CXCR4 and CXCL6 in cancer cells, and induced NRP1 expression in TAMs	VEGF blockade upregulates inflammatory pathways and NRP1	Xu 2009
		Recurrent glioblastoma	Increased TAMs and CD163+ phenotype in the tumor bulk and infiltrative areas, and increased TAMs after antiangiogenic therapy is associated with poor survival	TAMs participate in immune escape from antiangiogenic therapy and represent potential biomarkers of resistance	Lu-Emersom 2013
		Glioblastoma	Accumulation of Tie2+ macrophages in surgical glioblastoma specimens and overexpressed MMP9	TEMs are associated with glioma recurrence after anti-VEGF therapy	Gabrusiewicz 2014
		Glioblastoma	Downregulated macrophage MIF and an increase in harbored M2 protumoral macrophages	Resistance is driven by reduced MIF causing proliferative expansion of M2 macrophages	Castro 2017
		Metastatic colorectal cancer	Genes that regulate TAMs-related functions are significantly associated with clinical outcomes	TAM-related gene variations predict outcomes of bevacizumab treatment	Sunakawa 2015
	Gefitinib/Erlotinib	Advanced non-small-cell lung cancer	Most TAMs were located in the tumor stroma and positively costained with the M2 marker CD163, and TAM counts were significantly higher in patients with progressive disease	TAMs are correlated with response to EGFR-TKI and independently predict survival in patients treated with EGFR-TKI	Chung 2012
		Advanced lung adenocarcinoma	M2 were significantly higher in patients with progressive disease, and M2 were shown to be significantly related to poor progression-free survival and overall survival	M2-TAMs are related to response of EGFR-TKIs and independently predict survival in patients treated with EGFR-TKI	Zhang 2014
		EGFR mutated lung adenocarcinoma	Blood monocytic S100A9+ MDSC counts were higher and were associated with poor treatment response and shorter progression-free survival	TAMs and S100A9+ MDSC-mediated EGFR-TKI resistance	Feng 2018
	Cetuximab	Colorectal cancer	M2 macrophages revealed high levels of Fc-gamma receptors (FcgRs) and PD-L1 and production of IL-10 and VEGF but not IL-12	Tumor-promoting M2 macrophages are activated by the therapeutic mAb cetuximab in the local tumor microenvironment	Pander 2011

Immunotherapy

The changes to TAMs after immunotherapy were also of great significance for the efficacy and prognosis of patients, and the changes in various subtypes of TAMs have different levels of significance for prognosis. Immune checkpoint blockade (ICB) has been the representative of immunotherapy in the past few years. A clinical study assessed the changes to cells in the TME post-ICB treatment of intrahepatic cholangiocarcinoma by single-cell RNA sequencing technology. The number of TAMs increased, and the expression of SPP1 gene was upregulated and has a core role in tumor progression. Additionally, the MIF signaling pathway between tumor cells and TAMs or T cells was increased, which has been shown to promote cancer progression [30]. A clinical trial of the PD-1 blocker pembrolizumab in combination with cyclophosphamide chemotherapy for sarcoma reported an increased infiltration of CD163-positive macrophages and immunosuppressive effects in treated tumors and that these macrophages expressed indoleamine 2 and 3-dioxygenase 1 (IDO1) to produce kynurenine. The activation of the IDO1/kynurenine pathway may be an important mechanism leading to resistance and anti-PD-1 therapy [31]. Additionally, a type of cancer-associated macrophage-like cells (CAMLs), which are circulating multinucleated myeloid cells, can be detected in the blood of some patients with

malignant tumors. A study on atezolizumab and carboplatin or paclitaxel in combination with non-small-cell lung cancer demonstrated an increase in the number and size of CAMLs. They are also associated with tumor progression and a poor survival rate [32]. A study on a toripalimab (PD-1 blocker), carboplatin, and pemetrexed combination in the treatment of non-small-cell lung cancer reported that M2-like macrophage infiltration was reduced, M1/M2 ratio was significantly increased, and the survival time of patients was prolonged after immunotherapy was combined with chemotherapy [33]. In a clinical trial on camrelizumab combined with chemoradiotherapy in the treatment of esophageal cancer, the proportion of PD-L1-negative macrophages in the tumor lumen increased post-treatment, and the survival time was prolonged. Additionally, the closer the tumor cells were to PD-L1-negative macrophages, the better the prognosis [34]. Along with PD-1 blocker therapy, TAMs changes appeared in the clinical trials of several other types of immunotherapies. For example, the biopsy results of CTLA4 inhibitor ipilimumab combined with bevacizumab in the treatment of metastatic melanoma demonstrated extensive TAM infiltration [35]. In a clinical trial on anti-CD19 chimeric antigen receptor T cells (CAR-T) for B-cell non-Hodgkin's lymphoma, RNA sequencing demonstrated an increase in TAM infiltration post-treatment, with a greater increase in CD68 + and CD163 + cells (the latter representing M2-like TAMs) in the PR group compared with the CR group. This indicates that increased TAM infiltration is negatively correlated with remission status, and this impacts the efficacy of CAR-T [36].

Vascular targeted therapy

Recombinant humanized monoclonal antibodies and VEGFR/EGFR tyrosine kinase inhibitors (TKIs) have been widely applied in the treatment of metastatic colorectal cancer, glioblastoma, as well as non-small-cell lung cancer [37]. Although the list of vascular-targeted drugs is still expanding, latent adverse effects have been reported in clinical practice. Numerous studies have demonstrated a significantly higher number of CD68+ macrophages and CD163+ M2-like phenotypes in the tumor mass and within infiltrative areas of glioblastoma patient post-bevacizumab therapy [38–41]. Microarray analysis indicated that a reduced level of macrophage migration inhibitory factor can be the most pertinent mediator of this, thus resulting in polarization to pro-tumoral M2 and specific localization to the glioblastoma rim [38]. The accumulation of highly proangiogenic Tie2-expressing macrophages (TEMs) was demonstrated in malignant glioma surgical samples that relapsed post-anti-VEGF treatment, and the TEMs were shown to secrete more gelatinase enzymatic proteins to improve the invasive characteristics of glioma cells [39]. After

bevacizumab treatment of rectal cancer patients, a high level of circulating stromal cell-derived factor 1α (SDF1α) was reported in association with rapid distant disease progression. This was predicted, since the SDF1α pathway is a known independent regulator of angiogenesis and metastasis [42]. Bevacizumab also induced significant changes to neuropilin 1 (NRP1) expression in TAMs, and NRP1 was shown to modulate the alternatively activated M2 phenotype of macrophages. Such clinical evidence supports the role for TAMs in mediating the tumor response to vascular targeted therapy.

The therapeutic outcome of anti-angiogenic agents has been modest and transitory, with drug resistance reported to develop after a period of pharmaceutical response [43]. Numerous studies in the literature have suggested that tumor-promoting TAMs are involved in angiogenesis and immune suppression, inducing resistance to vascular-targeted therapy [38, 42–46]. When mediating immune escape from anti-VEGF therapy, TAMs may apply additional mechanisms rather than depend on the VEGF pathway to rescue tumor invasion, migration, and angiogenesis [47–49]. Intravital imaging recorded tumor cells interacting with TAMs to exit their primary site into blood vessels and seed to distant metastatic organs, a process relying on the function of macrophages [14, 50]. The DSC-MR imaging technique offers direct evidence that CCL2 expression by TAMs can raise the resistance to bevacizumab [51]. The genetic deletion of macrophages or medical inhibition of their recruitment has strongly attenuated these seeding events and primary tumor growth after being exposed to vascular targeted therapy [52–54].

In cancer patients treated with anti-vascular therapy, clinical evidence revealed that TAMs were significantly associated with poor clinical prognosis, including progression-free survival and overall survival in a broad range of tumors, such as advanced lung adenocarcinoma, colorectal cancer, and glioblastoma [40, 44, 55–57]. TRIBE and FIRE3 trials also demonstrated variations in genes regulating TAM-related functions that could predict the clinical outcomes of bevacizumab-based treatment in patients with metastatic colorectal cancer [56]. Moreover, a proangiogenic subset of macrophages was found to be closely related to glioma recurrence after anti-VEGF therapy, attributable to their direct role in tumor invasion and aggression [39, 40].

