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REVIEW

Tumor-associated macrophages as a potential therapeutic target in thyroid cancers

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Abstract

Macrophages are important precursor cell types of the innate immune system and bridge adaptive immune responses through the antigen presentation system. Meanwhile, macrophages constitute substantial portion of the stromal cells in the tumor microenvironment (TME) (referred to as tumor-associated macrophages, or TAMs) and exhibit conflicting roles in the development, invasion, and metastasis of thyroid cancer (TC). Moreover, TAMs play a crucial role to the behavior of TC due to their high degree of infiltration and prognostic relevance. Generally, TAMs can be divided into two subgroups; M1-like TAMs are capable of directly kill tumor cells, and recruiting and activating other immune cells in the early stages of cancer. However, due to changes in the TME, M2-like TAMs gradually increase and promote tumor progression. This review aims to discuss the impact of TAMs on TC, including their role in tumor promotion, gene mutation, and other factors related to the polarization of TAMs. Finally, we will explore the M2-like TAM-centered therapeutic strategies, including chemotherapy, clinical trials, and combinatorial immunotherapy.

Keywords Tumor-associated macrophages · Tumor microenvironment · Cancer metastasis · Thyroid cancer · Immunotherapy

Abbreviations

ATC	Anaplastic thyroid cancer
APC	Antigen-presenting cells
APOE	Apolipoprotein E
BRAF	V-Raf murine sarcoma viral oncogene homolog B
CAR-TAMs	Chimeric antigen receptor-tumor-associated macrophages
CCL	Chemokine C-C motif ligand
CCR	C-C chemokine receptor type
CSF-1	Colony-stimulating factor
CSF-1R	Colony-stimulating factor receptor

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CTLA-4	Cytotoxic T-lymphocyte-associated protein-4
CXCL	Chemokine C-X-C motif ligand
CXCR	C-X-C chemokine receptor
DC cell	Dendritic cell
DTC	Differentiated thyroid cancer
EGF	Epidermal growth factor
EMT	Epithelial-mesenchymal transition
EVs	Extracellular vehicles
FGF	Fibroblast growth factor
FTC	Follicular thyroid cancer
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HDAC	Histone deacetylase
HER2	Receptor tyrosine-protein kinase erbB-2
HGF	Hepatocyte growth factor
HIF-1α	Hypoxia inducible factor-1α
IDO	Indoleamine 2,3-dioxygenase
IFN-γ	Interferons-γ
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LILRB1/2	Leukocyte immunoglobulin-like receptor subfamily B1/2
LPS	Lipopolysaccharide
MARCO	Macrophage receptor with collagenous structure
MDSC	Myeloid-derived suppressor cells
MEK	Mitogen-activated protein kinase
MET	Receptor tyrosine kinase of MET proto-oncogene
MHC-II	Major histocompatibility complex class II
MTC	Medullary thyroid cancer
miRNA	MicroRNA
MR	Mannose receptor
NF-κB	Nuclear factor-κB
NK cell	Natural killer cell
ONJ	Osteonecrosis of the jaw
PARP	Poly ADP ribose polymerase
PD-1/2	Programmed cell death protein 1/2
PDGF	Platelet-derived growth factor
PI3K	Phosphoinositide 3-kinases
PD-L1/2	Programmed death-ligand 1/2
PTC	Papillary thyroid cancer
scRNA-seq	Single-cell RNA sequencing
SIRP-α	Signal regulatory protein-α
SPP1	Secreted phosphoprotein 1
STAT3	Signal transducer and activator of transcription 3
TAMs	Tumor-associated macrophage
TC	Thyroid cancer
TGF-β	Transforming growth factor-β
Th17 cell	T helper 17 cell
TIM3	T cell immunoglobulin and mucin domain-containing protein 3
TKIs	Tyrosine kinase inhibitors
TLR	Toll-like receptor
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-α
TNM	Tumor, node and metastasis
Treg cell	Regulatory T cell
TREM2	Scavenger receptor-triggering receptors expressed on myeloid cells 2
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VSIG4	V-set and immunoglobulin domain containing 4

Introduction

Thyroid cancer (TC) is one of the most common endocrine tumors in the world, with a high incidence rate, attracted more and more attention [1–3]. There are several subtypes of TC, with a variety of prognostic and therapeutic options. For example, follicular-cell-derived cancer accounts for the majority of TC and divided into follicular thyroid cancer (FTC), invasive-encapsulated follicular variant papillary cancer, papillary thyroid cancer (PTC), oncocytic carcinoma of the thyroid, poorly differentiated thyroid cancer, differentiated high-grade thyroid cancer, and anaplastic thyroid cancer (ATC) based on the cell of origin, pathologic features, biological behavior, and molecular classification [2, 4]. Among them, PTC and FTC are "mild" and have a good prognosis, while ATC is fierce, highly malignant and has a poor prognosis [2]. Currently, the conventional treatment for TC includes surgery, radiation therapy and thyroid hormone preparation, but satisfactory outcomes are sometimes difficult to achieve [5]. Tumors mainly through tumor-infiltrating immune cells, immunomodulatory molecules and soluble factors interact with the surrounding immune microenvironment during their development, to weaken the anti-tumor activity of the immune system, thereby mediating the immune tolerance and causing tumor escape [6, 7].

Macrophages constitute a substantial portion of the stromal cells in the tumor microenvironment (TME) (referred to as tumor-associated macrophages, or TAMs) and exhibit conflicting roles in the development, invasion, and metastasis of TC [8–10]. TAMs can be divided into two subgroups, M1-like TAMs and M2-like TAMs. M1-like TAMs are capable of directly killing tumor cells, and recruiting and activating other immune cells in the early stages of cancer. However, M2-like TAMs promote tumor progression. Moreover, TAMs play a crucial role in the behavior of TC due to their high degree of infiltration

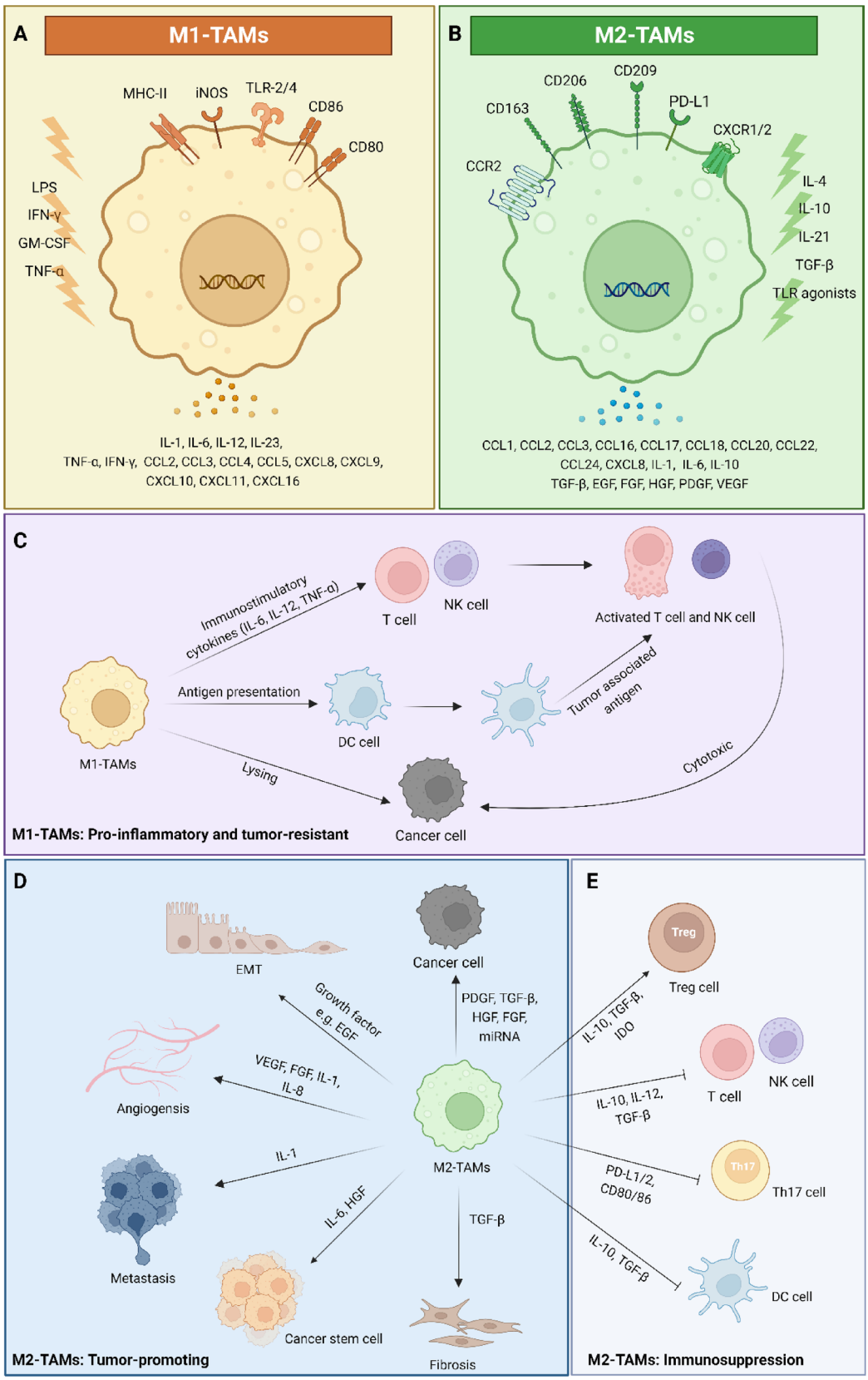
and prognostic relevance [7, 9, 11]. It has been found that TAMs correlate with extrathyroidal extension and capsular invasion in poorly DTC [12]. ATC also had the highest density of TAMs in TME resulting in decreased survival rates [7]. And in PTC, the density of TAM positively correlates with lymph node metastasis, larger tumors and poorer survival rates [9, 13]. In addition, TAMs were increased and correlated with tumor size, epithelial characteristics, lymph node metastases, and a reduced CD4/CD8 positive T cell ratio in the v-Raf murine sarcoma viral oncogene homolog B (BRAF) mouse model [14, 15]. The previous studies have also demonstrated that chemokine C-C motif ligand 2 (CCL2) levels are associated with TAM levels [16, 17], and the presence of large amounts of TAMs was more frequently associated with the poor prognosis of patients with TC [14]. This review aims to discuss the impact of TAMs on TC, including their role in tumor promotion, gene mutation, and other factors related to the polarization of TAMs.

