Interaction of tumor-associated macrophages with stromal and immune components in solid tumors: Research progress (Review)

ANNA KAZAKOVA[1], TATIANA SUDARSKIKH[1], OLEG KOVALEV[2], JULIA KZHYSHKOWSKA[1,3] and IRINA LARIONOVA[1,2]

[1]Laboratory of Translational Cellular and Molecular Biomedicine, National Research Tomsk State University, Tomsk 634050; [2]Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk 634009, Russian Federation; [3]Institute of Transfusion Medicine and Immunology, Institute for Innate Immunoscience (MI3), Medical Faculty Mannheim, University of Heidelberg, D-68167 Mannheim, Germany

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Abstract. Tumor-associated macrophages (TAMs) are crucial cells of the tumor microenvironment (TME), which belong to the innate immune system and regulate primary tumor growth, immunosuppression, angiogenesis, extracellular matrix remodeling and metastasis. The review discusses current knowledge of essential cell-cell interactions of TAMs within the TME of solid tumors. It summarizes the mechanisms of stromal cell (including cancer-associated fibroblasts and endothelial cells)-mediated monocyte recruitment and regulation of differentiation, as well as pro-tumor and antitumor polarization of TAMs. Additionally, it focuses on the perivascular TAM subpopulations that regulate angiogenesis and lymphangiogenesis. It describes the possible mechanisms of reciprocal interactions of TAMs with other immune cells responsible for immunosuppression. Finally, it highlights the perspectives for novel therapeutic approaches to use combined cellular targets that include TAMs and other stromal and immune cells in the TME. The collected data demonstrated the importance of understanding cell-cell interactions in the TME to prevent distant metastasis and reduce the risk of tumor recurrence.

Correspondence to: Dr Irina Larionova, Laboratory of Translational Cellular and Molecular Biomedicine, National Research Tomsk State University, 36 Lenina Avenue, Tomsk 634050, Russian Federation
E-mail: larionovaiv@onco.tnimc.ru

Abbreviations: BMDM, bone marrow-derived macrophage; CAF, cancer-associated fibroblast; CM, conditioned medium; DC, dendritic cell; EC, endothelial cell; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EndoMT, endothelial-mesenchymal transition; IHC, immunohistochemistry; LEC, lymphatic endothelial cell; LVD, lymphatic vessel density; MDM, monocyte-derived macrophage; MMT, mesenchymal-mesenchymal transition; MVD, microvessel density; NK cell, natural killer cell; PoEM, podoplanin-expressing macrophage; PvTAM, perivascular tumor-associated macrophage; TAM, tumor-associated macrophage; TEC, tumor endothelial cell; TEM, Tie2-expressing macrophage; TME, tumor microenvironment; TMEM, tumor microenvironment of metastasis

Key words: TAMs, TME, CAFs, ECs, immune cells, T cells, combined therapy

Contents

1. Introduction

Tumors exist in constant interaction with components of the tumor microenvironment (TME), which includes stromal cells [such as cancer-associated fibroblasts (CAFs), endothelial cells (ECs) and adipocytes], and immune cells [such as tumor-associated macrophages (TAMs), cancer-associated neutrophils, dendritic cells (DCs), natural killer (NK) cells, T lymphocytes and B lymphocytes], as well as extracellular matrix (ECM) (1,2). Cells in the TME are involved in reciprocal interaction with tumor cells, which eventually leads to enhanced proliferation, metastasis and chemoresistance (1,3,4).

TAMs are key innate immune cells involved in regulation of primary tumor growth, antitumor adaptive immune response, tumor angiogenesis, ECM remodeling and metastasis (5,6). TAMs originate either from circulating monocytes derived from bone marrow hematopoietic stem cells (recruited) or yolk sac progenitors (resident) (7). These cells are attracted

into the primary tumor and activated by various signals in the TME (6).

TAMs are classified as M1 (classically activated macrophages) and M2 (alternatively activated macrophages) (5). M1 TAMs secrete pro-inflammatory cytokines IL-12, TNFα, C-X-C motif chemokine ligand (CXCL)-10 and IFN-γ, and produce high levels of nitric oxide synthase (NOS), while M2 TAMs secrete anti-inflammatory cytokines IL-10, IL-4 and IL-13, and express scavenger receptors, including CD163, CD206, CD204, macrophage receptor with collagenous structure (MARCO) and stabilin-1 (5,6). TAMs are plastic cells that can change their polarization from M1 to M2 and vice versa in response to various stimuli from the TME, including cytokines, growth factors and matrix remodeling proteins (8,9). Cells in the TME are genetically more stable compared with tumor cells, which makes them useful as therapeutic targets (10,11).

In the present review, data on the main mechanisms of the TAM interaction with crucial components of the TME, including CAFs, blood and lymphatic ECs (LECs), and diverse immune cell infiltrates, were collected. It also discusses possible therapeutic approaches that combine targeting of TAMs and other stromal or immune cells.

2. CAFs

CAFs are heterogenous stromal cells originating from different precursor cells, including resident tissue fibroblasts (via activation), bone marrow mesenchymal stem cells (via differentiation), hematopoietic stem cells (via differentiation), epithelial cells via epithelial-mesenchymal transition (EMT) and ECs via endothelial-mesenchymal transition (EndoMT) (12,13). Tumor cells activate EndoMT through production of cytokines and growth factors, among which TGF-α and TGF-β are the most studied (14,15). In some tumors, such as melanoma, pancreatic cancer and lung cancer, EndoMT provides 30-40% of CAFs (16,17).

In the TME, CAFs possess functions critical for supporting cancer cell proliferation, angiogenesis, lymphangiogenesis, invasion and metastasis. CAFs promote tumor progression via various mechanisms, including cytokine and chemokine secretion, as well as ECM remodeling that occurs due to basement membrane degradation and interstitial stroma disintegration (18-26).