EGFR-TKIs

Epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs) are the most common drugs applied in targeted therapy. The EGFR-TKI

representative drugs gefitinib and erlotinib increased the TAM count in the tumor stroma of patients with EGFR-mutated lung cancer and significantly attenuated therapeutic cytotoxicity [44, 55, 57]. In response to EGFR-TKIs, M2-TAMs, but not M1-TAMs, were higher in patients diagnosed with progressive disease than in those without it [55, 57]. In a phase III randomized clinical trial on metastatic colorectal cancer, the anti-EGFR monoclonal antibody cetuximab activated tumor-promoting M2 macrophages in the local TME, thus releasing multiple anti-inflammatory factors and pro-tumor mediators, and the infiltration of M2 macrophages was closely associated with poor prognosis [58, 59]. Additionally, a clinical trial on sunitinib or panitinib in patients with renal cell carcinoma (RCC) reported increased TAMs in tumor samples post-treatment, and it was shown to be associated with poor prognosis [60, 61].

Mechanisms by which therapies reprogram TAMs

Numerous clinical trials have demonstrated that the number of macrophages in tumor sites increases, and the phenotype changes post-conventional treatment, which are often closely associated with the prognosis of patients. Researchers have discussed the mechanism of the above phenomenon via clinical research. The research primarily concentrated on two aspects of chemotherapy and vascular targeted therapy (Table 2). Chemotherapy impacts the expression of specific genes in tumor cells and macrophages in the TME, regulates the secretion of cytokines, promotes the recruitment of monocytes in the blood to the tumor site, and polarizes the infiltrating macrophages to the M2 phenotype. The primary function of vascular-targeted therapy is the reduction in the tumor vascular bed, while subsequent hypoxia can be significantly increased [62–65]. Hypoxia also modulates innate immune cells to induce angiogenesis and immune evasion, and this regulates the production of cytokines and growth factors by tumor cells and further reprograms TAMs via paracrine activation [66–68]. Hypoxia can exert selective pressure on cancer cells with only aggressive phenotypes able to survive, thus causing invasive properties and limiting the efficacy of anti-cancer therapy [64, 65, 69]. Subsequently, we discuss the mechanisms by which chemotherapies and vascular targeted therapies reprogram TAMs in preclinical studies and concentrate on how to avoid the reeducation of TAMs.

Increased TAM recruitment

Monocytic lineage cells trafficking from the circulation into the tumor stroma are under the control of tumor-derived chemoattractants, and preclinical evidence revealed the impact of chemotherapy and anti-angiogenic drugs on proangiogenic macrophage recruitment.

Chemotherapy leads to the recruitment and infiltration of macrophages primarily by promoting the up-regulation of several chemokines. In an experiment on pancreatic cancer mice treated with gemcitabine, the expression of IL-8 in pancreatic cancer cells and the infiltration of macrophages at the tumor site were increased. Meanwhile, the infiltration of macrophages was reduced after the treatment with an IL-8 neutralizing antibody. This indicates that pancreatic cancer cells completed the recruitment of macrophages by upregulating the expression of IL-8 [70]. After the treatment of breast cancer mouse models with neoadjuvant chemotherapy drugs, macrophages expressed more YKL-39, which is a newly discovered chemokine promoting the recruitment and infiltration of monocytes from blood to tumor sites [71]. In a paclitaxel-treated mouse model of breast cancer, tumor cells upregulated the expression of colony-stimulating factor 1 (CSF-1) and resulted in the recruitment of TAMs and resistance to paclitaxel. Conversely, the introduction of the CSF-1R inhibitor pydatinib in combination with paclitaxel blocked macrophage recruitment and significantly increased CD8+ T cells. This demonstrates that CSF-1 has a crucial role in the recruitment of macrophages induced by chemo-therapy [72]. Another experiment on the treatment of lung cancer mice by paclitaxel combined with cisplatin demonstrated that the macrophages in tumors significantly increased post-treatment, while the number of macrophages in heparanase knockout mice did not change post-treatment, suggesting that the activation of macrophages by chemotherapy was dependent on heparanase [73]. Additionally, a study on durvalumab (PD-L1 blocker) combined with albumin paclitaxel and doxorubicin/cyclophosphamide in the treatment of triple-negative breast cancer also demonstrated that the expression of CCL3, CCL5, and other chemokines increased post-chemotherapy, and these chemokines promoted the recruitment of macrophages to the tumor site [26].

Multi-target VEGFR therapy has been demonstrated to rapidly induce intratumor hypoxia and improve the infiltration of macrophages into tumors, which may be vital to the development of drug refractoriness and consequent tumor progression [54, 74–76]. The remaining tumor cells can exploit hypoxia to their own advantage [64]. In the hypoxic milieu, tumor cells produce and secrete multiple chemokines and cytokines to entrap macrophages from the bloodstream into the tumor [69]. Sorafenib was reported to significantly increase the peripheral recruitment and intratumoral

Table 2. TAM reprogramming driven by tumor therapies.

TAM Reprogramming	Drug	Tumor	Effects on tumor	Potential extrinsic inhibitors	References
Increased TAM recruitment	Gemcitabine	Pancreatic cancer	After treatment with gemcitabine, pancreatic cancer cells promoted the recruitment of macrophages and tumor progression through IL-8	IL-8 neutralizing antibody	Sachin Kumar Deshmukh 2018
	Neoadjuvant chemotherapy	Breast cancer	The recruitment of monocytes increased through the expression of YKL-39. TAMs promote the angiogenesis and metastasis of breast cancer	YKL-39 blocker	Liu 2018
	Paclitaxel, pexidartinib	Solid tumor	The expression of CSF-1 increased, leading to the recruitment of TAMs and drug resistance, while combined treatment with pexidartinib could inhibit the recruitment	Pexidartinib	Robert Wesolowski 2019
	Paclitaxel, cisplatin	Lewis lung cancer	TAMs increased after treatment with paclitaxel and cisplatin, while the number of macrophages does not change in the heparanase knockout mice	Heparanase inhibitor	Udayan Bhattacharya 2020
	Sorafenib	Metastatic liver cancer	Tumor progression	Clodrolip or ZA	Zhang 2010
		Liver cancer	Tumor growth, neovascularization, progression, and drug resistance	Anti-Ly6G antibody	Zhou 2016
	Bevacizumab	Breast cancer	Tumor malignancy and drug resistance	Blockade of Oncostatin M/Eotaxin	Tripathi 2014
Polarization to M2-TAMs	Sunitinib	Glioblastoma	Tumors developed aggressive mesenchymal features and increased stem cell		Piao 2012
	Cisplatin, carboplatin	Cervical and ovarian cancer	Cervical and ovarian cancer cell lines showed increased production of PGE2 and IL-6, which promote macrophages to polarize towards the M2 subtype and promote drug resistance	COX inhibitors, anti-IL-6R	Eveline M Dijkgraaf 2013
	Paclitaxel	Breast cancer	A large accumulation of ROS in the TME. ROS stimulate the secretion of cytokines such as IL-10, IL-4, IGFBP-3, and CXCL1	Anti–PD-L1 blockade	Cecilia Roux 2019
	Neoadjuvant chemotherapy	Esophageal squamous cell carcinoma	APOE, APOC1, and SPP1 are highly expressed in TAMs, leading to the increase in M2 macrophages and drug resistance		Chen 2021
	Temozolomide	Melanoma	Exocytic vesicles shed by melanoma cells after temozolomide treatment promote macrophages towards the M2 phenotype, leading to tumor repopulation and treatment failure		Luciana Nogueira de Sousa Andrade 2019
	Bevacizumab	Glioblastoma	Induces resistance to antiangiogenic therapy	AZD1480	de Groot 2012
		Breast cancer	Tumor malignancy and drug resistance	Blockade of Oncostatin M/Eotaxin	Tripathi 2014
	Sorafenib	Pancreatic neuroendocrine tumor	Immune suppression, reneovascularization, and tumor regrowth	IPI145	Rivera 2015
Promotion of proangiogenic TAM subset	CA4P	Breast cancer	Limited therapeutic efficacy of agent	AMD-3100	Welford 2011
	Bevacizumab	Glioblastoma	Enhanced invasive properties and secretion of high levels of gelatinase enzymatic proteins		Gabrusiewicz 2014
	DC101	Glioblastoma	Increased signal for tumor-remodeling properties and invasive tumor growth	Inhibitor of Ang-Tie2 axis	Cortes-Santiago 2016
Enhanced proangiogenic TAM activities	Clone 3.19.3	Breast cancer	Upregulated expression of several proangiogenic genes, such as Vegfa, Vegfb, Pdgfb, Sdf1, and Mmp9		Mazzieri 2011
	Bevacizumab	Ovarian cancer	Enhanced expression of alternative proangiogenic chemokines and cytokines including G-CSF and PDGF	ZA (depletion of macrophages)	Daltion 2017