Thyroid cancer and tumor microenvironment

TME is primarily made up of stromal cells, innate and adaptive immune cells, endothelial cells, cytokines, and chemokines [18, 19]. And it changes metabolic, secretory, immunological, and other factors that affect cancer development and promotes the growth and spread of tumors [20, 21]. It has been demonstrated that TME, infiltrating immune cells and immunotherapeutic effect were different for subtypes of TC [10, 14, 22, 23]. Furthermore, it has been confirmed that the disruption of the delicate balance of the original microenvironment encouraged the migration and proliferation of TC [8, 24]. Contrarily, tumor immune escape is another way for TC cells to survive and proliferate in vivo through TME [25]. Although tumor cells are often destroyed by immune cells in the early stages of cancer, TME can help tumor cells evade immune surveillance and even prevent immune cells from producing cytotoxic effects on the tumor cells [10, 20, 26, 27]. Macrophages occupy high percentage in the TME referred to as TAMs, play a crucial role in the regulation of the immune system and TC cells [28–30]. The different functions of TAMs have been classified into two opposing phenotypes, M1-like TAMs with a pro-inflammatory pathogen-killing capacity and M2-like TAMs that promote tissue remodeling, angiogenesis, and a key role in TC progression [8, 31–33]. In addition, as the degree of infiltration of M2-like TAM was strongly associated with the progression of TC suggested that the TAMs-targeting therapeutic approach could be the potential approach for TC [6, 9, 13, 34].

The classifications and functions of TAMs

TAMs are generally divided into two phenotypes: M1-like TAMs, which contribute to the ability of the immune system to control malignancy, and M2-like TAMs, which accelerate tumor growth and reduce the anti-tumor effect of the immune system [35, 36]. Figure 1 A and B describe the subpopulations and functions of TAMs with identifiable markers and secretions. In detail, M1-like TAMs could activate innate or adaptive lymphocyte-mediated mechanisms of tumor resistance. The immunostimulatory cytokines such as interleukin (IL)-6, IL-12, and tumor necrosis factor-α (TNF-α) from M1 phenotype TAMs can enhance the anti-tumor ability of T cells and natural killer (NK) cells [37, 38]. Meanwhile, M1-like TAMs can promote can act as specialized antigen-presenting cells (APCs) when properly activated [39]. Also, the M1-like TAMs have the potential to kill tumor cells, relying mainly on antibody-dependent cellular cytotoxicity and autophagocytosis, which can cause vascular damage and tumor necrosis [40]. In contrast, TAMs are predominantly of the M2 phenotype in most solid tumors and promote the proliferation of cancer cells, angiogenesis in the TME, and suppression of innate and adaptive immune responses [27, 41, 42]. Several studies have shown that M2-like TAMs secretion of fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) are essential to supporting the progress of the tumor-associated vascular system, a process by which new blood vessels sprout from existing vessels or through the proliferation, motility, and accumulation of vascular endothelial cells [13, 43–45]. Moreover, M2-like TAMs cause immunosuppression by expressing inhibitory receptors or immune checkpoint ligands, such as programmed death-ligand1/2 (PD-L1/2), and CD80/CD86 [42, 46, 47] and the cytokines including IL-10 and transforming growth factor-β (TGF-β). In addition, M2-like TAMs promote metastasis of tumors by secreting growth factors that support tumor angiogenesis and neointimal formation as well as epithelial-to-mesenchymal transition (EMT) and tissue remodeling [30, 45, 48]. The extracellular vehicles (EVs) released by M2-like TAMs are also responsible for cancer metastasis by transferring certain microRNA (miRNA) in the colorectal cancer model [49]. TAMs from different polarization may perform different functions in the TME of cancer, which provides an opportunity to target immunotherapies more precisely (Fig. 1 C-E). Hence, the ideal strategy would involve selective targeting of M2-like TAMs and maintaining the functionality of M1-like TAMs without compromising the homeostatic immune system in vivo.


A
M1-TAMs
MHC-II
iNOS
TLR-2/4
CD86
CD80
LPS
IFN-γ
GM-CSF
TNF-α
IL-1, IL-6, IL-12, IL-23,
TNF-α, IFN-γ, CCL2, CCL3, CCL4, CCL5, CXCL8, CXCL9,
CXCL10, CXCL11, CXCL16
B
M2-TAMs
CD206
CD209
CD163
PD-L1
CXCR1/2
CCR2
IL-4
IL-10
IL-21
TGF-β
TLR agonists
CCL1, CCL2, CCL3, CCL16, CCL17, CCL18, CCL20, CCL22,
CCL24, CXCL8, IL-1, IL-6, IL-10
TGF-β, EGF, FGF, HGF, PDGF, VEGF
C
Immunostimulatory
cytokines (IL-6, IL-12, TNF-α)
T cell
NK cell
Activated T cell and NK cell
Antigen presentation
DC cell
Tumor associated
antigen
M1-TAMs
Lysing
Cytotoxic
Cancer cell
M1-TAMs: Pro-inflammatory and tumor-resistant
D
EMT
Cancer cell
PDGF, TGF-β,
HGF, FGF,
miRNA
Growth factor
e.g. EGF
VEGF, FGF, IL-1,
IL-8
Angiogensis
M2-TAMs
IL-1
IL-6, HGF
TGF-β
Metastasis
Cancer stem cell
Fibrosis
M2-TAMs: Tumor-promoting
E
Treg
Treg cell
IL-10, TGF-β,
IDO
T cell
NK cell
IL-10, IL-12,
TGF-β
PD-L1/2,
CD80/86
Th17
Th17 cell
IL-10, TGF-β
DC cell
M2-TAMs: Immunosuppression

◂**Fig. 1** Surface markers and the functions with secretions of TAMs in tumor microenvironment. TAMs are classified as M1 and M2 polarizations, and plasticity is an important characteristic. TAMs can be characterized by the expression of different surface markers, explaining the variation of M1/M2-like TAMs in the TME for the same or different markers and receptors. In **A**, M1-like TAMs that could be induced by LPS + IFN-γ with anti-tumor functions can be stimulated by immunostimulatory cytokines, and MHC-II molecules are required for effective antigen presentation. In addition, some surface proteins of M1-like TAMs, CD80, and CD86, were also upregulated. M1-like TAMs also produce chemokines such as CXCL10 that promote T cell recruitment and activation. On the right, M2-like TAMs that could be induced by IL-4 with pro-tumorigenic functions are regulated by the hypoxic tumor microenvironment and immunosuppressive mediators (IL-10, TGF-β etc.). Similarly, some surface proteins of M2-like TAM were upregulated, including CD163, and CD206. The M1-like TAMs have the functions of phagocytosis and lysis of tumor cells and can promote inflammation and anti-tumor effect. Moreover, M1-like TAMs enhance the activity of antigen-presenting cells (DC cells) and promote the cytotoxic effects of other cancer killing leukocytes (T cells and NK cells) (**C**). However, M2-like TAMs are tumor-promoting activities, commonly through the secretion of growth factors (including EGF, FGF, HGF, PDGF, VEGF, and TGF-β, etc.) that support tumor angiogenesis and neointima formation as well as EMT and tissue remodeling (**B**). Meanwhile, M2-like TAMs promote and induce the proliferation and metastasis of cancer cells by creating an immunosuppressive TME (**D** and **E**). This figure was created using BioRender.com. Abbreviations: CCR2, C-C chemokine receptor type 2; CXCL8, chemokine C-X-C motif ligand 8; CXCR1/2, C-X-C chemokine receptor 1/2; DC cell, dendritic cell; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transition; FGF, fibroblast growth factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IDO, indoleamine 2,3-dioxygenase; IL-1, interleukin-1; IFN-γ, interferons-γ; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MHC-II, major histocompatibility complex class II; NK cell, natural killer cell; PDGF, platelet-derived growth factor; PD-L1/2, programmed death-ligand 1/2; TGF-β, transforming growth factor-β; Th17 cell, T helper 17 cell; TLR, toll-like receptor, TNF-α, tumor necrosis factor-α; Treg cell, regulatory T cell; VEGF, vascular endothelial growth factor