CAFs induce monocyte recruitment. Numerous studies have demonstrated that CAFs contribute to monocyte recruitment (Fig. 1A) (27-29). In a Transwell migration assay, conditioned medium (CM) of colon cancer-derived CAFs was more efficient in attracting monocytes compared with CM of macrophages, differentiated from peripheral blood mononuclear cells, or human HCT116 and DLD-1 colon cancer cells (27). There are two key factors promoting monocyte recruitment: Macrophage colony-stimulating factor [M-CSF or colony stimulating factor 1 (CSF1)] and monocyte chemoattractant protein 1 [MCP-1; or C-C motif chemokine ligand (CCL2)] (27,30,31). Co-culture of CAFs with monocyte-derived macrophages (MDMs) revealed high expression of CCL2 in MDMs, indicating CAFs to be one of the major inducers of CCL2 production in macrophages (27). M-CSF is mainly produced by CAFs but not by tumor cells or macrophages (27). Inhibition of M-CSF/M-CSF receptor (M-CSFR) signaling results in decreased CCL2, CD163 and M-CSFR expression (27). The role of M-CSF in myeloid cell survival, differentiation and function has been demonstrated in other studies (32,33). IL-8 produced by CAFs derived from human colorectal cancer (CRC) tissue has been reported to recruit monocytes, while IL-6 promoted their adhesion to the tumor cells (28). CM from CAFs induced vascular cell adhesion molecule 1 (VCAM-1) expression in CRC cells, which is associated with enriched infiltration of TAMs in the TME (28). A Transwell assay revealed that CAF-derived C-X-C motif chemokine receptor (CXCR)2 and IL-8 facilitated monocyte migration in a dose-dependent manner (28).

THP-1 human monocytes co-cultured with human oral squamous cell carcinoma (OSCC)-derived CAFs acquired the M2 phenotype, which manifested in elevated expression levels of M2 markers IL-10 and TGFβ and increased adhesion, compared with control propidium monoazide-treated macrophages (34). Triple co-culture of THP-1 monocytes, CAFs and OSCC cells revealed a more pronounced effect on monocyte differentiation and further macrophage polarization (34). Furthermore, tumor cells from colon, breast and oral cancer stimulate CAFs to produce higher levels of IL-6, CXCL5 and granulocyte M-CSF (GM-CSF/CSF-2) (34). CAFs isolated from human lung squamous cell carcinoma expressed monocyte- and neutrophil-attracting chemokines, including CCL2, CCL7, CXCL1, CXCL5 and CXCL8 (35). CAFs in co-culture with macrophages exhibited higher expression levels of M-CSF, IL-6, IL-8, hepatocyte growth factor and CCL2 (36). In this *in vitro* system, macrophages were differentiated from peripheral blood monocytes of healthy donors, and CAFs were obtained by mesenchymal stem cell co-cultivation with esophageal squamous cell carcinoma cell lines (36). CAFs obtained from human breast cancer (BC) tissue induced the recruitment of monocytes via CCL2 and stromal cell-derived factor-1 (SDF-1), and promoted M2 polarization (37).

In human hepatocellular carcinoma (HCC), CAFs express endosialin, a transmembrane glycoprotein that is also expressed in tumor cells (38). Endosialin can interact with CD68, thereby recruiting macrophages into the TME (38). Endosialin-positive CAFs can promote M2 polarization of macrophages through growth arrest specific 6 factor secretion (Fig. 1A) (38). In the TME, CAFs are the main producers of CXCL12 and CXCL16, which are monocyte chemoattractants that induce M2 polarization (29). In TAMs differentiated from the THP-1 cell line, CXCL12 stimulated the secretion of plasminogen activator inhibitor-1, inducing tumor cell proliferation, angiogenesis, metastasis, EMT, cell apoptosis inhibition and drug resistance (29). Immunohistochemistry (IHC) analysis of primary triple-negative BC (TNBC) revealed that both tumor cells and CAFs expressed CXCL16 (39). CM of CAFs isolated from human tumors affected the migration of human peripheral blood monocytes and, to a lesser extent, M2 macrophages (39). Monocyte migration towards CXCL16 was more pronounced compared with that towards CXCL12 (39). *In vitro*, CAFs isolated from human prostate carcinoma tissue induced the recruitment of macrophages, obtained from healthy donor monocytes, towards tumor cells and macrophage M2 polarization via SDF-1 (40). Other