infiltration of macrophages in metastatic liver cancer, accompanied by an elevation of SDF-1α, CSF-1, and VEGF in the tumor stroma [54]. In the hypoxic niches induced by sorafenib, TAMs promote the expression of galectin-3, and this further induces TAM infiltration [77]. Furthermore, the TAM-mediated promotion of tumor growth and metastasis in hypoxia was inhibited by the administration of a macrophage-depletion agent or galectin-3 inhibitor in a mammary model [77]. The depletion of macrophages by zoledronic acid and clodrolip in combination with sorafenib may significantly suppress tumor angiogenesis and distant organ metastasis, demonstrating the role of TAMs in tumor development in sorafenib therapy [54]. Sorafenib also mediated the infiltration of tumor-associated neutrophils (TANs) in hepatocellular carcinoma patients and animal models, while TANs further promoted more intratumoral macrophages and T-regulatory (Treg) cells through secreting CCL2 and CCL17 [76]. The injection of neutralizing antibodies against CCL12 and CCL17 into tumors caused an explicit reduction in tumor size and pulmonary metastasis, with a drop in the migratory activities of TAMs and Treg cells [76]. Additionally, sunitinib and bevacizumab treatments simultaneously inhibited the infiltration of macrophages and enhanced overall survival compared with bevacizumab therapy alone. However, gliomas developed a mesenchymal phenotype and expressed stem cell markers at the late tumor of tumor progression [74].

Polarization of TAMs to M2-like phenotype

Macrophages show remarkable plasticity in response to microenvironmental cues [78]. An alteration in macrophage polarization in the TME to an immune-suppressive phenotype was always reported after chemotherapy or vascular targeted therapy [75, 79, 80].

Unlike chemotherapy-induced recruitment of TAMs that is primarily dependent on various chemokines, chemotherapy-induced polarization of TAMs to the M2 phenotype has more diverse mechanisms. The experimental results suggest that prostaglandin E2 (PGE2) and IL-6 increased in cervical and ovarian cancer cell lines treated with carboplatin or cisplatin. These two inflammatory mediators promoted the polarization of macrophages to M2 subtype, while blocking the typical NF-κB signaling pathway could inhibit the impact of chemotherapy and prevent the production of PGE2 and IL-6 in tumor cell lines. Meanwhile, the enhancement of M2 phenotypic polarization by chemotherapy disappeared. These phenomena suggest that chemotherapy depends on two inflammatory mediators, PGE2 and IL-6, to promote M2-type polarization [81]. Additionally, paclitaxel treatment of breast cancer mice causes a large accumulation of reactive oxygen species (ROS) at the tumor site, which stimulates the secretion of cytokines such as IL-10, IL-4, insulin-like growth factor binding protein 3 (IGFBP-3), and CXCL1 and promotes the transformation of macrophages to the immunosuppressive phenotype [82]. Global single-cell transcriptome analysis using data from clinical trials demonstrated that TAMs highly expressed APOE, APOC1, and SPP1 genes in patients with esophageal squamous cell carcinoma (ESCC) post-neoadjuvant chemotherapy, and this leads to an increase in M2-like macrophages [83]. Additionally, in an experiment applying temozolomide to treat melanoma mice, it was found that exocytic vesicles exfoliated by melanoma cells post-treatment polarize macrophages towards the M2 phenotype by upregulating M2-like genes such as ARG-1 and IL-10 [84].

The mechanism of TAM polarization to M2 type induced by vascular-targeted drugs is similar to that of macrophage recruitment. Local hypoxia caused by vascular blockade remains the most important mechanism. A recent study suggested that hypoxia-primed breast cancer cells chemoattracted and polarized macrophages to a proangiogenic M2-like phenotype by elevating cytokines eotaxin and oncostatin M [75]. The blockade of eotaxin and oncostatin M augmented the therapeutic efficacy of anti-angiogenic bevacizumab for supporting tumor regression [75]. The hypoxic microenvironment has a vital role in cancer stemness acquisition and epithelial–mesenchymal transition, thus promoting tumor progression [85]. In glioblastomas after bevacizumab therapy, hypoxia can persistently induce the expression of phosphorylated signal transducer and activator of transcription 3 (p-STAT3) in glioma cells, which preserves the mesenchymal transformation of normal neuroglial cells and the stemness of glioma cells [79]. STAT3 was also responsible for the modification of TAMs to the tumor supportive M2-like subtype, while the administration of the STAT3 inhibitor combined with anti-angiogenic agents explicitly decreased microvascular density and tumor proliferation, with a lower number of p-STAT3 macrophages [79]. A recent study based on the hepatocellular carcinoma model indicated that sorafenib increased the synthesis and secretion of hepatocyte growth factor (HGF) by TAMs. HGF activates phosphoinositide-3-kinase/protein kinase B (PI3K/AKT) pathways in tumor cells and promoted the polarization of TAMs to the M2-like phenotype [86]. In a pancreatic neuroendocrine cancer model, sorafenib promoted the polarization of TAMs, TANs, as well as other myeloid cells to an immune-stimulating phenotype. However, this effective response was transient in that all these myeloid cell populations were skewed to the immune-suppressive type, causing tumor regrowth and neo-vascular formation [80]. The

pharmacological inhibition of phosphoinositide-3-kinase in myeloid cells can improve the endurance and efficacy of vascular-targeted therapy by reversing the subset of these myeloid cells [80].

Promoting proangiogenic TAM subset

TEMs are a proangiogenic subpopulation of macrophages characterized by both expression of macrophage markers and the angiopoietin receptor Tie2 and are found in the circulation and the tumor stroma of both humans and mice [87, 88]. Prior studies have suggested that clusters of TEMs surrounding blood vessels make contact with nearby endothelial cells to sustain the tumor microvessel network, which was correlated with therapeutic intolerance and poor prognosis [50, 89, 90]. The upregulation of pro-angiogenic TEMs is a mechanism by which vascular-targeted therapies reshape macrophages. The leading vascular disrupting agent (VDA), combretastatin A4 phosphate (CA4P), is a microtubule depolymerizing drug that causes the cytoskeletal and morphological destruction of vascular structures [91–93]. After treatment with CA4P in murine breast cancer models, tumors significantly increased their levels of chemokine CXCL12 and repopulated the infiltration of pro-angiogenic TEMs [94]. Inhibiting TEM recruitment by genetically depleting TEMs or pharmacologically inhibiting the CXCL12/CXCR4 axis significantly assisted the vascular-destroying impact of CA4P [94]. Recent research reported that hypoxia-inducible transcription factors HIF-1α in hypoxic conditions promote the infiltration of proangiogenic TEMs, while the HIF-2α suppresses this particular mechanism [95]. The two different types of HIFα subunits regulate Tie2-expressing macrophages [95]. The anti-VEGF therapy bevacizumab induced the invasive outgrowth of malignant gliomas via TEM accumulation [39]. In this pro-invasive TME, Ang2 was explicitly increased post-anti-VEGF treatment [96] and chemoattracted TEMs into tumors and aggravated signals of tumor-remodeling properties [97]. This suggests a vital role for the Ang2–Tie2 pathway in recurrent tumors following anti-angiogenesis therapies and offers rational therapeutic strategies.

The regulation of TAM proangiogenic activities

Prior work has suggested that TAMs facilitate resistance to anti-VEGF therapy by altering proangiogenic activities [98, 99]. The macrophage level increased with the emergence of VEGFA-targeted monoclonal antibody refractoriness in an ovarian-cancer-bearing mice model. The resistant macrophages involved in the development of refractoriness indicated heightened viability, aggression, and migration [100].

Compared with sensitive TAMs, resistant TAMs demonstrated a significantly enhanced expression of alternative proangiogenic chemokines and cytokines, including granulocyte CSF and platelet-derived growth factor (PDGF), rather than the secretion of VEGFR [100]. Moreover, the blockade of Ang2 upregulated the expression of several pro-vascular genes in a breast cancer mice model, such as Vegfa, Vegfb, Pdgfb, Sdf1, and Mmp9 [101]. Reported preclinical evidence suggests that inflammatory cytokines derived from monocytes or macrophages promoted vascular CXCR4 expression on endothelial cells, while reducing CXCR4 expression by the depletion of macrophages enhanced the anti-tumor impact of sorafenib in liver cancer [102].