The factors related to the polarization of TAMs and the treatment in TC

The gene mutations associated with polarization of TAMs in TC

Similar to other malignancies, TME of TC consists of immune cells (macrophages, mast cells, and lymphocytes) and soluble mediators (chemokines, cytokines, and growth factors) that are active in and around cancer cells [50, 51]. However, in contrast to other tumors, the prognosis of TC was often associated with complex genetic mutations [14, 52, 53]. For example, the BRAF mutations are most common in PTC or ATC [54]; RAS mutations are found predominantly in FTC [55]; and RET proto-oncogene mutations are thought to be the cause of the majority of medullary thyroid cancer (MTC) [56]. Also, current single-cell technologies, particularly single-cell RNA sequencing (scRNA-seq) demonstrated the impact of cellular subtypes on disease progression including TC, and improved the identification of biomarkers for stratification of patients. For example, the technology of scRNA-seq could quantify the cellular components and their interactions in the TME, and improve the understanding about the heterogeneity and gene mutation of TC [57]. At the same time, many gene mutations in different subtypes of TC have been proved to be associated with TAMs and the progression of the tumor [13, 15, 26, 43, 58–62]. A study has shown that protein levels of the CCL2, a major tumor-derived serum chemokine of monocytes, were regulated by RET/PTC in thyroid cells [58]. Simultaneously, previous studies have demonstrated that CCL2 levels are associated with TAMs levels [16, 17], and the presence of large amounts of TAMs was more frequently associated with the poor prognosis of patients with TC [14]. In the $BRAF^{V600E}$ mouse model, TAMs were increased and correlated with tumor size, epithelial characteristics, lymph node metastases, and a reduced CD4/CD8 positive T cell ratio, thus supporting a potential immunosuppressive effect of PTC [14, 15]. Additionally, the BRAF mutation was found to be higher in PTC than in benign thyroid tissues and was associated with poor prognostic factors such as M2-like TAMs, angiogenesis-related genes, elevated tumor, node, and metastasis (TNM) staging [43, 60]. The BRAF mutation also related with presence of myeloid-derived suppressor cells (MDSCs) [53], promoted the TAMs polarized toward an M2 phenotype, and can assist the TC cells in escaping from immune killing [18]. It has also been shown that the BRAF mutation has independent prognostic value as a recurrence of PTC and correlates with TAM polarization [15, 63]. Moreover, the TAMs account for a large proportion of tumor-infiltrating immune cells in TC compared with other tumors and are highly plastic [9, 13, 34, 64], and therapies targeting TAMs could be relevant in TC. Therefore, TAMs are the newly insightful therapeutic approach due to the polarization, pro-tumorigenic properties [6, 65, 66], gene mutation-related specificity[8, 9, 15, 64], and high density in the TC [6, 7, 67].

Cytokines associated with polarization of TAMs in the TC

M1/M2-like TAMs are highly plastic cells and their function can change significantly depending on microenvironmental signals from the TME of TC [52, 68–71]. For example, a previous study proved that the high expression of C-X-C chemokine receptor type (CXCR4) recruits more TAMs [72]. At the same time, CXCR4 is often overexpressed by TC cells because of RET rearrangements and the quantity of CXCR4 expressed by primary TC corresponds with the degree TAMs and lymph node metastasis [67, 73, 74]. Moreover, elevated chemokine C-X-C motif ligand (CXCL)16

expression in the medium mediated the invasion of PTC tumor cells when PTC cells and TAMs are co-cultured with the high percentage of M2-like TAMs has also been demonstrated [52]. Similarly, CSF-1 has also been studied in the TC as a major factor controlling the growth and differentiation of TAMs [14]. Previous studies had demonstrated that the coordination of autocrine and paracrine interactions between TC cells and TAMs is accomplished by chemokines and cytokines [6, 10, 14, 32, 60]. Also, the chemokines and cytokines in the TME of TC are core regulators and have been identified as one of the hallmark drivers of cancer [75]. The following types of factors have been shown to correlate with the development of TC and TAMs, including VEGF [28], CXCL1 [54], 7 [54], 8 [9, 18, 32], 12 [72, 76], 16 [43, 60], CXCR4 [67, 77–79], colony-stimulating factor 1(CSF-1) [14, 73], C-C chemokine receptor (CCR) type 2 [32, 75] and cytokines including IL-1 [18, 28], 6 [6], 8 [18, 34, 75, 80], 32 [80].

The treatment method associated with polarization of TAMs in TC

Currently, the main treatments for not-resectable cancerous diseases, radiotherapy, and chemotherapy, both cause tissue damage and cancer cell death due to local or systemic inflammation [18, 81–83]. Previous studies found that after ablative radiotherapy, the innate immune system was activated by inflammatory cytokines [84] and pro-fibrotic factors that recruited TAMs and promoted tumor recurrence and progression [69, 85]. Furthermore, the radiotherapy also induced senescence of TC cells, and the senescent cells triggered the polarization of M2-like TAMs accompanied by increased expression of CCL17, CCL18, IL-18, and TGF-β [69, 86]. In addition, differentiated M2-like TAMs promote the stemness and migration of tumor cells [30, 48, 68, 86, 87]. The study of TAMs should be more significant and necessary since radiotherapy is essential in the treatment of intractable TC. In addition to radiotherapy, chemotherapy for the TC, including systemic drugs targeting tumor angiogenesis [88], and targeted molecular drugs such as multikinase and rapamycin inhibitors, could also induce M2-differentiation of TAMs [18, 89, 90]. For example, in the treatment of ATC, Lenvatinib monotherapy and even in combination therapies with programmed cell death protein (PD-1)/PD-L1 inhibitor increased the density of M2-like TAMs [91]. Moreover, TAMs also modulate other immune cells in the TEM of TC. For example, TAMs express T cell immune checkpoint ligands and directly inhibit T cell functions, while also secreting cytokines such as IL-10 and TGF-β that contribute to the maintenance of a strong immunosuppressive TME [28, 45, 92, 93]. Since TAMs can promote tumor growth and metastasis by secreting cytokines or producing immunosuppressive TME, removal of TAMs or alteration of TME has been confirmed could reduce the progression of TC [14, 91, 94–96]. Considering the plasticity of TAMs, the concept that reprogramming the polarization may affect the function of TAMs, has also attracted significant attention in the treatment of TC [6, 45, 68, 70, 76, 77, 79, 97].

Other factors in TME that associated with polarization of TAMs in the TME of TC

As one of the most relevant intercellular communication mechanisms between cells in the TME, EVs could also reprogram the host cell and affect the polarization of TAMs [98, 99]. For example, colorectal cancer cell-derived EVs containing miR-934 induced CD163 positive M2 polarization of TAMs by activating the phosphoinositide-3 kinases (PI3K)/AKT signaling pathway and enhanced invasion and liver metastasis [100]. Similarly, a study reported that epithelial ovarian cancer-derived exosomal miRNA-222-3p induced polarization of TAMs to the M2 phenotype by activating the SOCS3/STAT3 signaling cascade [101]. Furthermore, it has also been demonstrated that colorectal tumor-secreted EVs with miRNA-145 promote the polarization of THP-1 to M2-like TAMs, leading to the downregulation of IL-12 and the upregulation of IL-10 [102]. In addition, it has been reported that exosomes derived from hypoxic epithelial ovarian cancer were enriched in miRNA-21-3p, miRNA-125b-5p, and miRNA-181-5p, and these miRNAs promoted M2 polarization of TAMs by activating the SOCS4/5/STAT3/hypoxia inducible factor-1α (HIF-1α) signaling cascade [103]. These studies demonstrated that miRNAs are primarily involved in EV-mediated M2-like TAM polarization and miRNAs are hallmarks of tumor-derived EVs a cargo consisting of multiple miRNAs (41.7% mature miRNAs of all RNAs in EVs) [104]. Additionally, the lactate in the TME also affect polarization of TAMs and has been shown to upregulate M2-like TAM by enhancing aerobic glycolysis in recent studied of TC [105, 106]. Therefore, an in-depth understanding of the changes in the complex relationship between tumor cells, TME and TAMs may provide new ideas for the treatment of TC.