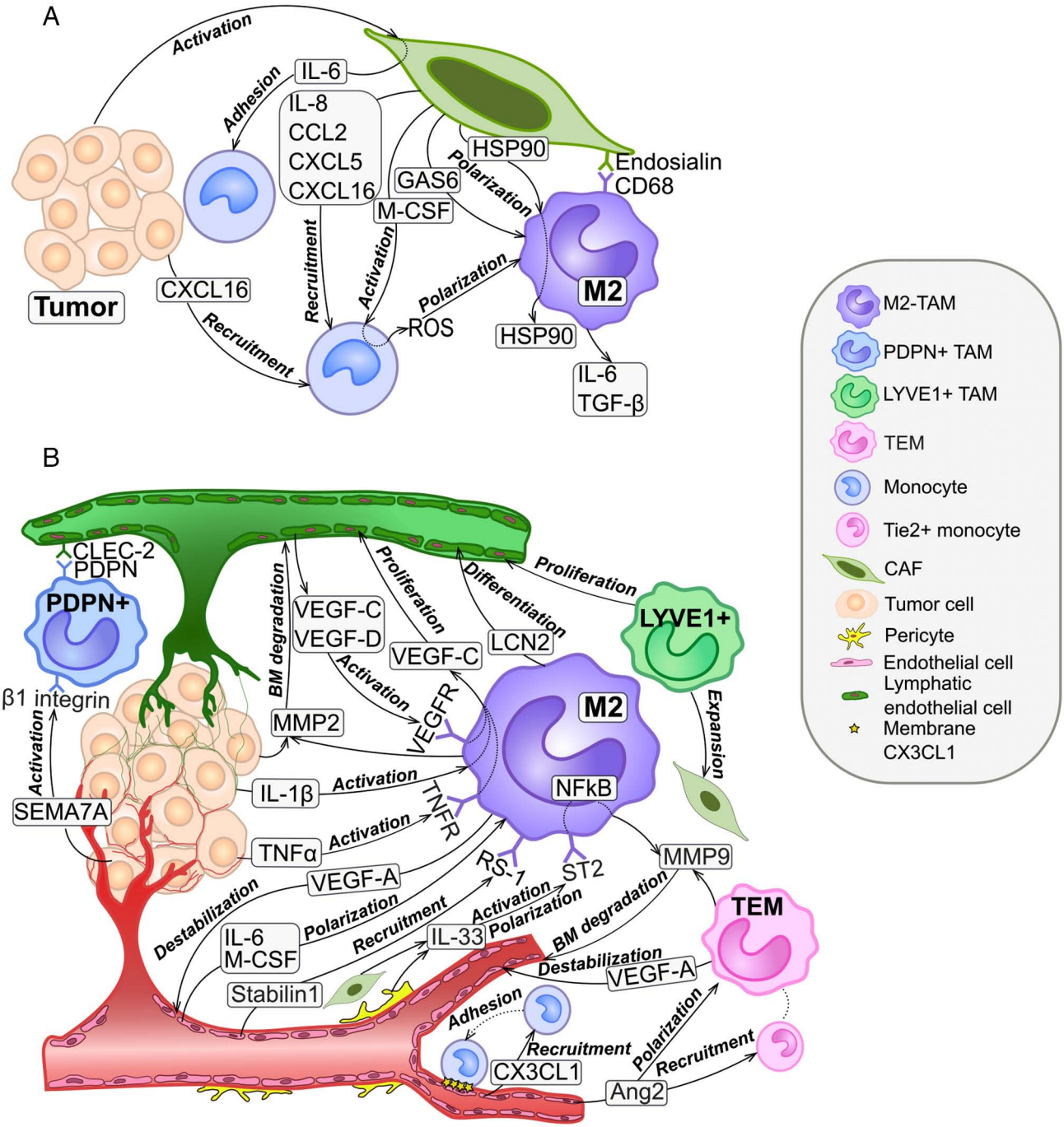

Figure 1. Functional crosstalk between TAMs and stromal components. (A) TAMs mutually interact with CAFs in the tumor microenvironment. CAFs produce various soluble factors that act as chemoattractants, activation and polarization agents for monocytes/macrophages. (B) TAMs are crucial regulators of tumor neovascularization and metastasis. In the TME, TAMs are polarized to the M2 state. Vascular ECs and LECs can recruit monocytes and macrophages and induce M2 polarization by producing various soluble (Ang2, VEGF-A, VEGF-C, IL-1β, IL-6, M-CSF and IL-33) and membranes (CX3CL1, GAL8 and stabilin-1) factors. M2 TAMs secrete proteins (LCN2, MMP9 and MMP2) and growth factors (VEGF-C and VEGF-A) that are essential for vascular and LEC proliferation and differentiation. M2 TAMs also facilitate degradation of the basement membrane of blood and lymphatic vessels and can destabilize EC junctions. Perivascular TAMs (PDPN+, LYVE1+ and TEM) are specific TAM subpopulations inducing angiogenesis. Ang2, angiopoetin 2; BM, basement membrane; CAFs, cancer-associated fibroblasts; CCL, C-C motif chemokine ligand; CX3CL1, C-X3-C motif chemokine ligand 1; CXCL, C-X-C motif chemokine ligand; EC, endothelial cells; GAL8, galectin-8; GAS6, growth arrest specific 6; HSP, heat-shock protein; LCN2, lipocalin 2; LEC, lymphatic EC; LYVE1, lymphatic vessel endothelial hyaluronan receptor 1; M-CSF, macrophage colony-stimulating factor; PDPN, podoplanin; ROS, reactive oxygen species; RS-1, receptor stabilin-1; SEMA7A, semaforin 7A; ST2, suppression of tumorigenicity 2; TAMs, tumor-associated macrophages; TEM, Tie2-expressing macrophages; Tie2, TEK receptor tyrosine kinase; TNFR, TNF receptor.

factors, including CCL2 and CXCL14, mainly affect myeloid cell recruitment to the tumor site; however, to the best of our knowledge, their role in macrophage polarization has not yet been studied (40).

CAFs facilitate M2 macrophage polarization. CAFs serve pivotal roles not only in monocyte recruitment and differentiation but also in M2 polarization in tumors (28,39). Cross-talk between CAFs and TAMs mediated by different factors has

been described in a number of studies and in various tumor types, including esophageal and lung cancer (35,36,41). *In vitro*, CAFs derived from human CRC tissue induced monocyte differentiation and M2 TAM polarization via the upregulation of M2 markers CD206 and CD163 (28). CAFs promoted M2 recruitment in a CRC xenograft mouse model by increasing VCAM-1 expression in tumor cells (28). Flow cytometry analysis of tumor tissue demonstrated that the expression levels of VCAM-1 in CRC cells were associated with higher infiltration of $CD11b^+CD68^+$ cells, specifically $CD163^+CD206^+$ TAMs (28). A positive association between CD163/CD206 and VCAM-1 expression in colon adenocarcinoma was observed (28). TAMs induced by CAFs promoted the migration of SW480 CRC cells and suppressed NK cell functions *in vitro* (28). Increased tumor cell invasion has been demonstrated in collagen gel co-cultures with TAMs and CAFs or in triple co-culture with colon cancer cells (HCT116 and DLD-1) (27). Human monocyte-derived TAMs weakly induced invasion, whereas human colon cancer-derived CAFs exhibited a more pronounced effect (27). CM derived from co-culture of CAFs and TAMs had the most prominent effect on tumor cell migration compared with CM from mono- and triple co-cultures (27).

CM obtained from CAFs isolated from human pancreatic ductal adenocarcinoma (PDAC) tissue induced M2 polarization of human peripheral blood monocytes in a co-culture system, as well as in monoculture (42). Stimulation of human peripheral blood monocytes by pancreatic CAF CM induced CD206 expression and increased reactive oxygen species production. M-CSF produced by CAFs is responsible for generating oxidative stress resulting in M2 polarization (Fig. 1A) (42). *In vitro*, CAF-stimulated TAMs enhanced pancreatic tumor cell proliferation, invasion and migration (42). Another factor involved in macrophage polarization is heat-shock protein 90 α (HSP90α) (43). CAFs isolated from murine PDAC tissue promoted M2 polarization in mouse RAW264.7 macrophages by secreting HSP90α, which induced a feedforward loop of HSP90α secretion in macrophages (43). In CRC, EndoMT-derived CAFs also exhibit high HSP90α expression (17).