Mechanisms of TAM-mediated drug resistance

During tumor treatment, drugs reprogram TAMs, and the mechanism of reprogrammed TAMs mediating drug resistance of tumor cells becomes more complex. In the following section, we discuss how TAMs mediate drug resistance of tumor cells using three treatment methods, namely chemotherapy, immunotherapy, and vascular targeted therapy.

Chemotherapy

The TAM mechanisms mediating chemoresistance comprise regulating tumor cell apoptosis, participating in epithelial–mesenchymal transition (EMT), metabolites competing with chemoresistance, and regulating autophagy, among others. Some researchers investigated the mechanism of TAMs mediating the resistance of colorectal cancer cells to 5-FU. Metabolomics analysis demonstrated that putrescine, one of the metabolites of TAMs, increased post-5-FU treatment. Further animal experiments demonstrated that putrescine could reduce the activation of apoptotic protein caspase-3, thus protecting tumor cells from the impact of the apoptosis mechanism. Some researchers investigated the mechanism of TAMs mediating the resistance of colorectal cancer cells to 5-FU. Metabolomics analysis suggests that putrescine, one of the metabolites of TAMs, increased post-5-FU treatment. Further animal experiments demonstrated that putrescine inhibits the activation of apoptotic protein caspase-3, thus protecting tumor cells from the impact of the apoptosis mechanism. The inhibition of putrescine production promotes the apoptosis of tumor cells, i.e., it restores the sensitivity of colorectal cancer cells to 5-FU. These studies demonstrated that TAMs inhibit the apoptosis of tumor cells through putrescine, one of its metabolites, and then causes colorectal cancer cells to become resistant to 5-FU [103]. One study reported that the cytokine CCL22 secreted by M2-type macrophages inhibited the cleavage of three

apoptotic proteins, caspase-3, caspase-8, and PARP, and increased the expression of p-PI3K and p-AKT, thus inhibiting 5-FU-induced apoptosis of colorectal cancer cells and mediating drug resistance [104]. Additionally, this study indicated that macrophages mediate 5-FU resistance in colorectal cancer by participating in epithelial–mesenchymal transition (EMT) [104]. In a study on gemcitabine in pancreatic cancer treatment, researchers applied C13 isotope labeling of glucose carbon atoms. They reported that compared with the M1-like macrophages, M2-like macrophages are more marked in the metabolism of glucose into the tricarboxylic acid cycle, and these marked carbon atoms were applied to synthesize more pyrimidine. Deoxycytidine (deoxycytosine nucleoside) was similar to gemcitabine in molecular structure and inhibits gemcitabine activity via molecular competition, thus leading to resistance to gemcitabine [105, 106]. In an oxaliplatin resistance experiment of liver cancer cells, after the co-culture of TAMs and hepatocellular carcinoma (HCC) cells, it was reported that HCC autophagy was activated, HCC was resistant to oxaliplatin, and the sensitivity of HCC cells to oxaliplatin was significantly enhanced when ATG5 siRNA was applied to inhibit autophagy of HCC cells. With this, TAMs can mediate oxaliplatin resistance in HCC cells by inducing autophagy [107].

Immunotherapy

In immunotherapy, the impact of TAMs on the prognosis of patients in various types of tumors is different. In a study on the mechanism of glioblastoma resistance, the combination of PD-1 and CTLA-4 antibodies was applied to treat glioblastoma mice. TAMs from the resistant mice were isolated and co-cultured with T cells, and it was reported that CD80 on the surface of T cells increased. CD80 was previously shown to substitute for PD-1 in binding to its ligand PD-L1, thus inhibiting CD4+T cell proliferation accompanied by an increase in Treg cells. Subsequently, PD-L1 antibody therapy was introduced to the previous regimen, which inhibited the interaction between CD80 and PD-1. The inhibition of CD4+T cell proliferation and the increase in Treg cell expansion were weakened, and the impact of ICB therapy was further enhanced. These studies reported that macrophages induced the inhibition of CD4+T cells and the expansion of Treg cells in the TME via the PD-L1/PD-1/CD80 signaling pathway, thus mediating the resistance of glioblastoma to the combination therapy of PD-1 and CTLA-4 blockades [108]. Additionally, in a clinical trial, the puncture biopsy of patients with hepatocellular carcinoma treated with PD1 blockade demonstrated that the expression of circTMEM181 (a circular RNA) was significantly upregulated in some drug-resistant

individuals. A series of animal and cell experiments demonstrated that circTMEM181 is an exosome secreted by HCC cells. It can absorb Mir-488-3p (a miRNA) in macrophages, thus upregulating the expression of CD39 in macrophages, a key enzyme in initiating the ATP-adenosine pathway. CD39 attenuates extracellular ATP (eATP), stimulating immune response signals in the TME by hydrolyzing eATP and ADP to AMP. The immune responses are weakened, thus mediating the resistance of HCC cells to PD-1 blockade therapy [109]. In an experiment in which PD-1 antibody and CTLA-4 antibody were combined to treat breast cancer mice, the expression of IFNγ was significantly upregulated post-treatment. IFNγ induces macrophages to produce more CXCL9 and CXCL10, two chemokines that bind to CXCR3 on the surface of T cells and promote their recruitment for anti-tumor immune response. The application of IFNγ neutralizing antibodies, knockdown of CXCL9/CXCL10 gene, or CXCR3 blockade of macrophages all cause the attenuation of anti-tumor immune response. This indicates that the production of CXCL9 and CXCL10 by macrophages induces T cell recruitment and is an important mechanism of immune checkpoint blockade in breast cancer treatment [110].

Vascular targeted therapy

TAM-mediated drug resistance in vascular targeted therapy is primarily related to the inhibition of tumor cell apoptosis. The treatment of lung adenocarcinoma with the EGFR inhibitor erlotinib cannot avoid drug resistance and gradually leads to tumor progression. In view of the causes of its drug resistance, some researchers explored its mechanism: TAMs in the TME secretes EREG (one of the ligands of EGFR), induces ERbB2 to form EGFR/ERbB2 heterodimer, downregulates cleaved caspase nine and other apoptotic proteins through its downstream PI3K/AKT pathway, inhibits the apoptosis of tumor cells, and then mediates the resistance of NSCLC to EGFR-TKI inhibitors [111]. Another study on EGFR-TKI inhibitors in NSCLC reported that their resistance was closely associated with alveolar macrophages (AMs) in the TME. In the EGFR signaling pathway, AM produced local proliferation and was gradually polarized into tumor-promoting the M2 phenotype, which mediates drug resistance by inhibiting tumor cell apoptosis and other mechanisms [112]. An animal experiment of bevacizumab, a representative drug of vascular targeted therapy, in the treatment of triple-negative breast cancer, demonstrated that it induced the co-activation of TLR4 and Fcγ receptors on the surface of macrophages, which made macrophages polarized to the M2b subtype (CD11b+ CD86+ IL10 high). This subtype of macrophages produces great

amounts of TNFα, which induces the expression of immunosuppressive molecule IDO1. It has been shown to promote drug resistance and is associated with poor prognosis. The inhibition of TNFα decreases the expression of IDO1 and enhances the therapeutic impact of bevacizumab. These findings show that M2b macrophages can induce bevacizumab resistance in breast cancer cells via the TNFα-IDO1 axis [113]. Additionally, researchers have investigated the resistance mechanism of bevacizumab in the treatment of glioblastoma (GBM) and found that GBM cells secrete two cytokines, IL-8 and CCL2, which stimulate TAMs to produce TNFα, which activates endothelial cells (ECs). EC activation has been reported to be associated with bevacizumab resistance and poor prognosis. This indicates that TNFα secretion by TAMs and activation of ECs is a salient molecular mechanism of bevacizumab resistance in GBMs [114].