TAMs-centered treatment strategy in TC

Therapeutic strategies aimed at targeting TAMs or modulating their activity are under development and are being applied in both clinical trials and animal experiments [27, 92, 107]. More than 90% of TC patients are PTC and FTC with relatively good prognoses, but there are still some patients with refractory TC. For example, the treatment and prognosis of patients with ATC were very limited, but the proportion of TAM is positively correlated with the aggressive tumor, so targeting TAM may provide new ideas for

refractory TC [7, 10, 34, 61]. Additionally, another study revealed significant differences in TAM density between subtypes, leading the researchers to hypothesize that TAM density may be a prognostic factor for TC [65]. Several TAM targeting techniques have been investigated, including TAM depletion to decrease the pro-tumorigenic activity of TAMs [15, 58, 107, 108], inhibition of TAM[14, 94, 108, 109] recruitment from monocytes [14, 75], reprogramming of the TAMs to an M1-like phenotype [28, 32, 68, 70, 110, 111], and dissolving the immunosuppressive environment with the recovery of tumor-killing activities of cytotoxic T cells [6, 91, 112, 113]. TAMs, the primary cells that mediate the relationship between cancer and inflammation, undoubtedly play a significant role in opening the door for a novel approach to the treatment of TC. Figure 2 summarized the studies reporting TAMs targeting strategies and methods for the dichotomous behavior of TAMs and the existing approach applied for TC was marked with asterisks *.

TAM depletion and inhibition of recruitment

Targeting the Elimination of TAMs

A tyrosine kinase receptor named CSF-1 receptor (CSF-1R), expressed by macrophages, activated the recruitment of monocytes to TAMs, leading to the reprogramming of these TAMs to the M2 phenotype, which has been demonstrated in many animal tumor models including TC [14, 114], primary human macrophages[115] and clinical trial [94]. Therefore, blockade of the CSF-1R and CSF-1 axis may be a viable

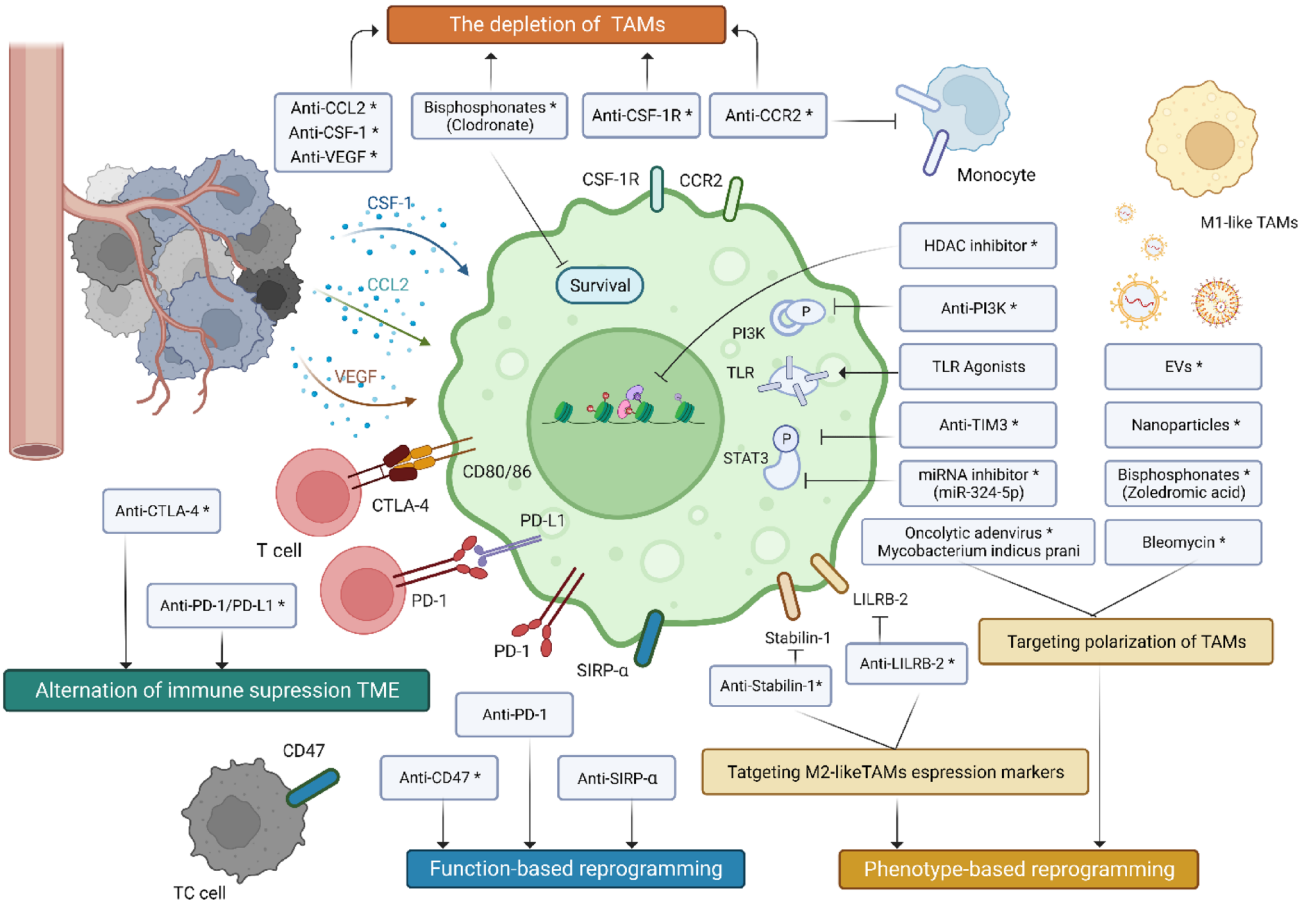


Fig. 2 Therapeutic strategies targeting and reprogramming TAMs: The strategies are divided into four main categories: (1) elimination of TAMs and inhibition of monocyte differentiation to TAMs; (2) reprogramming TAMs to the anti-tumor activity based on the polarization to the M1-like TAMs and expression of markers targeting M2-like TAMs; (3) reprogramming based on the phagocytosis function of TAMs; (4) inhibiting the immune suppression microenvironment and allow cytotoxic T cells activity. *Articles marked with asterisk are studies for thyroid cancer. This figure was created using BioRender.com. Abbreviations: CCR2, C-C chemokine receptor type 2; CCL2, chemokine C-C motif ligand 2; CSF-1, colony-stimulating factor-1; CSF-1R, colony-stimulating factor-1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; EVs, extracellular vesicles; HDAC, histone deacetylase; LILRB-2, leukocyte immunoglobulin-like receptor subfamily B member 2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinases; SIRP-α, Signal regulatory protein α; STAT3, signal transducer and activator of transcription 3; TIM3, T cell immunoglobulin and mucin domain-containing protein 3; TLR, toll-like receptors; VEGF, vascular endothelial growth factor

strategy for targeting tumor suppressor TAMs with an M2 phenotype [114–116]. In many clinical studies, including TC, various antibodies and small compounds predominantly targeting CSF-1R are being investigated [65, 92]. Small molecules such as PLX3397 [94, 117] and JNJ-40346527 [108, 109] have been examined in the clinical trials, while other small molecules such as ARRY-382 [118], PLX7486 [119], and BLZ945 [120] are currently under clinical trials investigation. Other monoclonal antibodies targeting CSF-1R or its ligand CSF-1, such as emactzumab [121], AMG820 [122, 123], cabiralizumab [124, 125], and MCS110 [126], are also currently being clinical trials investigated as monotherapy or in combination.

Clinical trials [94] and experimental animal studies [127] using CSF-1R antibodies or in combination with other checkpoints clinical trials [128, 129] have also been conducted for TC. The findings from phase I and phase II trials demonstrated that PLX3397 was well tolerated at a dosage of 1000 mg, and the extension study found that 12 of 23 patients (52%) had an anti-tumor response after treatment [130]. Furthermore, CSF-1/CSF-1R-targeted therapy is tolerable to date, suggesting the possibility of combination therapy with current immunotherapy options, including immune checkpoint inhibitors. Additionally, conditional activation of $BRAF^{V600E}$ increased the expression of the TAM chemoattractant CSF-1, and targeting CSF-1-expressing cells reduced TAMs had been proved in animal models [14, 65]. This strategy also induced smaller tumors, reduced PTC proliferation, and restored the thyroid follicular architecture. The CSF-1R inhibitor treatment also impaired the progression of PTC and TAM recruitment. This study primarily focused on PTC and FTC and demonstrated that TAMs are pro-tumorigenic in TC and can be used as targeting pharmacology. Moreover, it may be potentially useful for patients with advanced TC, such as ATC. The clinical immunotherapy strategies for TC are listed in Table 1.