In a transgenic mouse model of BC, genetic ablation of chitinase 3 like 1 (CHI3L1) in CAFs attenuated tumor growth, macrophage recruitment and M2 polarization (44). *In vivo*, injection of CHI3L1 facilitated macrophage infiltration and increased angiogenesis (44). Several studies have reported that overexpression of IL-33 in CAFs induced repolarization of M1 macrophages into M2 macrophages (45,46). Genome-wide expression profiling demonstrated upregulation of M2-related genes [arginase 1 (Arg1), C-C motif chemokine receptor (CCR)3, Cd163, Cdh1, F13a1, Hmox1, Il1r2, mannose receptor C-type 1 (MRC1), Pdcdl1g2, Serpinb2 and Stab1] in IL-33-stimulated macrophages compared with non-stimulated macrophages (46). In a study in humans, as well as in a mouse model, it has been demonstrated that IL-33-stimulated TAMs actively promoted cancer metastasis (45,46). The possible mechanism is associated with the IL-33-NF-κB-MMP9-laminin axis (45,46).

CAFs express fibroblast-specific protease fibroblast-activated protein (FAP), which is involved in metastasis and modification of collagen matrices, as well as inflammation (47). *In vitro* and *in vivo*, class A scavenger receptor (SR-A)-expressing macrophages exhibited higher adhesion to FAP-cleaved collagen (47). In a BC mouse model, CAFs increased peritoneal macrophage adhesion to FAP-cleaved type I collagen recognized by macrophages (47). Macrophages with a lack of SR-A on their surface exhibited decreased attachment compared with SR-A-expressing ones (47).

Macrophages induce transdifferentiation of fibroblasts. Macrophages are able to affect 'mesenchymal-mesenchymal transition' (MMT) in fibroblasts, thereby activating their pro-tumor phenotype (48). MMT is the process during which fibroblasts acquire the properties of mesenchymal cells after undergoing transdifferentiation into myofibroblasts (48). In a human prostate cancer model, M2 macrophages activated healthy fibroblasts through MMT and converted them into CAFs, which are traditionally referred to as myofibroblasts (40,49). M1 macrophages are also able to activate fibroblasts but to a lesser extent than M2 macrophages (40). In a TNBC model, macrophages actively expressed CD163 and the immunosuppressive factors S100A9 and collagen VI, activating CAFs (39). Myeloid cells induced the functional differentiation of fibroblasts into α-smooth muscle actin $(\alpha SMA)^+$ CAFs. In turn, CAFs facilitated the migration of monocytes via CXCL16 secretion (39).

In conclusion, the evidence indicates that CAFs serve a major role in recruiting and pro-tumor polarization of monocytes/macrophages, while TAMs can induce transdifferentiation of CAFs.

3. Blood vessel ECs

The vascular system is a highly branched network lined by ECs that supply tissues with oxygen and nutrients (50). Lack of oxygen is a primary stimulus for angiogenesis (50). During this process, ECs require nutrients and energy to maintain motility and biosynthesis of biomolecules, which are essential for cell duplication (50). Tumor cells produce several factors that induce angiogenesis, including VEGF, the main angiogenesis activator, fibroblast growth factor (FGF), which stimulates EC proliferation and induces neovascularization, angiopoetin 2 (Ang2), responsible for remodeling and stabilization of novel capillary tubes, IL-8, which induces EC proliferation, and MMP2, which is a key factor for basement membrane degradation and ECM remodeling (51). Tumor-associated vessels are structurally abnormal; they are dilated, convoluted and exceptionally permeant due to transcellular holes and the lack of the basement membrane (51,52). Additionally, tumor vessel walls may consist of both endothelial and tumor cells (51-53). Tumor cells recruit ECs from adjacent tissues to invade into the tumor stroma and form neovessels (54). Tumor ECs (TECs) exhibit higher expression levels of proangiogenic factors, such as VEGFR-1, VEGFR-2, VEGFR-3, VEGF-D, angiopoietin receptor TEK receptor tyrosine kinase (Tie2) and angiopoietin 1, compared with normal ECs (53). TECs also express adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), VCAM-1 and E-selectin, which are necessary for interaction with stromal and tumor cells (53). TECs are highly proliferative and self-sustaining (53).

TAMs serve an emerging role in the stimulation of neoangiogenesis (55). IHC analysis of PDAC mice tissue revealed a positive association between M2 subpopulations and microvessel density (MVD) (56). An association between CD31 and CD206, as well as CD31 and CD163, was identified (56). In a lung adenocarcinoma model, M2 macrophages exhibited high microRNA-942 expression, which was associated with lung cancer metastasis (56). M2 macrophage-derived exosomes consistently increased the migration of both tumor cells and HUVECs, and increased the formation of blood vessels *in vitro* and *in vivo* (56).

Macrophages can contribute to tumor angiogenesis by secreting basic FGF, macrophage migration inhibitory factor, platelet-activating factor, prostaglandin E2, osteopontin, adrenomedullin, VEGF-A, epidermal growth factor, placental growth factor, TGF-β, TNFα, IL-1β, IL-8, CCL2, CXCL8 and CXCL12 (57-59). A specific subpopulation of TAMs, which highly expresses immune checkpoint molecule B7 homolog 3 protein, also known as CD276, promoted angiogenesis and induced an immunosuppressive TME in a mouse model of TNBC (60).

TAMs can induce vascular mimicry, a formation of new blood vessels associated with an acquisition of vascular cell features or functions by tumor cells of a non-vascular origin (61). This phenomenon has been described in BC, ovarian cancer, prostate cancer, lung cancer and glioma (61,62). Macrophage-induced vascular mimicry is an IL-6- and cyclooxygenase-2 (COX-2)-dependent process (63). Vascular mimicry density is positively associated with M2 polarization (63). This is explained by the presence of hypoxia in the TME, which promotes macrophage infiltration and vessel formation (63).