Therapeutic potential of targeting TAMs

Through investigating the mechanism of TAM reprogramming and resistance induced by TAMs, researchers have produced many new drugs targeting TAMs for tumor treatment. These drugs regulate the immune function of TAMs and induce their transformation in an anti-tumor direction. They are currently primarily applied in combination with chemotherapy, immunotherapy, vascular targeted therapy, and other conventional treatment methods to overcome the resistance of conventional treatment methods and have an adjuvant therapeutic effect. According to the various mechanisms and targets, macrophages can be classified into reducing or depleting TAMs, repolarizing TAMs towards M1-like macrophages, enhancing the immune function of T cells, and other potential therapeutic targets (Figure 1).
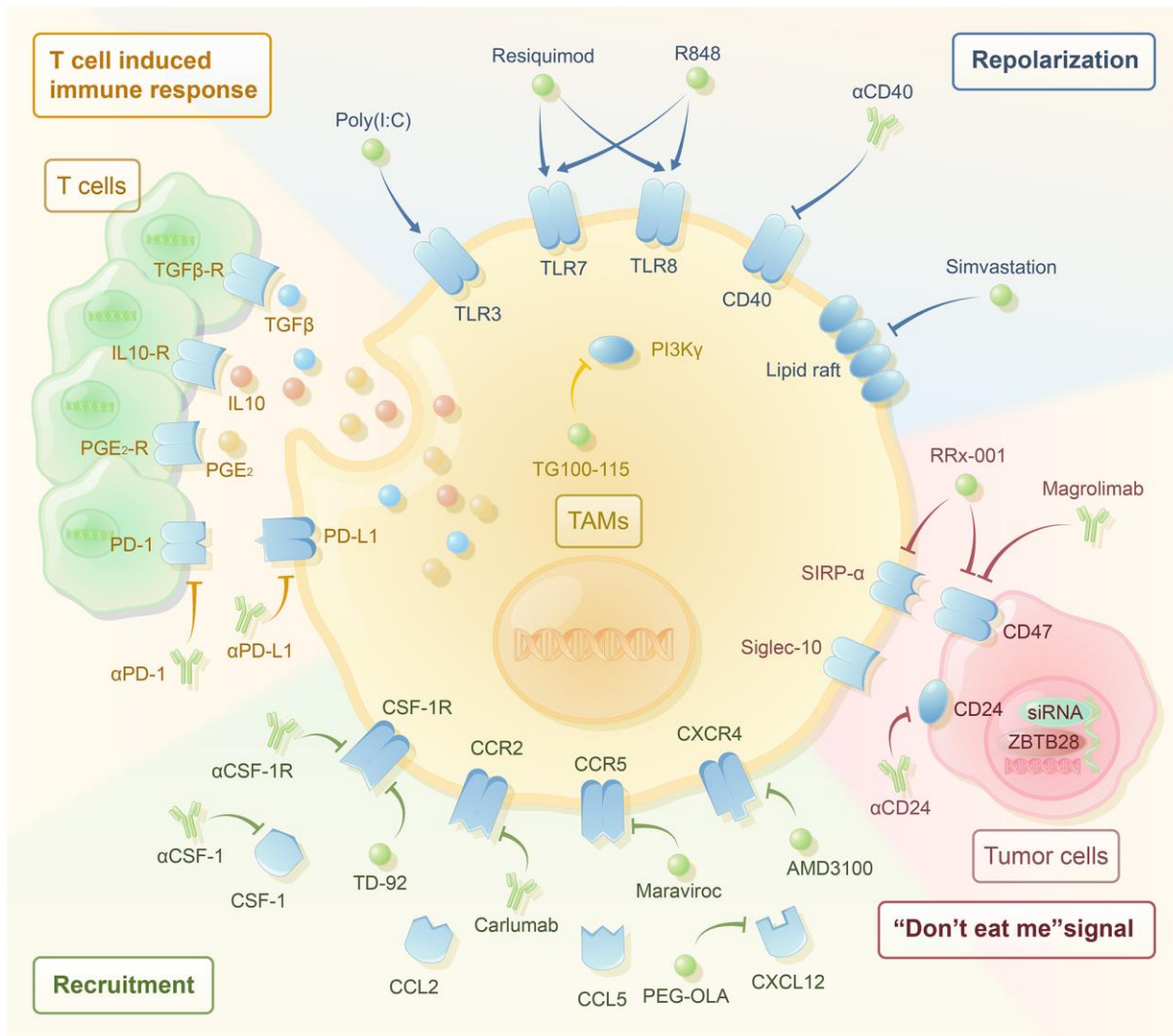

Figure 1. The therapeutic strategies targeting macrophages have been noticeable in recent years. Single application and combined application with traditional drug therapy have great potential. According to their mechanisms, they are mainly divided into the following categories. Reducing the recruitment of TAMs includes the use of αCSF-1, αCSF-1R, TD-92 (CSF-1R inhibitor), carlumab (αCCR2),

maraviroc (CCR5 inhibitor), OLA-PEG (CXCL12 inhibitor), and AMD3100 (CXCR4 inhibitor). Reprogramming TAMs to the M2-like phenotype includes the use of TG100-115 (PI3Kγ inhibitor), poly (I:C) (TLR3 agonist), resiquimod (TLR7/8 agonist), R848 (TLR7/8 agonist), αCD40, and simvastation. TAMs inhibit the T-cell-induced immune response through PD-1/PD-L1, PGE2, IL-10, and TGF-β. The use of αPD-1, αPD-L1, and macrophage targeted therapy may activate T-cell-induced immune response. Blocking the "don't eat me" signal includes the use of αCD24, magrolimab (αCD47), Rx-001 (both SIRP-α and CD47 inhibitor), and siRNAs against JMJD1A.

Additionally, the application of nanotechnology and other biomaterials can help achieve the delivery of drugs targeting TAMs to the tumor site and monitor the immune function of TAMs, which is another important strategy to enhance anti-tumor therapy development.

Reducing the recruitment of TAMs

The primary approach to reduce the number of TAM infiltrates is to inhibit the recruitment of monocytes. Several preclinical studies demonstrated that chemokine inhibitors reduce TAM infiltration and effectively inhibit tumor progression [41, 115, 116]. The combination of TAM chemokine inhibitors with chemotherapy or immunotherapy has significant potential in tumor treatment. CSF-1, also known as M-CSF, is a key proliferation and differentiation factor for monocyte–macrophage lineages [117, 118] that recruits macrophages to the tumor site and promotes TAM polarization. Therefore, CSF-1/CSF-1R represents a target for the direct or indirect medical intervention of TAMs [78]. A recent preclinical study of CSF-1 inhibition combined with immunotherapy in non-small-cell lung cancer reported that TD-92 (a novel erlotinib derivative) enhanced the antitumor effect of PD-1 blocker by downregulating CSF-1R and depleting TAMs in the TME [119]. Other animal experiments demonstrated that the introduction of CSF-1R inhibitors after anti-VEGF drug resistance reduced the tumor size to little or no measurable degree in high-grade serous ovarian cancer [120]. To simulate clinically adaptive conditions, mice were treated with bevacizumab and paclitaxel until the emergence of resistance, then CSF-1R inhibitors markedly attenuated the function of macrophages and restored the response to anti-angiogenesis treatment, thus causing robust anti-tumor effects [120]. In addition to CSF-1, both CCL2 and CCL5, as two important chemokine ligands, have an important role in TAM recruitment. Many scholars have investigated them as targets to inhibit TAMs, but most of their impacts were negative [121–123]. Additionally, blocking the chemokine-receptor axis CXCR4/CXCL12 inhibited the recruitment of TAMs. For example, introducing an SDF-1α (CXCL-12) inhibitor to anti-VEGF antibodies significantly reduced the level of TAMs and prolonged the survival time of glioblastoma-bearing rodents compared with the VEGF blockade alone [116]. Inhibiting CXCR4-dependent immunosuppressive monocytes similarly enhanced anti-angiogenic therapy in colorectal cancer by regulating the recruitment of these myeloid cells [124].