In addition, VEGF can lead to massive infiltration of TAMs into the TC, and a previous study indicated upregulation of VEGF-A expression in ATC patients, which demonstrated that suppression of VEGF might also be a potential strategy for the depletion of TAMs in the TC [65, 131]. Previous studies in hepatocellular carcinoma cell lines [44] and patients of colorectal cancer [132] have observed that a VEGF-depleted environment attenuates the tumor-promoting function of TAMs by reducing cytokine secretion. However, the results also demonstrated that the inhibition of VEGF secretion by cancer cells did not alter the M2 polarization of macrophages in TME. The proangiogenic of TAMs and their assistance in tumor metastasis has been reported in several studies including experiment research and the tissue of patients [43, 44, 133]; however, there are limited studies targeting this modality in TC. Furthermore, another therapeutic strategy is the selective depletion of TAM, employing bisphosphonates including clodronate and zoledronic acid. The previous result of the animal model has shown that injection of clodronate with liposomes into the mice reduced the M2-like TAMs and inhibited the lung metastasis of ATC [95]. In another retrospective clinical study, zoledronic acid was effective in reducing new metastases and improving survival in patients with bone metastases with FTC [134]. Moreover, it was also indicated that the potential therapeutic mechanism may be due to zoledronic acid inhibiting the growth of TAMs, which often overexpress osteoclast-inducing factors to prompt bone resorption or osteolysis [135].

Targeting the inhibition of monocyte recruitment

TAM expansion in cancers is typically mediated by monocyte recruitment via the CCL2-CCR2 axis, including TC [14, 32, 64]. Several investigations have established the role of CCL2, a potent chemoattractant for monocytes, T cells, and NK cells, in the accumulation of TAMs in animal tumor models and the sample of patients [14, 16, 17, 32, 75]. Additionally, it has been demonstrated that patients with ATC have elevated serum CCL2 levels [75], indicating that CCL2 and its receptor, CCR2, may be potential therapeutic targets for TC patients. Another study revealed that vitamins can function as an independent factor to decrease the migration of TC cell lines by lowering the levels of CCL2 and CCL8 [136]. The relationship between vitamins and inflammation in tumors is currently the subject of one clinical trial; additional findings may be attained in the future [137]. In addition, the lack of experimental and clinical trials of TC and the findings from other animal models of cancer calls for careful consideration of anti-CCL2 drugs as monotherapy [138]. The researchers emphasized the TME as a key determinant of successful anti-metastatic therapy and indicated the need for additional biological knowledge to effectively inhibit TAMs. For example, CCL2 inhibition severely depletes monocytes while also increasing the risk of compensatory macrophage growth if recruitment is inhibited, and CCL2-CCR2 communication is essential for monocytes to enter the circulation from the bone [139]. However, prolonged systemic depletion of TAMs may lead to host immunosuppression and susceptibility to opportunistic infections, so targeting downstream mediators of TAMs may be an alternative strategy [92, 140].

Reprogramming of TAMs

TAMs are typically pro-tumorigenic but can be reprogrammed to suppress tumor development by triggering the immune system [27, 97, 141]. According to this scenario, it may be possible for TC to employ plasticity therapeutically to restore the anti-cancer capabilities of TAMs [6, 69, 70, 86, 142].

Table 1 Immunotherapy strategies and therapeutic targets for thyroid cancer

Drug	Therapeutic targets	Patient population	Status	Trial registry number
LY3022855	CSF-1R	Head and neck carcinoma	Completed	NCT01346358
LY3022855 plus Tremelimumab and Durvalumab	CSF-1R plus PD-1	Advanced solid tumors	Completed	NCT02718911
Tremelimumab plus Durvalumab	PD-1	Metastatic TC	Recruiting	NCT03753919
Pembrolizumab	PD-1	ATC	Completed	NCT02688608
Pembrolizumab	PD-1	ATC	Recruiting	NCT05119296
Pembrolizumab	PD-1	Advanced solid tumors (TC)	Recruiting	NCT02628067
Pembrolizumab	PD-1	FTC	Completed	NCT02054806
Pembrolizumab plus Docetaxel	PD-1	TC	Recruiting	NCT03360890
Pembrolizumab plus SO-C101	PD-1	Advanced solid tumors (TC)	Recruiting	NCT04234113
Pembrolizumab plus Lenvatinib	PD-1 plus VEGFR	ATC	Recruiting	NCT04171622
Pembrolizumab plus Lenvatinib	PD-1 plus VEGFR	DTC	Active, not recruiting	NCT02973997
Pembrolizumab plus Dabrafenib and Trametinib	PD-1 plus BRAF and MEK	ATC	Recruiting	NCT04675710
PDR001	PD-1	ATC	Completed	NCT02404441
PDR001 plus Dabrafenib and Trametinib	PD-1 plus BRAF and MEK	TC	Active, not recruiting	NCT04544111
Vudalimab	PD-1 and CTLA-4	ATC	Recruiting	NCT05453799
Nivolumab plus Ipilimumab	PD-1 plus CTLA-4	Rare tumor (TC)	Active, not recruiting	NCT02834013
Nivolumab plus Ipilimumab and Cabozantinib	PD-1 plus CTLA-4 and VEGFR	Advanced DTC	Active, not recruiting	NCT03914300
Nivolumab and Cabozantinib	PD-1 plus VEGFR	Advanced tumor (TC)	Recruiting	NCT04514484
Nivolumab and Lenvatinib	PD-1 plus VEGFR	ATC	Recruiting	NCT05696548
Nivolumab plus Encorafenib and Binimetinib	PD-1 plus BRAF and MEK	TC	Recruiting	NCT04061980
CemIplimab plus Dabrafenib and Trametinib	PD-1 plus BRAF and MEK	ATC	Recruiting	NCT04238624
Tislelizumab plus Surufatinib	PD-1 plus VEGFR	Advanced solid tumors (ATC)	Active, not recruiting	NCT04579757
Tislelizumab plus Anlotinib and Radiotherapy	PD-1 plus VEGFR	ATC	Recruiting	NCT05659186
AIC100 Chimeric Antigen Receptor (CAR) T cells	PD-1 and CTLA-4	TC	Recruiting	NCT04420754
Atezolizumab plus Cabozantinib	PD-L1 plus VEGFR	ATC	Active, not recruiting	NCT04400474
Atezolizumab plus Cobimetinib	PD-L1 plus MET	TC	Completed	NCT01988896
Durvalumab and Radiotherapy	PD-L1	TC	Active, not recruiting	NCT03215095
Vorinostat	HDAC	TC	Completed	NCT00134043
PCI-24781 plus Pazopanib	HDAC plus VEFGR	Metastatic solid tumors (TC)	Recruiting	NCT01543763

Abbreviations: ATC, anaplastic thyroid cancer; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CSF-1R, colony-stimulating factor 1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; HDAC, histone deacetylase; MEK, mitogen-activated protein kinase; MET, receptor tyrosine kinase of MET proto-oncogene; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinases; TC, thyroid cancer; VEGFR, vascular endothelial growth factor receptor

Targeting the specific marker of TAMs

Targeting immunosuppressive TAMs effectively is significantly hampered by the absence of specific protein markers expressed on M2-like TAMs. Several new ATC-specific immune checkpoint genes have been experimentally identified by using the tissue sample of patients, including the immunosuppressive molecule leukocyte immunoglobulin-like receptor subfamily B member-2 (LILRB-2) [10]. The combination of antibodies to LILRB-2 and anti-PD-L1 attenuates the inhibitory effect of TAMs on T cell proliferation and alters the TME to induce anti-tumor immunity in the animal model [143]. Furthermore, stabilin-1 has been shown to be expressed primarily by TAMs in human gastric

cancer tissues, and a higher density of stabilin-1-positive cells was linked with a lower survival rate [144]. In addition, $BRAF^{V600E}$ expression in mice models of PTC showed the high recruitment of stabilin-1-positive TAMs and induced the immunosuppressive effect [54]. Moreover, increasing evidence suggests that targeting the mannose receptor (MR), CD206, which is highly expressed on M2-like TAMs, is a valuable alternative [145, 146]. In addition, a synthetic peptide, RP-182, can modulate the conformational switch of the MR expressed on M2-like TAMs, induce phagocytosis, phagosome-lysosome formation in macrophages, and transfer TAMs from the M2 to the M1 phenotype, increasing innate and adaptive anti-tumor immune responses and improving tumor treatment outcomes [147]. Both in vitro and in vivo experiments have demonstrated that TC-derived medium significantly increased MR expression in TAMs [6, 148]. Also, activated TAMs can establish a tumor-promoting environment and promote the progression of TC cells [6]. These findings indicate that targeting M2-like TAM markers may be a potential therapeutic approach for patients with TC.