ECs recruit monocytes/macrophages. Monocytes and TAMs can be recruited to the perivascular sites by ECs themselves (63). ECs express Ang2, stabilin-1 and C-X3-C motif chemokine ligand 1 (CX3CL1), facilitating the recruitment of macrophages (63). *In vitro*, Tie2+ monocytes differentiated from THP-1 cells actively migrated towards EC-derived Ang2 (Fig. 1B) (64). High Ang2 expression is associated with increased MVD and poor prognosis in several cancer types, including high grade serous ovarian, lung and gastric cancer (63,65,66). Ang2 expression is upregulated in response to anti-VEGF therapy, resulting in treatment failure due to increased TAM infiltration (64). Therefore, anti-VEGF and anti-Ang2 combined therapy can improve the effectiveness of anti-angiogenic therapy (67).

ECs are able to recruit monocytes and TAMs through direct interaction via adhesion molecules (68). Stabilin-1 (Clever-1) is an adhesion molecule that is expressed by ECs and involved in monocyte/macrophage and regulatory T cell (Treg) recruitment (68,69). Macrophages interact with stabilin-1 via the scavenger receptor stabilin-1 (Fig. 1B) (70). Stabilin-1 blockade in mice decreased monocyte binding to tumor vessels by 70%, whereas no inhibition of lymphocyte binding was observed (69).

In a mouse model of ovarian cancer, apoptosis signal-regulating kinase 1, expressed by the vascular endothelium, was responsible for EC activation and TAM recruitment, without affecting lymphocyte recruitment (71). CX3CL1 expression in ECs is involved in C-X3-C motif chemokine receptor 1 (CX3CR1)-dependent recruitment of NK cells, $CD8^+$ T cells and $CX3CR1^+$ non-classical monocytes (63). CX3CL1 exists both in a soluble form, acting as a monocyte chemoattractant, and in a membrane form, promoting CX3CR1 monocyte adhesion (Fig. 1B) (63).

Perivascular macrophages. In perivascular sites, macrophages are present in two forms: Migratory TAMs and perivascular TAMs (PvTAMs) (72). Migratory TAMs are responsible for tumor cell migration, thereby promoting cancer metastasis (73). An *in vitro* migration assay demonstrated that rat mammary adenocarcinoma tumor cells migrating in streams with TAMs, obtained from murine bone marrow, moved at higher speeds, from greater distances towards HUVECs coated onto Sephadex beads compared with tumor cells migrating without TAMs (73). PvTAMs are a specific subpopulation of TAMs residing close to blood vasculature (<15-20 μm), which serves an important role in proangiogenic niche formation and tumor metastasis (74,75). PvTAMs are associated with increased tumor angiogenesis, distant metastasis, poor prognosis and tumor recurrence after chemotherapy (75). PvTAMs are found in structures defined as the TME of metastasis (TMEM), and are responsible for VEGF-A production, resulting in transient vascular leakiness, as well as tumor cell extravasation and distant metastasis (76). The TMEM consists of PvTAMs, invasive tumor cells and ECs (76). In macrophage-depleted mice, the $CD68^+$ TAMs amount returned to normal levels in 4 days, and TAMs were rarely found in tight proximity to $CD31^+$ ECs (72). TAMs accumulated in perivascular sites and developed PvTAM properties after 7 days (72). It has been demonstrated that PvTAMs are originated from $CCR2^+$ monocytes and are recruited to the perivascular space by perivascular CAFs (77). Perivascular CAFs secrete CXCL12, IL-33 and SDF-1α in response to cancer cell activation (63). High infiltration of macrophages in vascular sites can be responsible for pro-metastatic niche formation (78). In a BC model, perivascular macrophages were activated by the cancer cell-derived ECM protein tenascin (TNC) (78). PvTAMs contributed to vascular niche formation via nitric oxide and TNF secretion, activating ECs (78). TNC deficiency decreased metastasis formation *in vivo* (78). In BC, PvTAMs are originated mainly from bone marrow-derived interstitial macrophages, but not from resident macrophages, and have a mixed M1/M2 phenotype (78). Immunofluorescence analysis of metastatic lung tissue demonstrated that $VEGFR1^+F4/80^+$ interstitial macrophages were found in close proximity to $CD31^+$ ECs (78). This suggested their pivotal role in induction of the perivascular niche (78). PvTAMs in mouse mesentery mainly express the M2 marker CD206 (79). Co-culture of M1 and M2 TAMs with ECs demonstrated that M2 TAMs exhibited greater binding to ECs compared with M1 TAMs (79). Immunofluorescence analysis of human glioblastoma multiforme (GBM) tissues revealed that $CD68^+CD206^+$ macrophages were localized in proximity to $CD31^+$ ECs (80). Similarly, in an orthotopic genetic murine GBM model, $F4/80^+CD206^+$ macrophages were localized near ECs (80). GBM-derived ECs induced M2 polarization of macrophages via M-CSF and IL-6 expression (80). IL-33 secreted by pericytes and CAFs promotes M2 polarization and induced MMP9 expression in M2 TAMs facilitating metastasis development via the IL-33-ST2-NF-κB-MMP9-laminin

pathway in a mouse model of pancreatic cancer (Fig. 1B) (46). PvTAMs can serve an immunosuppressive role in perivascular sites (75). They exhibit high secretion of IL-10, which leads to cytotoxic T cells and Treg suppression in perivascular sites (75).

Anticancer therapy causes vascular damage and hypoxia, leading to increased recruitment of myeloid cells, proliferation of ECs and migration of pericytes, which are involved in reconstruction of the vessels in order to restore oxygen levels and provide nutrients for tissue repair (81). The main role in this process is assigned to the Ang-Tie2 pathway (63,75). Tie2 is a receptor that is broadly expressed on vascular ECs and on a subpopulation of macrophages [Tie2-expressing macrophages (TEMs)] (75). Ang2 is a proangiogenic factor and chemokine for TEMs, which also serves a role in regulating the recruitment and/or activation of perivascular macrophages in the TMEM (75). TEMs are a critical subpopulation involved in tumor angiogenesis and are able to adhere to ECs (81). TEMs are essential for vascular anastomosis and formation of new vessels (75,81). Ang2 acts as an inducer of M2 polarization and $Tie2^+$ monocyte recruitment via the upregulation of M2 markers (IL-10 and MRC1) and angiogenesis-related genes (cathepsin B and thymidine phosphorylase) (63).