Reprogramming TAMs to M1-like phenotype

Chemokines can activate phosphoinositol 3-kinase γ subtype (PI3Kγ) in myeloid cells within the TME, thus promoting the recruitment of monocytes to tumor sites, and are closely related to the M2-type polarization of TAMs [125]. In the past few years, the inhibition of PI3Kγ to assist other drugs in tumor treatment has gained widespread attention. An animal experiment has proven that the combination of PI3Kγ inhibitor and temozolomide in the treatment of glioblastoma overcame the resistance of temozolomide and enhanced the anti-tumor effect [126]. Poly (l-glutamic acid)-combretastatin A4 conjugate (PLG-CA4), as a novel class of vascular disrupting agents (VDAs), can induce the polarization of TAMs towards the M2-like phenotype in breast cancer. Compared to the monotherapy of PLG-CA4, the combination of PLG-CA4 and PI3Kγ inhibitor potentially enhances the impact of cytotoxic T lymphocytes and significantly extends the mean survival time through decreasing the number of M2-like TAMs [127]. TLRs are important pathogen recognition receptors expressed by immune system cells. The stimulations to TLR3, TLR4, TLR7/8, and TLR9 lead to the rapid activation of innate and adaptive immunity. A recent study observed that some M1-type markers (CD86, CD80, and CD40) were upregulated in macrophages in response to TLR3 stimulation both *in vivo* and *in vitro*, while M2-type specific indicators such as CD206 decreased [128]. Fibrosarcoma mice treated with a combination of TLR3 agonist poly (I:C) and TLR7/8 agonist resiquimod demonstrated increased M1 macrophages, decreased M2 macrophages, and increased infiltration of CD8+T cells and CD4+T cells. Compared with single TLR agonist treatment, the impact of the above combined treatment was more significant, and the anti-tumor effect was significantly better [129]. Several studies have demonstrated that oxaliplatin resistance is primarily related to the reduction in myeloid derived suppressor cells (MDSCs) and their differentiation into M1-type macrophages. Treatment with TLR7/8 agonist combined with oxaliplatin can significantly promote the differentiation of MDSCs into M1-type macrophages, thus overcoming drug resistance [130]. Additionally, researchers have used nanoscale metal–organic frameworks (nMOFs) to co-deliver TLR7 and CD47 antibodies to the tumor site and cooperated with PD-L1 immune checkpoint inhibitors to treat colorectal cancer. This repolarized M2-like macrophages into the M1 type, achieving excellent anti-tumor efficacy [131].

The cell surface molecule CD40 is a highly conserved costimulatory protein on antigen presenting cells. Recent studies have reported that agonistic CD40 antibodies can activate macrophages and promote the repolarization of TAMs to M1 type, thus enhancing anti-tumor immune responses [132–134]. In preclinical studies, the combination of CD40 agonist antibodies and imatinib in gastrointestinal stromal tumor treatment promoted TAMs towards the M1 type, significantly overcoming resistance to tyrosine kinase inhibitors individually [135]. Poly (ADP-ribose) polymerase inhibitor (PARPi) is approved for the treatment of ovarian or breast cancers with BRCA1/2 mutations (BRCAmut), many studies have demonstrated that PARPi olaparib could cause reprogramming of TAMs to higher cytotoxicity and phagocytosis with anti-tumor efficacy [136]. Researchers have found olaparib induce increased glycolysis and oxidative phosphorylation, leading to more reactive oxygen species (ROS) and TAMs transcriptional reprogramming. Further analysis has revealed that administration of CD47 antibodies combined with olaparib may improve tumor control [137]. In addition to the typical targets above, one preclinical study suggested the application of the cholesterol-lowering drug simvastatin to reduce cholesterol synthesis [138]. On the one hand, it inhibits the lipid raft/integrin/FAK pathway; on the other hand, it inhibits the cholesterol-dependent LXR/ABCA1 mechanism (hepatic X receptor/ATP-binding cassette transporter A1), repolarizing TAMs, thus reducing the generation of TGFβ. The two mechanisms jointly overcome the paclitaxel resistance induced by epithelial–mesenchymal transition (EMT). Paclitaxel combined with simvastatin in non-small-cell lung cancer treatment achieved good efficacy.

Targets of activating T-cell-induced immune response

Macrophages, as innate immune cells, present antigens to stimulate the activation signal of T cells and are potent effector cells that activate adaptive immune responses [139–141]. However, the infiltration of M2-like TAMs results in an immunosuppressive TME that inhibits the activation of cytotoxic T lymphocytes during tumor treatment [142–144]. This can be achieved through expression of inhibitory immune checkpoint molecules, including PD-L1 [145] and secretion of immunosuppressive cytokines (including IL-10, TGF-β, prostaglandin E2) [146]. Through the therapeutic targeting of anti-inflammatory TAMs, the disinhibition of CD8+ T-cell-dependent immune responses may enhance the therapeutic efficacy of vascular-targeted therapies. The CCL2/CCR2 axis mediates TAM infiltration, while the application of a natural CCR2 antagonist decreased the number of TAMs in the tumor stroma and shifted them towards the M1-like phenotype,

further elevating the number of CD8+ T cells [147]. The CCR2 antagonist, combined with low-dose sorafenib, potentiated anti-liver tumor effects via upregulating intratumoral CD8+ T cells and enhanced the distribution of CD8+ T cells in the tumor milieu, without obvious toxicity [147]. C-C motif chemokine receptor-like 2 (CCRL2) is a nonsignaling atypical receptor cloned from LPS-activated macrophages. Clinical data indicate that melanoma patients with high CCRL2 expression exhibit increased infiltration of CD8+T cells with stronger antitumor activity. Researchers have proven that CCRL2 retains TLR4 on the surface of the macrophage membrane via animal experiments and then activates macrophages to the M1 phenotype via the Myd88-NFκB signaling pathways. It amplifies the antitumor response of CD8 + T cells, and CCRL2 may thus be a potential target for cancer immunotherapy [148]. A recent preclinical study on the CSF-1/CSF-1R inhibitor pexidartinib in the treatment of sarcoma demonstrated that, in addition to decreasing TAM infiltration and phenotypic changes from M2 to M1, increased CD8+T cell infiltration and decreased Treg cell infiltration were observed in the TME post-treatment. These results may offer a reference for antitumor therapy targeting macrophages to enhance CD8+T cell activity [149]. CXCL12/CXCR4 is a key signaling pathway that recruits TAMs, and the blockade of the CXCL12/CXCR4 possesses great potential for cancer treatment [150]. A recent preclinical study on hepatocellular carcinoma demonstrated that a novel CXCR4 antagonist combined with sorafenib increased cytotoxic CD8+ T cell infiltration more significantly, and the overall survival was more remarkably extended than using sorafenib alone [150]. Such a combination based on the relief of TAM-mediated immunosuppression enhanced the anti-tumor function of vascular-targeted therapy. Currently, the blockade of immune checkpoint signals has demonstrated durable therapeutic responses in clinics [151]. Although these immunotherapies have demonstrated great potential to treat tumors, immune checkpoint inhibitors only function when CD8+ T cell are infiltrated within the TME [152]. Numerous studies have shown that the repolarization of macrophages to the M1 phenotype restores the infiltration and cytotoxicity of CD8+ T cells, thus limiting tumor progression and metastasis [151–153]. Adding checkpoint inhibitors to the combination between vascular-targeted agents and vascular-targeted therapy may yield improved clinical benefits. A preclinical study investigated the application of CSF-1R inhibitors PLX3397 (pexidartinib) and PLX5622 in combination with anti-PD-1 immunotherapy in lung squamous cell carcinoma. The inhibition of CSF-1R reduced the infiltration of macrophages at the tumor site, inhibited the activity of CD8+T cells by M2 macrophages, and enhanced the migration and

infiltration of CD8+T cells into tumor islets. Its combination with anti-PD-1 therapies further increased the close contact between CD8+T and tumor cells, eventually delaying tumor progression [154].

Other potential molecular targets

CD24 and CD47 are two types of membrane proteins broadly expressed by tumor cells, which can bind to signal proteins on the surface of macrophages, trigger the "don't eat me" signal, and inhibit macrophage phagocytosis, thus escaping anti-tumor immunity. Therefore, the inhibition of CD24 and CD47 has become a new strategy of anti-tumor immunotherapies and has prompted great research potential in recent years. Preclinical studies have demonstrated that CD24 promotes immune evasion in ovarian cancer and triple-negative breast cancer by interacting with the inhibitory receptor sialic acid binding ig-like lectin 10 (Siglec-10) expressed by tumor-associated macrophages (TAMs). Both genetic ablation of CD24 or Siglec-10 and the monoclonal antibody blockade of the CD24–Siglec-10 interaction enhance the phagocytosis of macrophages to tumor cells, inhibit tumor growth, and prolong overall survival time [155]. A research team developed a CD47 mAb using hybridoma technology and tested it in preclinical studies. It was combined with a standard chemotherapy regimen to treat mice with triple-negative breast cancer and significantly inhibited tumor growth [156]. Another preclinical study demonstrated that the combination of CD47 mAb Hu5F9-G4 and trastuzumab in the treatment of Her2+ breast cancer cells significantly overcame the resistance to trastuzumab monotherapy and effectively inhibited tumor growth [157]. CD24 inhibits the antitumor effect of macrophages by binding to signal-regulatory protein alpha (SIRPα) on the surface of macrophages. Transcription factor ZBTB28 is a tumor suppressor with extensive expression in normal tissue. A series of preclinical studies have demonstrated that the gene expression of CD24 and CD47 is beneficial to increase the anti-tumor phagocytosis of macrophages. However, the gene is always silent in breast cancer, so activating this gene can have a significant anti-tumor effect. This study provides novel ideas and research directions for the immunotherapy of breast cancer [158]. In addition to the two targets above, researchers have reported several unique targets for macrophage therapy in the field of vascular targeted therapy, which are mechanistically suitable for the combined application with vascular targeted therapy. Following the management of vascular-targeted therapies, hypoxia and nutrient starvation collaborate to prompt aggressive properties that resist anti-angiogenic attacks [159, 160]. Recent research has thus focused on alleviating hypoxia outcomes or even normalizing the tumor vasculature to improve anti-