Targeting the polarization signaling pathway-PI3K inhibitor

The PI3K signaling pathway is involved in almost all types of signaling and acts as a molecular switch that increases immunosuppressive to immunostimulatory activity in the TAMs [92]. A previous study confirmed that the genetic ablation of PI3K decreased hypoxic stabilization and the TAMs-related proangiogenic factors while inducing the secretion of proinflammatory cytokines [11]. Furthermore, it has been confirmed that M2-like TAMs could activate the PI3K pathway and promote TC stem cell proliferation and metastasis in the ATC in experiment research and the tissue of patients [30]. Moreover, a multicenter phase II pilot study showed that PI3K inhibitors can reduce tumor growth in rats; however, no survival benefit was obtained, which may be due to incomplete inhibition of oncogenic pathways and/or escape mechanisms [149]. These results suggest that the PI3K inhibitor is not sufficient alone, but it could reprogram TAMs and reduce the formation of TC stem cells. Therefore, PI3K could be a potential future therapeutic target for TC treatment.

Targeting the polarization signaling pathway-Histone deacetylase (HDAC) inhibitor

HDAC inhibitors are well-known epigenetic modulators with therapeutic potential for a variety of cancer by modifying the polarization of TAMs [27, 150, 151]. Recently, a study has linked HDAC inhibitors with immune-mediated anti-cancer effects, influenced the efficiency of immunotherapy, and reduced the M2-like TAMs in the animal model [150]. In other animal experiment, researchers found the release of inflammatory cytokines was increased as a result of MP195, a selective HDAC2 inhibitor with the highest concentration, which increased the proportion of M1-like TAMs [151]. Furthermore, celastrol, a novel HDAC inhibitor, was shown to modulate TAM polarization from M2 to M1 and inhibited colorectal cancer growth in the animal model [152]. However, in phase II clinical study designed to evaluate the objective response to HDAC inhibitor (vorinostat) in 19 patients with progressive TC, no patients achieved a partial or complete response [153]. Recently, the combination of TMP195 and PD-1 blockade may provide a therapeutic strategy for colorectal cancer-bearing mice [154], which may provide a novel combination therapy for TC as HDAC inhibitors have no significant effect as monotherapy against TC [153, 155, 156].

Targeting the polarization signaling pathway-signal transducer and activator of transcription 3 (STAT3) inhibitor

An experimental study demonstrated the regulating potential of the T cell immunoglobulin and mucin domain 3 (TIM3) pathway in TC where it was found that TIM3 blockage partially reversed TAM polarization [6]. Furthermore, one animal study indicated that TIM3 activated the STAT3 signaling, increased M2-like TAM polarization, promoted the epithelial-mesenchymal transition of the tumor cells, and finally induced the lung metastasis of osteosarcoma [87]. Clinical trial exploring the therapeutic effects is currently being conducted for solid cancers, and in vitro study showing the therapeutic potential of anti-TIM3 antibodies have shown encouraging results in ATC [6, 157]. Therefore, TIM3 blockers have tremendous potential for TC immunotherapy in conjunction with the reprogramming of TAMs. In addition, STAT3 has been shown to directly induce the expression of the marker protein CD163 in macrophages and induce the change in TAMs from the M1 to the M2 phenotype of human monocyte-derived macrophages and animal models [158, 159]. Moreover, another experimental study in TC found miRNA-324-5p could affect the polarization of TAMs through the STAT3 signaling pathway [142]. The findings also suggested that miRNA-324-5p induced the invasion or migration of endothelial cells and the polarization of M2-like TAMs via VEGF and IL-4 or IL-13, respectively. Several STAT3 inhibitors are being tested in clinical trials, including TTO101 [160–163], OPB-31121 [164–166], and Imx110 [167], but trials for TC patients are still not available. Although some methods were still not applied in TC, TAMs targeting strategies are classified in Table 2.

Table 2 Therapeutic strategies aimed into TAMs

Treatment strategies	Mechanisms	Targets	References
The depletion of TAMs	Metastasis and Angiogenesis	Anti-VEGF	[131]*
	Apoptosis of the TAMs	Bisphosphonates	[95]*
	Monocyte recruitment	CSF-1 and CSF-1R axis	[14]*
		CCL-2 and CCR-2 axis	[75, 136]*
Phenotype-based reprogramming	Targeting polarization of TAMs	PI3K signaling pathway	[30, 105]*
		HDAC signaling pathway	[156]*
		STAT3 signaling pathway	[6]*
		TLR signaling pathway	[169–171]
		Reagents	[68, 70]*
		miRNA inhibitor	[142]*
		Viruses and bacteria	[32, 110, 187]*
		EVs	[33]*
		Nanoparticles	[219, 220]*
	Targeting M2-like TAMs expression markers	Anti-Stabilin-1	[54]*
		Anti-LILRB	[10]*
		Anti-MARCO	[251]
		Anti-MR	[147]
Function-based reprogramming	Targeting phagocytic activity of TAMs	PD-1 and PD-L1 axis	[230]
		CD47 and SIRP-α axis	[10, 111]*
	Macrophage engineering	Anti-HER2 CAR-TAMs	[256]
Alternation of Immune suppression TME	Activation of T cells	PD-1 and PD-L1 axis	[91, 112, 231, 234]*
		CTLA-4 and CD80/86 axis	[235, 264]*

*Articles marked with asterisk are studies for thyroid cancer

Strategies to deplete or inactivate TAMs (by targeting cytokines, the CSF1-CSF1R axis, or using bisphosphonates) and strategies to inhibit monocyte recruitment to TAMs (targeting the CCL2-CCR2 axis) have been widely used in the treatment of tumors, including TC. Furthermore, changing the phenotype of TAMs from a protumor effect to an anti-tumor state may be another preferable therapeutic approach. It can primarily be divided into two types: (1) phenotype-based reprogramming and (2) function-based reprogramming. These recommendations are under development, and several reprogramming strategies have been tested, some of which are already applicable to TC. Additionally, TAMs also have protumor effects by suppressing immune activation. Therefore, TC therapy involves blocking immunosuppressive molecules in TAMs, which has been investigated in TC. The expression of chimeric antigen receptors (CARs) by TAMs which is currently in clinical trials for breast cancer but has not yet been studied in TC, is another provocative therapeutic strategy

Abbreviations: CAR-TAMs, chimeric antigen receptor-tumor associated macrophages; CCR2, C-C chemokine receptor type 2; CCL2, chemokine C-C motif ligand 2; CSF-1, colony-stimulating factor; CSF-1R, colony-stimulating factor receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; EVs, extracellular vesicles; HER2, receptor tyrosine-protein kinase erbB-2, HDAC, histone deacetylase; LILRB-2, leukocyte immunoglobulin-like receptor subfamily B member 2; MARCO, macrophage receptor with collagenous structure; MR, mannose receptor; PD-1, programmed cell protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinases; SIRP-α, signal regulatory protein-α; STAT3, signal transducer and activator of transcription 3; TC, thyroid cancer; TIM3, T cell immunoglobulin and mucin domain-containing protein 3; TLR, toll-like receptor; VEGF, vascular endothelial growth factor

Targeting the polarization signaling pathway with toll-like receptor (TLR) agonists

TAMs have been observed to become pro-inflammatory when exposed to TLRs in TME and restricted tumor progression in the animal tumor model [23, 168]. For example, intra-tumor administration of TLR-7 and TLR-9 increased monocyte infiltration and repolarized TAMs toward a proinflammatory phenotype in breast tumor mice models [169]. Furthermore, due to changes in the TAM phenotype, a similar effect was observed with TLR-7 and TLR-8 agonists that cause tumor regression in the mice models of melanoma [170, 171]. TLR-4 expression in TC is related to tumor metastasis, aggressiveness, and the $BRAF^{V600E}$ mutation, according to two studies using the tissue of patients and animal experiments [172, 173]. However, the therapeutic role of TLR agonists in TC with TAMs has not been studied. Currently, four TLR7 agonists (DSP-0509 [174], BNT411 [175], BDC-1001 [176], BDBD018 [177] and three TLR9 agonists (SD101 [178–180], CMP-001 [181–183], and tilsotolimod [184–186]) are being tested in clinical trials for their anti-tumor properties, and several clinical trials for solid tumor [175, 177, 186] and advanced cancer [184] may include patients with TC.