In a mouse model of fibrosarcoma, tumor relapse after chemotherapy was associated with active vessel reconstruction within 14 days (81). FACS analysis revealed that the proportion of $CD11b^+Tie2^+$ cells was increased compared with that in untreated mice (81). Gene expression profiling of TEMs isolated from mouse mammary tumors revealed increased expression of pro-tumoral genes, including MMP9, VEGFA, CXCL12, toll like receptor 4, neuropilin 1 (NRP1) and platelet derived growth factor (PDGF) subunit B (75). Immunofluorescence analysis of the TMEM obtained from tumor-bearing mice demonstrated that a major fraction of PvTAMs was $Tie2^+/VEGFA^+$ macrophages (82). VEGFA expression in TEMs was elevated compared with that in the adjacent ECs and surrounding tumor tissue (82). TMEM-associated macrophages exhibited expression of the TEM markers MRC1, CD11b and F4/80 (82). Anti-VEGFA treatment decreased the amount of circulating tumor cells and vascular permeability (82). In a mammary mouse model, $Tie2^+$ PvTAMs increased vessel permeability via VEGF-A-dependent destabilization of EC junctions (Fig. 1B) (82).

Another specific subpopulation of PvTAMs exhibit lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) expression, which is considered to be a marker for lymphatic endothelium (77). In a mouse model of BC, LYVE1 was expressed by pro-angiogenic TAMs located near the blood vasculature (77). $LYVE1^+$ PvTAMs formed nest structures in perivascular niches in a CCR5-dependent manner (77). CCR5 depletion led to decreased tumor growth in mice (77). Impaired nest formation resulted in increased chemosensitivity in tumor-bearing mice treated with fluorouracil (77). $LYVE1^+$ PvTAMs are also responsible for αSMA^+ CAFs expansion within the perivascular niche (Fig. 1B) (74). PvTAMs are a major source of PDGFC in the perivascular niche, which is the ligand for PDGF receptor α expressed on αSMA^+ CAFs (74). PDGF blockade led to decreased migration of αSMA^+ CAFs (74). This observation revealed reciprocal interactions between PvTAMs and perivascular CAFs (PvCAFs), since PvCAFs are responsible for monocyte/macrophage recruitment into perivascular sites (77).

4. LECs

Several studies have demonstrated the important role of TAMs in tumor lymphangiogenesis (83-87). TAMs are positively associated with lymph node metastasis and lymphatic vessel density (LVD) in numerous cancer types, including lung cancer, tongue OSCC, pancreatic cancer, gastric cancer, cervical cancer and ovarian cancer (88-95).

VEGF-C is a known lymphangiogenic factor that is most essential for LEC proliferation and lymphatic vessel sprouting (96). TAM expression of VEGF-C is stimulated by different stimuli, such as TNFα/TNF receptor 1 (TNFR1) signaling (97-99), IL-1β secretion by tumor cells (98), and via VEGFR activation by endothelial cell-derived VEGF-C and VEGF-D (Fig. 1B) (99,100).

TAMs induce lymphangiogenesis. In a murine BC model, sphingolipid sphingosine-1-phosphate receptor 1 (S1PR1) overexpression in TAMs promoted pulmonary metastasis and tumor lymphangiogenesis *in vivo* (101). The mechanism included the upregulation of inflammasome-related gene NLR family pyrin domain containing 3 in $S1PR1^+$ TAMs followed by IL-1β production (101). Lung-derived LECs stimulated by IL-1β exhibit increased VEGF-C expression and a high proliferation rate (101). M2 TAMs activated by tumor cell-derived IL-1 promote lymphangiogenesis and lymph node metastasis through the secretion of VEGF-A and VEGF-C (102). S1P protein derived from dying breast tumor cells stimulated the expression of lipocalin 2 (LCN2) in TAMs in mouse mammary tumor virus-polyoma middle tumor-antigen mice (103). LCN2 promoted LEC differentiation and tube formation via activation of VEGF-C expression (103).

TNFα stimulates morphological changes and migration of LECs in a VEGFR-3-dependent manner *in vitro* (97). Interaction of tumor cell-derived TNFα with macrophage TNFR1 triggers VEGF-C secretion by $CD206^+$ TAMs, amplifying lymphangiogenesis and lymphatic metastasis in a murine lung cancer model (97). TNFα and IL-1β secretion by tumor cells stimulated VEGF-C expression in macrophages in a co-culture of a melanoma cell line and murine peritoneal macrophages (98). Macrophages differentiated from monocytes of healthy donors promoted BC cell adhesion to LECs *in vitro* in an IL-1β-dependent manner, suggesting a possible mechanism of lymphatic metastasis (104). It has been suggested that lymph node metastasis associated transcript 1-induced CCL2 expression in bladder cancer cells could promote TAM recruitment, which contributed to lymphangiogenesis and lymphatic metastasis via VEGF-C expression (105).

CM from co-culture of cervical cancer cell lines and macrophages differentiated from THP-1 monocytes stimulated tube formation of human LECs (93). IL-1β, IL-8, VEGF-C and VEGF-A secretion was elevated in CM (93). LECs isolated after a tube formation assay exhibited increased expression levels of VEGFR-3 and podoplanin (PDPN) (93). *In vitro*, CM from TAMs isolated from human epithelial ovarian cancer (EOC) ascites induced LEC proliferation, migration and tube formation (95).

The interaction between TAMs differentiated from human peripheral monocytes and LECs isolated from metastatic lymph nodes of human gastric cancer has been examined in co-culture (106). Expression levels of MMP9 and adhesion molecules (CD44, neural cell adhesion molecule 1, ICAM-1, VCAM-1, E-selectin and osteopontin) were upregulated in capillary-forming LECs (106). TAMs in contact co-culture with LECs exhibited increased expression levels of various cytokines, including IL-1β, IL-6, IL-8, IL-10, IL-12 and IL-18 (106). CXCL2 expression was upregulated, whereas CXCL6 and CXCR2 expression was downregulated in macrophages in contact with LECs (106). In human papillary thyroid carcinoma, both M2 TAMs and cancer cells secrete MMP2 responsible for lymphatic vessel basement membrane degradation that could further lead to lymphatic invasion (107).