angiogenic therapy. Microarray analysis identified *in vitro* upregulation of the functional driver JMJD1A, a histone demethylase, under long-term hypoxic conditions and *in vivo* prior to the activation of angiogenesis or the refractory phase of anti-angiogenic drugs [161]. JMJD1A inhibition explicitly suppressed tumor progression by decreasing macrophage infiltration and the angiogenic switch, thus enhancing the anti-tumor effects of anti-VEGF agents [161]. The medical inhibition of the VEGF/VEGFR pathway failed to prolong overall survival in patients with glioblastoma [162, 163], and studies demonstrated that circulating Ang-2 levels rebounded after the administration of the pan-VEGFR inhibitor cediranib [164]. Moreover, combination therapy using cediranib and an anti-Ang-2 neutralizing antibody morphologically and structurally transformed and normalized the highly aberrant and dysfunctional tumor vessel network [165]. Dual targeting of Ang-2 and the VEGF pathway reshaped the pro-tumor M2 subtype towards anti-tumor M1 macrophages, thus reducing the tumor burden and mediating survival benefits in glioblastoma [165, 166].

The clinical trials of TAM-targeting therapy

Clinical trials have recently been completed for a variety of drugs targeting TAMs (Table 3). The targets of TAMs mainly include CSF-1R, CCL, CD40, TLR, PI3Kγ, and CD47, most of them are in phase I clinical trials with good therapeutic efficacy. Among the drugs that inhibit the recruitment of TAMs, the CSF-1R inhibitor pexidartinib in clinical trials has excellent clinical benefits in solid tumors such as in tenosynovial giant-cell tumors (TGCT), unresectable sarcoma, and malignant peripheral nerve sheath tumors. The current study has found that pexidartinib combined with paclitaxel result in a completed remission (CR) rate of 3% and a partial remission (PR) of 13%. Especially, the most promising signal of clinical activity has been noted in patients with platinum-resistant or -refractory epithelial gynecologic malignancies, which patients have experienced a CR. Moreover, the phase III trial of pexidartinib for the treatment of TGCT has been completed [167–169]. The clinical trial has shown that Pexidartinib is shown a robust tumour response in TGCT with improved patient symptoms and functional outcomes and could be considered as a potential treatment. Emactuzumab (CSF-1R inhibitor) has also shown excellent efficacy against TGCT [170] but has shown poor efficacy against other solid tumors [171–173]. In addition, surufatinib, which targets CSF-1R, has shown encouraging antitumor activity in the treatment of well-differentiated neuroendocrine tumors. Currently, the phase II trial of surufatinib has been completed, and other two phase III trials are ongoing [174]. The trial of ARRY-382 (CSF-1R inhibitor)

Table 3. Clinical trials of TAMs targeted therapies.

Targets	Drugs	Phase	Tumor	Status	Time	NCT
CSF-1	PD-0360324	Ib/II	Advanced Cancer	Active	2015.11.9-present	NCT02554812
	JNJ-40346527	I	Relapsed or Refractory Hodgkin Lymphoma	Completed	2012.7.17-2013.8.13	NCT01572519
		I	Prostate Adenocarcinoma	Active	2017.6.7-present	NCT03177460
		II	Acute Myeloid Leukemia	Terminated	2018.10.5-2020.9.28	NCT03557970
	TPX-0022	I/II	Solid Tumor	Recruiting	2019.9.21-present	NCT03993873
	Cabiralizumab	I	Advanced Solid Tumor	Completed	2015.9.8-2019.11.18	NCT02526017
		II	Advanced Pancreatic Cancer	Active	2017.12.19-present	NCT03336216
		I	Advanced Malignancies	Completed	2017.5.25-2019.10.23	NCT03158272
		I	Cancer	Active	2018.3.15-present	NCT03431948
		I	Advanced Cancer	Completed	2018.5.7-2021.3.31	NCT03335540
		I	Advanced Melanoma and non-small Cell Lung Cancer, renal Cell Carcinoma	Active	2018.6.9-present	NCT03502330
		II	Pancreatic Cancer	Terminated	2018.7.31-2020.6.15	NCT03599362
		II	Pancreatic Cancer	Suspended	2019.10.31-present	NCT03697564
		II	Peripheral T Cell Lymphoma	Active	2019.4.25-present	NCT03927105
		II	Hepatocellular Carcinoma	Active	2019.9.12-present	NCT04050462
		I/II	Triple Negative Breast Cancer	Recruiting	2020.11.19-present	NCT04331067
		II	Head and Neck Squamous Cell Carcinoma	Recruiting	2021.4.24-present	NCT04848116
CSF-1R	IMC-CS4	I	Advanced Solid Tumor	Completed	2011.6.1-2018.5.31	NCT01346358
		I	Pancreatic Cancer	Active	2018.9.27-present	NCT03153410
	SNDX-6352	I	Solid Tumor	Completed	2017.9.1-2020.11.20	NCT03238027
		II	Unresectable Intrahepatic Cholangiocarcinoma	Active	2021.8.24-present	NCT04301778
	BLZ945	I/II	Advanced Solid Tumor	Terminated	2016.10.21-2022.12.1	NCT02829723
	DCC-3014	I/II	Advanced Malignant Neoplasm Pigmented Villonodular Synovitis Giant Cell Tumor of Tendon Sheath	Recruiting	2017.2.16-present	NCT03069469
		III	Tenosynovial Giant Cell Tumor	Recruiting	2021.10.14-present	NCT05059262
	ARRY-382	Ib/II	Solid Tumor	Completed	2016.9-2019.10	NCT02880371
	PLX73086	I	Solid Tumor	Terminated	2016.2.1-2018.1	NCT02673736
	Emactuzumab	Ib	Combine with Atezolizumab in Advanced Solid Tumor	Completed	2015.1.19-2020.8.21	NCT02323191
		Ib	Combine with Selicrelumab in Solid Tumor	Completed	2016.5.9-2018.4.6	NCT02760797
		I	Combine with Paclitaxel in Solid Tumor	Completed	2011.12.20-2018.2.7	NCT01494688
		III	Tenosynovial Giant Cell Tumor	Active	2022.7.18-present	NCT05417789
		III	Tenosynovial Giant Cell Tumor	Completed	2015.5-2016.9	NCT02371369
	PLX3397	II	Recurrent Glioblastoma	Completed	2011.12.3-2013.11.5	NCT01349036
		I/II	Tenosynovial Giant Cell Tumor	Completed	2012.9-2014.4	NCT01004861
		I	Combine with Sirolimus in Unresectable Sarcoma and Malignant Peripheral Nerve Sheath Tumor	Completed	2015.4-2018.9	NCT02584647
		I	Combine with MEK162 in Gastrointestinal Stromal Tumor	Completed	2017.4.15-2021.4.28	NCT03158103
CCR2	MLN1202	II	Metastatic Cancer	Completed	2010.3.1-2012.12	NCT01015560
		I	Melanoma	Terminated	2016.6.22-2018.5.11	NCT02723006
	PF-04136309	II	Metastatic Pancreatic Ductal	Terminated	2016.5.4-2017.9.15	NCT02732938