Targeting other factors related to the reprogramming of TAMs

Drugs could be used for the reprogramming of TAMs in addition to signaling pathway regulators in TC [68, 70]. For example, bleomycin, which primarily inhibits DNA synthesis, reverses the M2-like into M1-like TAMs and significantly decreases the cell proliferation, migration, and invasion of the TPC-1 cell line [70]. The M2-like TAM marker CD206 was suppressed by treatment with bleomycin, whereas the M1 phenotype marker CD80 and the major M1 secretagogues (TNF-α and IL-1β) were increased. Similarly, zoledronic acid treatment prevented the M2 polarization of the THP-1 monocytes cell line, thus inhibiting the stemness and metastasis of TC cells [68]. Furthermore, zoledronic acid with radioactive iodine has been proven effective in reducing new metastases and improving survival in patients with DTC bone metastases in one retrospective review conducted on 50 patients [134]. Zoledronic acid inhibits the growth of TAMs in TC cell lines, and TAMs often overexpress osteoclast-inducing factors, which contribute to bone resorption or osteolysis [135]. Therefore, targeting TAMs may be a potential therapeutic mechanism for the treatment of TC bone metastasis. Except for the reagents, studies on altering the differentiation of TAMs by the virus have also been conducted for the treatment of TC. For example, two experimental studies have confirmed that the oncolytic virus inhibited ATC growth [187] and switched M2-like TAMs toward an M1 phenotype [32]. In addition, the oncolytic activity of the virus (dl922-947) could be increased by a poly ADP ribose polymerase (PARP) inhibitor and inhibited the progression of ATC both in vitro and in vivo experiment [110]. Expect the virus, bacteria (e.g., Mycobacterium indicus pranii (Mw)) can also increase TAMs to repolarize to the M1 phenotype with the reduction of regulatory T cells in the animal models of melanoma [65, 188]. Additionally, Mw upregulated the expression of CD80/CD86 positive macrophages in a tuberculosis model by stimulating the nuclear factor-κB (NF-κB) signaling pathway [189]. Further research is required to determine whether these novel bacteria and the combination therapy could be used in TC.

EVs in TME have been demonstrated in many studies to influence TC development by mediating intercellular signaling and also affecting TAM polarization [33, 190, 191]. For example, research on the TC mice model showed that CXCR4 expression in PTC is restricted by EVs containing miRNA-655-3p, which prevents TAM growth, invasion, and M2 polarization [33]. By targeting various transcription factors and bridging proteins, miRNA-29a-3p [192], miRNA-103 [193], miRNA-145 [102], miRNA-203 [194], miRNA-222 [101], miRNA-934 [100], and miRNA-940 [195] induced M2 polarization. On the other hand, the miRNA-9 [196], miRNA-16 [197], miRNA-21 [198], miRNA-127 [199], miRNA-125b [200, 201], miRNA-155 [200] contained in the EVs related to M1 polarization have been reported by various experimental studies. In addition, the surface glycosylation profile of the EVs has been found to contain a significant amount of mannose, making it a suitable ligand for MR, which can target M2-like TAMs [202, 203]. Additionally, modification of the EVs by molecular engineering could help reduce the immunosuppression of TME [145]. Furthermore, a study has demonstrated that EV-mimics from M1 macrophages can directly repolarize M2 into M1-like TAMs that release proinflammatory cytokines, induce anti-tumor immune responses, and enhance the anti-cancer efficacy of PD-L1 [204]. This approach offers the possibility of programmed polarization of TAMs, and previous studies have already provided possible candidate strategies [145, 205]. In addition to the immunomodulation ability, several studies have shown that miRNAs in EVs are highly stable and protected by lipid bilayers, making them suitable and promising tumor markers for the clinical diagnosis of TC [206–209].

In addition to the EVs, nanoparticles alone or with chemotherapy can also be intelligently designed to promote M1-polarization and inhibited the progress in the mice model of melanoma [210–212]. Additionally, nanoparticles that mimic NK cell membranes can modulate TME, increase the percentage of M1-like TAMs, and polarize TAMs, improving both in vitro and in vivo immunotherapy for breast cancer [213]. Also, the effects of glycocalyx-mimetic nanoparticles on mouse primary peritoneal macrophage polarization have been investigated. The findings revealed that macrophage cells of mice were successfully repolarized to the M1 phenotype with increased expression of CD86 markers and elevated IL-12 levels [214]. Cytokines such as IL-12 was considered a typical candidate marker for promoting the reversal of M2-like TAMs to an M1 phenotype including TC both in clinical and animal study [13, 93, 215]. Previous research focusing on this characteristic has created pH-sensitive polymeric nanoparticles to encapsulate IL-12 for targeted immunotherapy. The nanoparticles loaded with IL-12 can passively accumulate and release IL-12 at tumor sites and exert therapeutic effects by promoting the polarization of the TAMs to the M1 phenotype in tumors by using the melanoma mice model [216]. Similarly, a plasmid DNA encoding the IL-12 gene is delivered into TAMs using a multifunctional fusion peptide-modified macrophage and tumor-targeted delivery system. This in vitro study indicated the nanoparticles enhanced IL-12 production, increased the release of proinflammatory cytokines, upregulated the M1 marker (CD80), and downregulated the M2 marker (CD206) [217]. Furthermore, to promote the repolarization of TAMs toward the M1 phenotype, clinical trials have respected for various transcriptional signaling drugs that can be flexibly loaded into nanoparticles, such as CD47-signaling

regulatory protein-α (SIRP-α) antibodies [218] and TLR agonists [23]. In addition, it is reassuring to note that nanoparticles are typically decorated with specific targeting ligands, which can facilitate the successful transfer of signaling modulators in solid tumor mice models, including TC [219, 220]. The unmodified gold nanoparticles limited the growth of PTC cells (BCPAP and TPC-1), including cell proliferation, migration, and invasion, as demonstrated in a previous study [220]. The novel gold nanomedicine CYT-21625, which was developed for the targeted delivery of TNF-α with paclitaxel, has also shown significant inhibition of the progression of ATC in animal models [219].

Targeting phagocytic activity of TAMs

Tumor cells can evade clearance by macrophages by overexpressing anti-phagocytic surface proteins. The CD47 associated with macrophage SIRP-α is the source of anti-phagocytic signals that have been the subject of most research and documentation [221–223]. According to the study using the ATC mouse model, inhibiting CD47 increased phagocytosis and resulted in the overexpression of CD11B and CD80 on TAMs [111]. Moreover, in addition to the CD47 antibody, TTI-621, a fully human recombinant protein that blocks CD47-SIRP-α has been applied in-human phase I clinical trials [224]. One experiment study also confirmed the LILRB1 on TAMs is a novel signal to inhibit phagocytosis of cancer cells that evade SIRPα-CD47 blockers and the expression was increased in the ATC patients [10, 225]. While, the clinical trials for the TC are still being developed, and dozens of drugs targeting CD47 are currently being recruited; their names cannot be listed here in detail. Monoclonal antibodies that target the interaction between PD-1 and PD-L1 have shown clinical significance in combating a variety of cancers [226–228]. Recent experiment and clinical studies have demonstrated that TAMs also express PD-1 and are related to the progress of tumors [46, 229]. Moreover, a previous study confirmed that the PD-1 expression of TAMs was negatively correlated with phagocytic potency against tumor cells [230] and that blocking PD-1 reduced tumor growth in the model of orthotopic murine ATC [231].