Lymphatic macrophage subpopulations. In a murine BC 4T1 model, a specific subpopulation of TAMs was localized near lymphatic vessels (83). TAMs isolated from 4T1 tumors exhibited high expression levels of PDPN, a heavily O-glycosylated small mucin-type transmembrane glycoprotein, and were referred to as PDPN-expressing macrophages (PoEMs) (83). PoEMs interact with LECs via PDPN-galectin 8 interaction and promote tumor lympangiogenesis (83). PDPN knockout in mice led to reduced tumor lymphatic growth and lymphatic metastasis (83). In murine mammary tumors with high SEMA7 expression, an elevated amount of $PDPN^+$ TAMs was observed (84). *In vitro*, treatment of murine macrophages with recombinant SEMA7A increased PDPN expression as well as macrophage motility and adherence to the human dermal LEC monolayer and promoted lymphangiogenesis (84). The adhesion of macrophages to the LEC is mediated by the upregulation of β1 integrin and the interaction of PDPN with its receptor CLEC-2 (Fig. 1B) (84).

IHC staining of human cervical squamous cell carcinoma tissue demonstrated that, under hypoxic conditions, lymphatic vessels were encapsulated by $CD163^+$ TAMs, and the LVD was higher compared with that under normoxic conditions (108). These structures were referred to as lymphatic vessels encapsulated by TAMs (LVEM) (108). Hypoxic TAMs exhibited high IL-10 expression (108). A popliteal lymphatic metastasis mouse model revealed that IL-10 promoted lymphangiogenesis and LVEM formation (108). TAM-derived IL-10 activated LEC production of CCL1, which resulted in further TAM recruitment and sustained LVEM formation and lymphatic metastasis (108).

VEGF-C and VEGF-D-expressing TAMs form small clusters close to lymphatic microvessels and tumor surfaces of human cervical squamous carcinoma (99). All VEGF-C and VEGF-D-expressing TAMs also express VEGFR-3, but in a granular intracellular pattern, and not on the cell surface membrane (99). In human mammary carcinoma, VEGF-C-expressing TAMs have been reported as morphologically different from other macrophages (109). They were generally larger, oval or irregular in shape and had abundant cytoplasm, and were located mainly in peritumoral regions (109). Macrophage numbers and VEGF-C expression were positively associated with LVD and LEC proliferation (109).

TEMs that interact with ECs can also be enriched in lymphovascular regions (85). TEMs express β4 integrin, which interacts with LECs that express laminin-5, a β4 integrin ligand (85). In human BC tissues, TEMs are mainly found in the tumor center and tumor invasive edges and account for 95% of the whole population of $CD14^+$ cells (86). Confocal microscopy analysis of human BC tissue revealed that TEMs expressed the lymphatic markers EGFR-2, VEGFR-3, LYVE1, PDPN and prospero homeobox 1 protein (PROX-1) (86). TEMs exhibited lymphangiogenic activity (86). Injection of human breast tumor-derived TEMs into BC xenograft mice resulted in increased tumor size and vascularization (86). Injection of TEMs into mouse cornea resulted in 800-fold higher LVD compared with that of cornea injected with buffer only (87). Additionally, TEMs are associated with lymph node metastasis in patients with BC (86).

Myeloid cells can contribute to lymphangiogenesis by differentiating into myeloid-LEC progenitors (M-LECP) (110-112). In human BC, M-LECP have been identified as cells co-expressing CD68 and LEC markers (LYVE1, PDPN, VEGFR-3 and PROX-1) (113). Human M-LECPs are usually identified by additional expression of a marker of progenitor cells, such as CD133 (111). The density of M-LECP is associated with LVD and lymphatic metastasis in human BC (113).

$LYVE1^+$ macrophages have been reported to be closely localized to the developing embryonic lymphatic vasculature in mice (114). In some cases, $LYVE1^+$ macrophages were integrated into jugular lymph sacs and dermal lymphatic vessels (114). Reverse transcription-quantitative PCR analysis revealed that $LYVE1^+$ macrophages expressed LYVE1, MRC1, Cd163, Stab1, NRP1, Plxnd1 and Sema6d, which revealed overlap with the gene signature of embryonic and tumor-derived TEMs, suggesting a role of $LYVE1^+$ macrophages in tumor lymphangiogenesis (114).

5. $CD4^+$ T cells

$CD4^+$ lymphocytes include several subsets: T helper 1 (Th1), T helper 2 (Th2), Tregs and follicular helper T cells (115). Tumor-infiltrating $CD4^+$ cells express increased levels of forkhead box P3 (Foxp3; specific for Treg), IL-17 (specific for Th17), and Th2-associated cytokines IL-4 and IL-13 (115). Cytokines secreted by Th1 lead to the classical activation of M1 macrophages, and cytokines secreted by Th2 contribute to the polarization of macrophages towards M2 (116,117). The cytokine profile of Th1 and M1 macrophages is associated with the stimulation of antitumor immunity, in contrast to the cytokine profile of Th2 and M2 macrophages, which are pro-tumoral (117).

Th1. Th1 cytokines affect the polarization of macrophages, and the latter, in turn, can change the differentiation of Th1 and Th2 (117). The predominance of Th1 in the tumor inhibits the maturation of tumor-infiltrating $CD11b^+F4/80^+$ macrophages isolated from mouse liver cancer tissue (117). It has also been suggested that $CD11b^+F4/80^+$ macrophages, rather than Tregs, serve a major role in Th1 suppression (117). Fragile site-associated tumor suppressor $(Fats)^{-/-}$ bone marrow-derived macrophages (BMDMs) isolated from fat-deficient mice stimulated $CD4^+$ T lymphocyte differentiation to the Th1 phenotype *in vitro* (118). *In vivo*, a similar effect was observed when

Fats$^{-/-}$ BMDMs were transferred to mice injected subcutaneously with melanoma cells (118). CD4$^+$ Th1 cytokines activate CD8$^+$ T cells, which display antitumor functions *in vivo* (118). In addition, CD4$^+$ Th1 produce IFN-γ, which promotes additional polarization of macrophages towards the M1 phenotype (Fig. 2) (118). Receptor-interacting serine/threonine protein kinase 1 (RIP1) regulated macrophage differentiation into a pro-tumor phenotype, and RIP1 inhibition in TAMs altered the macrophage phenotype towards M1 in a mouse model of PDAC (119). This induced Th differentiation toward a mixed Th1/Th17 phenotype via a TNFα-dependent mechanism (119). The antitumor effect of gemcitabine in combination with anti-programmed cell death protein 1 (PD-1) antibodies was mediated by activation of Th1 and M1 macrophages in a mouse model of liver metastasis of pancreatic cancer (120).