Target	Drug	Phase	Cancer/Condition	Status	Date	NCT number
			Adenocarcinoma			
		I	Pancreatic Neoplasms	Completed	2012.4-2013.10	NCT01413022
	CCX872-B	I	Pancreas Cancer	Completed	2015.2.1-2020.5.6	NCT02345408
CCL2	Carlumab	Ib	Solid Tumor	Completed	2010.5-2010.11	NCT01204996
		II	Metastatic Castration-Resistant Prostate Cancer	Completed	2009.9-2011.11	NCT00992186
CCL5	Maraviroc	I	Colorectal cancer	Completed	2018.5-2018.11	NCT03274804
CXCR4	AMD3100	I	Pediatric Acute Myeloblastic Leukemia and Lymphoblastic Leukemia	Terminated	2012.6-2014.4	NCT01655875
		I/II	Acute Myeloid Leukemia	Completed	2007.7.1-2010.6	NCT00512252
PI3Kγ	BYL719	III	Advanced HER2+ Breast Cancer	Active	2020.7.16-present	NCT04208178
		I	Ovarian Cancer, Breast Cancer	Completed	2012.9.1-2019.5	NCT01623349
		I	Carcinoma, Non-Small-Cell Lung	Completed	2013.4.1-2017.10.17	NCT02128724
	BKM120	II	High Risk Prostate Cancer	Terminated	2013.4.23-2015.2.5	NCT01695473
		I	Breast Cancer	Completed	2012.10.1-2014.2	NCT01513356
TLR-8	Motolimod	Ib	Combine with Cetuximab in Head and Neck Squamous Cell Carcinoma	Completed	2014.10.28-2016.8.11	NCT02124850
TLR-7/8	R848	I	Melanoma (Skin)	Completed	2006.4.1-2011.10	NCT00470379
		I/II	Nodular Basal Cell Carcinoma	Terminated	2013.2.1-2013.8	NCT01808950
	ABBV-428	I	Solid Tumor	Completed	2016.11-2018.6	NCT02955251
	Selicrelumab	I	Resectable Pancreatic Cancer	Completed	2015.10-2018.11	NCT02588443
	Sotigalimab	II	Combine with Nivolumab in Metastatic Pancreatic Cancer	Completed	2018.8-2019.6	NCT03214250
CD40	APX005M	I	Combine with Cabiralizumab with or without Nivolumab in Melanoma, Kidney Cancer, or Non–Small Cell Lung Cancer	Completed	2018.6-2019.4	NCT03502330
		I/II	Metastatic Pancreatic Ductal Adenocarcinoma	Recruiting	2021.9.17-present	NCT04888312
	ADC-1013	I	Solid Tumor	Completed	2015.4.1-2017.3.8	NCT02379741
		I	Solid Tumor	Completed	2015.4-2016.12	NCT02379741
	Chi Lob 7/4	I	Non-Hodgkin Lymphoma	Completed	2007.7.1-2014.10	NCT01561911
CD47	Hu5F9-G4	Ib	Relapsed or Refractory non-Hodgkin's Lymphoma	Completed	2016.10-2017.11	NCT02953509
	CC-90002	I	Relapsed/Refractory Acute Myeloid Leukemia or High-risk Myelodysplastic Syndromes.	Completed	2016.3-2018.7	NCT02641002
SIRP-α	TTI-621	I	Relapsed or Refractory Hematologic Malignancies	Completed	2016.1.31-2022.12.31	NCT02663518
CD47 and SIRP-α	RRx-001	I	Advanced, Malignant, Incurable Solid Tumor	Completed	2011.10-2013.3	NCT01359982
		I/II	Brain Metastases	Completed	2015.2.6-2016.11.28	NCT02215512
		II	Colorectal Cancer	Completed	2014.5-2018.4.13	NCT02096354

combined with pembrolizumab (PD-1 monoclonal antibody) for solid tumors has not demonstrated positive efficacy [175]. In addition, other targets that inhibit recruitment CCL2 and CCL5 have good tolerance but poor anti-tumor activity in clinical trials [121–123, 176].

Besides inhibiting the recruitment of TAMs, regulating the repolarization of M2-type TAMs and targeting CD40 have also been tested in clinical trials [177–179]. Duvelisib, a PI3Kγ inhibitor, has shown promising clinical benefits in phase I trials, and the phase II and III trials are being further studied [180, 181]. Clinical responses have been seen across a range of doses and disease subtypes: iNHL overall response rate 58%; relapsed/refractory CLL 56%; peripheral TCL 50%; and cutaneous TCL 32%. In addition, as a dual inhibitor of SIRP-α and CD47, RRx-001 has shown excellent efficacy in the studies of solid tumors such as brain metastases, small cell carcinoma, and colorectal cancer. At present, some phase II trials of RRx-001 have been completed with promising

efficacy [182–184]. Hu5F9-G4, TTI-621, and other drugs targeting CD47 have also shown good clinical activity in phase I trials [185–187]. In terms of safety, most of drugs have shown tolerable adverse side effects, with only fatigue, pruritus, headache, nausea, vomiting, edema, and other common adverse reactions reported. In some drug trials targeting CSF-1R, patients showed elevated liver enzymes, which may be related to the destruction of Kupffer cells in the liver [167, 173, 174]. Meanwhile, some clinical trials of hematological tumors and highly malignant endocrine tumors have shown changes in the blood system such as neutropenia and lymphopenia [168, 174, 180]. In addition, the results of phase III clinical trials of PLX3397 have shown obvious hepatotoxicity, which may be related to the expression of CSF-1R in Kupffer cells in the liver [167].

Clinical trials targeting TAMs with positive clinical efficacy have not been observed, and we summarize the reasons as follows. Firstly, the main purpose of phase I trials is to test the safety of drugs, so the groups are often divided by dose escalation, which leads to a small number of cases in the high-dose group to achieve therapeutic effect. Therefore, researchers suggest to increase the dosage of the drugs if patients in clinical trials can tolerate the side effects [173, 175, 188]. Secondly, some patients stopped the trial because of obvious adverse reactions in phase I trials, leading to only a small sample size and no meaningful efficacy evaluation [189]. Therefore, it may be necessary to further increase the sample size or seek means to reduce drug toxicity. Thirdly, some drugs are off-target, so they cannot effectively target TAMs [121–123, 172, 176]. The off-target effect also has an impact on normal immune response, such as infections, autoimmunity, and cancer. Some studies have analyzed that the drug concentration in peripheral blood may be low due to the M2-type TAMs in the skin [172]. Thus, it is necessary to further analyze its pharmacokinetics and pharmacodynamics in order to improve drug development.

Perspectives

Currently used tumor drug therapy has great limitations, and it is difficult to overcome resistance in long-term application. A large number of clinical studies emphasize the crucial role of the TME and TAMs in immune response, leading to poor clinical response and drug resistance. Preclinical studies have demonstrated that conventional drug therapy reprograms macrophages, improves immunosuppressive effects, and promotes tumor proliferation and metastasis [69, 76, 80]. TAM reprogramming after drug treatment may occur through several mechanisms, including increased TAM recruitment, TAM polarization to the M2-like phenotype, the promotion of pro-angiogenic TAM subsets, and the regulation of TAM proangiogenic activities. In various treatments (chemotherapy, immunotherapy, and targeted therapy), the mechanisms of reprogramed TAMs mediating drug resistance are different. Through extensive research on the interaction between the TME and TAMs, TAM reprogramming, and the mechanism of resistance mediated by TAMs, researchers have developed drugs targeting TAMs and applied them in combination with conventional drug therapy. Reducing or depleting TAMs, repolarizing TAMs M1-like types, enhancing the immune function of T cells, inhibiting the "don't eat me" signal, and combining with emerging nanomaterials technology, drug resistance was significantly overcome, and the efficacy of traditional drug treatment was improved. Phase I clinical trials have been completed for many drugs, and most of them have good safety without obvious side effects. Although some drugs failed to advance to phase II trials due to poor clinical efficacy and the off-target effect, the reasons for their poor efficacy were analyzed and summarized, and researchers improved some drugs via a combination with biological materials to enhance the drugs. Therefore, the synergy of multiple therapeutic strategies centered on TAMs may further promote the development of cancer therapy, have great development potential and exploration value, and merit further research.

A large number of TAM targeted therapy clinical trials are ongoing, so there are still many challenges that need to be faced. Whether it is necessary to check the number of macrophages in the tumor microenvironment before TAM targeted therapy, and how to select suitable patients are the priorities of treatment. There are multiple mechanisms of targeting TAM therapy, thus the individualized treatment is also worth taking into consideration. During the process of treatment, we should pay attention to the detection of relevant immune indicators. We still need to explore the more reasonable plan of TAM targeted therapy and make it better for clinical translation.

AUTHOR CONTRIBUTIONS

Hanjiao Qin and Dan Zhang performed literature search. Sheng Li and Jiyao Sheng wrote the manuscript. Hanjiao Qin drafted the figures. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

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