Alteration of the immune suppression of TME

In the mice model of breast cancer and osteosarcoma, targeting PD-1/PD-L1 in TAMs, which converts its phenotype into an anti-tumor phenotype, directly leads to increase T cell-mediated immune surveillance [46, 232]. Another animal study of melanoma also demonstrated that anti-PD-L1 treatment increased M1-like TAM cell proliferation, survival, and activation, as well as upregulated proinflammatory-related pathways [47]. In another animal study of melanoma, targeted TAM depletion created a favorable environment to facilitate local and systemic delivery of antibodies against PD-1 antibody-adherent platelets [233]. The TME was further reprogrammed and promoted T cell infiltration into the tumor tissue by eliminating TAM. The antitumor of targeting PD-1/PD-L1 was also performed to enhance the efficacy of Lenvatinib by altering the TME in the mice of ATC [91]. In addition, another study showed that when a combination of BRAF inhibitors and anti-PD-1/PD-L1 antibodies was used, the reduction in MDSCs was usually accompanied by an increase in M1-like TAMs and reduced tumor volume in an orthotopic mouse model [231]. Except for the experimental studies, the clinical trials of immunotherapy against PD-1/PD-L1 have also been applied in TC [234], and the results show promise in patients with ATC [112]. In detail, two of 22 patients in a clinical trial of the anti-PD-1 antibody (pembrolizumab) in patients with advanced and PD-L1-positive TC confirmed a partial response [234]. In another phase II clinical trial for ATC, 42 patients had three complete responses and five partial responses to anti-PD-1 therapy [112]. Although it is well established that PD-1/PD-L1 blockade activates T cells, little is known about the role of a combination of targeting TAMs and TME in TC. The role of PD-1/PD-L1 blockers on TAMs in TC should not be neglected by the focus on T-cell signaling, as the effect on TAMs may inform the assessment of therapeutic efficacy and suggest alternative treatments.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another immune checkpoint inhibitor of TC that functions by unbreaking the T cells to turn on the anti-tumor immune response [113, 235]. In a phase II trial for TC, anti-CTLA-4 and anti-PD-1 combination therapy resulted in an objective response rate of 12%, with two partial responses in 17 patients [113]. In another phase 1 dose-escalation study, tumor reduction was demonstrated with anti-CTLA-4 and anti-PD-1 combination therapy, but the sample of patients with TC patients in this study was too small [235]. Despite the rapid advancement of immunotherapy technology, particularly with the development of immune checkpoint inhibitors, there are limited studies for TC [236, 237].

The advantages and prospects of TAM-targeted therapy in TC

As mentioned, the polarization of TAMs was strongly associated with TME of TC and correlated with aggressiveness of the cancer, which may provide a new platform for the treatment of TC that are refractory to conventional treatment strategies [13, 14, 18, 34, 58, 61, 62, 238]. First of all, the density of TAMs is increased in PTC tissues compared to benign thyroid disease [13]; and PTC with BRAF mutation significantly increases the expression of CSF-1 and CCL2 which attracted the TAMs [14]. Moreover, the

TAMs correlated with lymph node metastasis [9, 13] and were used to assess the prognosis of TC [34]. Thus, developing TAM-targeted therapies requires a thorough understanding of the role of TAMs in the progression of TC as well as the effects of therapeutic strategies on TME. Also, it has been previously suggested that TAM-targeting therapeutics may offer a new prospect for EV-mediated tumor immunotherapy [205]. For example, EVs have been shown to act as effective immunomodulators of TAM depletion through the synthesis of paclitaxel-containing microvesicles and an ultrasound-mediated delivery method [239]. Moreover, a previous study found that nanovesicles from M1-like TAMs can directly regulate the transition of M2 to the M1 phenotype by modulating miRNA expression profiles [204], and the IL-4 receptor [240]. Therefore, the design of new therapeutic EVs, combined with the TAMs-targeted strategy, may herald a new era in cancer immunotherapy, including TC. Unfortunately, there is limited research on TAM in TC, particularly in patients who have recently undergone chemotherapy or radiotherapy. Due to the high plasticity of TAMs and the high density in TC, TAM-centered therapy, and the combinatorial treatment with chemotherapy, radiotherapy, or immunotherapy may become a new therapeutic opportunity for TC.

The limitation of the existing strategies

Appealing therapeutic strategies in TC include the depletion of TAMs and inhibition of monocyte recruitment to inhibit tumor development while preserving the cell types that support a protective immune response [27, 41, 66, 92, 97, 241]. However, the successful clinical application of these strategies requires careful investigations to overcome the current limitations. For instance, clodronate is a drug that can completely eliminate TAMs and hence is a simple and effective strategy. However, the drug may cause high toxicity if patients are treated for prolonged periods [92]. Moreover, osteonecrosis of the jaw (ONJ), a rare but severe side effect in TC patients, was previously linked to oral and systemic administration of bisphosphonates [242]. In addition, ONJ may worsen in patients using a combination of bisphosphonates and tyrosine kinase inhibitors (TKIs) for DTC and ATC [89, 243]. Furthermore, at the clinical level, this approach has not been inconsistently tested in clinical trials in different cancers [244–246]. These results suggest that different cancers or even various subtypes of the same cancer such as triple-negative breast cancer, and ATC may have side effects due to high doses application of the drugs. On the other hand, the depletion of TAM also affects other cells, e.g., M1-like TAM produces pro-inflammatory cytokines and up-regulates major histocompatibility complex class II (MHC-II) that promotes the anti-tumor activity of T cells [247, 248]. Research has shown that T cell-mediated immunity depends on monocytes and macrophages [247], also for anti-PD-1 [249] and anti-CTLA-4 therapies [250]. Complete TAM depletion makes it challenging to combine checkpoint inhibitors and immunotherapy [66]. In addition, the complex composition of the TME leads to dynamic interactions between TAMs and other immune cells that may vary with the progression of cancer, for which deletion of TAMs may disrupt the equilibrium structure and promote tumor progression. Another strategy is to target cancer-associated myeloid immature progenitors, which are now known to be highly heterogeneous and complex, posing a challenge to the development of myeloid cell-targeted immunotherapies [19, 248]. One of the greatest challenges is identifying specific markers [92], and the massive cell depletion in immature populations may result in multi-organ side effects. Hence, feasible alternatives to consider include temporary TAM ablation and targeting the recovery periods during which monocytes can be attracted before becoming pro-tumoral TAMs.

Therefore, a better strategy in the future would be to enhance the activity of anti-tumor TAMs or repolarize existing TAMs to produce anti-tumor activity, but the results for TC are rare. For example, the methods to repolarize M2 to M1-like TAMs for new characteristic gene markers have been used in melanoma and breast cancer, such as macrophage receptor with collagenous structure (MARCO) antibody therapy [27, 66, 92, 251], but no experimental or clinical trials have been conducted for TC. Additionally, the novel signature genes of TAMs have been identified, including scavenger receptor-triggering receptors expressed on myeloid cells 2 (TREM2) [252], apolipoprotein E (APOE) [169], secreted phosphoprotein 1 (SPP1) [10, 253], and V-set and immunoglobulin domain containing 4 (VSIG4) [10]. Additional single-cell RNA-seq studies also indicated that TAMs were frequently present with both pro-tumor and anti-tumor signatures [254]. This phenomenon suggests that macrophages in the TME may not have conventional M1/M2 polarization [253]. Understanding the role of novel TAMs subsets in TME may require new technologies like spatial transcriptomics and multiplex immunofluorescence [255]. Therefore, the identification and discovery of targets for reprogramming TAMs is critical for transforming TME from a pro-cancer to an anti-cancer function. An additional provocative therapeutic strategy of TAM manipulation has been introduced, including the engineering of macrophages to express chimeric antigen receptors (CAR) [27]. To date, CAR-TAMs studies are mainly at the preclinical stage, with data confirming their efficacy (growth-inhibiting tumor phagocytosis) in solid tumors [256–258]. However, whether it is the identification and discovery of targets for reprogrammed TAMs or clinical trials of CAR-TAMs, there is limited research in TC.

In addition to the issues of appeal and opportunities, many aspects need to be expanded upon. How can a balance be struck between TAMs and other immune cells to favor the acquired immune system over tumor development in the ever-changing state of TME? Does the composition of TME change before and after treatment? Does this change allow TAMs to develop chemotherapy resistance? How should subsequent treatment modalities and medications be organized for TAMs that have developed resistance? How can different subtypes of TC affect the polarization of TAMs, and what are the different therapeutic approaches that need to be proposed for the different subtypes? How could patients of different genders be applied in the clinical setting to develop treatment modalities for TAMs? Many studies have previously shown that sex hormones directly influence the characterization of TAMs, although this has not yet been explored in TC [259–263]. These are the major questions that need to be explored and answered subsequently.

Conclusions

To date, tremendous efforts have been made to promote immunotherapy to TC. TME plays an important role in TC genesis, metastasis, and stem cell proliferation, and TAM accounts for the largest proportion of TME cells. Although it is currently believed that high infiltration of M2-like TAMs supports TME and promotes TC growth, the study of TAM in TC is still a new field. Meanwhile, targeting therapy of TAMs in TC has the following advantages: 1. TAMs have a high degree of infiltration in TC and related with the prognosis of the cancer; 2. common genetic mutations in TC related with the polarization of TAMs, e.g., BRAF mutation has been shown to cause the TAMs polarization into M2 phenotype; 3. Since the gene mutation of BRAF correlated with high densities of M2-like TAM, targeted therapies can be better developed based on the subgroup of TC. Numerous studies have demonstrated the importance of innate immune cells in preventing the onset and progression of cancer, and TAMs may be a promising target in the future. Thus, targeting therapy of TAMs provides a platform to be considered for immunotherapy of TC. Despite the favorable prognosis of TC, more therapeutic strategies based on or in combination with TAMs need to be explored in the future.

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Declarations

Competing interests The authors declare no competing interests.

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