Th2. Th2, similarly to M2 macrophages, are pro-tumor cells, and associated with tumor progression and metastasis (121,122). Th2 cytokines are involved both in repolarization of macrophages towards M2, and in the suppression of Th1 and activation of tumor growth signaling pathways (121). In a mouse model of spontaneous pancreatic islet carcinogenesis, tumor macrophages with altered polarization after irradiation of the pancreatic region synthesized an increased level of inducible NOS (iNOS; specific for M1 macrophages), which activated the cytokine profile of Th1 and inhibited Th2 cytokines (121). M2 pro-tumor macrophage activity was enhanced by CD4$^+$ cells expressing higher levels of IL-4, IL-13 and IL-10 (specific for Th2) compared with IFNγ (specific for Th1) or IL-17 (specific for Th17) expression in a mouse BC model (Fig. 2) (123). In another study using a mouse model of BC, it was demonstrated that depletion of TAMs in the tumor resulted in a decrease in the number of CD4$^+$ T cells that express Th2 cytokines (122).

Th17. Th17 are a subset of CD4$^+$ T cells that predominantly synthesize IL-17 (115,123). Th17 serve a role in inflammatory and autoimmune diseases, including cancer development (124,125). Th17 in cancer are considered as pro-inflammatory cells with an antitumor function; however, there are conflicting results depending on the type and stage of cancer (125-129). A high level of Th17 is associated with improved survival in patients with ovarian cancer (126). Th17 is positively associated with IFN-γ$^+$CD8$^+$ and IFN-γ$^+$CD4$^+$ T cells but negatively associated with Tregs (126). *In vitro*, TAMs isolated from ovarian tumors induce Th17 predominantly through IL-1β synthesis (Fig. 2). Despite the fact that TAMs serve an important role in the activation of Th17 in the TME, the increase in the amount of Th17 is limited by Tregs (126). A high Treg/Th17 ratio in patients with EOC is associated with increased tumor burden, shorter survival time and cancer metastasis (127). The imbalance in the Treg/Th17 ratio is mediated by exosomes released from human monocyte-derived TAMs (127). Exosomes contain microRNA, which suppresses the synthesis of pro-inflammatory cytokines (IL-6 and TNFα) and the anti-inflammatory cytokine IL-4 by T cells, and promotes the activation of anti-inflammatory cytokines (TGFβ and IL-10) (127). In a mouse intestinal adenoma model, production of IL-17 promoted tumor growth (128). *In vivo*, blockade of IL-1β synthesized by intestinal macrophages reduced the differentiation of Th17 in tumors and reduced the growth of polyps in the intestine (128). Furthermore, in patients with gastric cancer, an increase in Th17 has been observed at an early stage and their decrease has been observed in advanced stages of cancer (129).

Tregs. Tregs belong to the population of CD4$^+$ T lymphocytes, serving a crucial role in adaptive immunity by suppressing immune cells to attack tumor cells (130). In normal non-tumor tissues, Tregs are important regulators of autoimmune reactions (130). Tregs can be recruited to pathological sites, e.g., inflammation and tumor sites (131). This process occurs due to a gradient of C-C motif and C-X-C motif chemokines, which are expressed by abnormal cells (131). Tregs induced by the TME differ from the host ones by exhibiting more pronounced immunosuppressive activity (132). Usually, Tregs are defined as Foxp3$^+$ cells; however, due to inherent heterogeneity they include both immunosuppressive and non-suppressive cells (133). This fact complicates the study of Tregs in various types of cancer and the use of Tregs in anticancer therapy (133).

An increase in the number of TAMs along with Tregs is observed during carcinogenesis and associated with unfavorable prognosis in patients with colorectal (134), lung (135) and ovarian (136) cancer. In the tumor stroma of lung cancer, MARCO-expressing macrophages have an immunosuppressive phenotype, increasing the proliferation of Tregs, which is associated with a negative prognosis (135). In liver cancer in mice, intratumor triggering receptor expressed on myeloid cells 1 (TREM-1)$^+$ macrophages suppress the activity of CD8$^+$ T cells by activating Tregs (137). The inhibition of TREM-1$^+$ macrophages does not eliminate the depletion of CD8$^+$ T cells, indicating that Tregs cause CD8$^+$ T cell dysfunction (137).

Direct interaction of TAMs with Tregs has been demonstrated in numerous studies (137-141). TAMs synthesize a large amount of chemoattractants that facilitate the recruitment of Tregs in tumors (Fig. 2) (138). The key chemokines include CCL17 and CCL22 (138). Therapeutic use of immunomodulator imiquimod reduced the production of CCL22 of CD11b$^+$ TAMs in a melanoma model, resulting in a decrease in the population of Foxp3$^+$ Tregs and an increase in the antitumor response (139). In the hypoxic tumor environment, TREM-1$^+$ macrophages activated the synthesis of the CCL20 ligand, which has an affinity to the CCR6 receptors on Tregs, stimulating Treg recruitment, immunosuppression and tumor growth in a mouse orthotopic liver tumor model (137). Macrophages isolated from malignant pleural effusions of patients with lung cancer exhibit increased CCL22 expression (140). CCL22 induces the recruitment of Tregs, which, through positive feedback, affect macrophages via the production of IL-8 (140). IL-8 increases the production of TGF-β by macrophages, which suppresses the immune system and induces carcinogenesis (140). TAMs from lung (3LL-R) tumor-bearing mice were treated with agonists to liver X receptor (a transcription factor from the nuclear receptor family), which inhibited the secretion of CCL22 and CCL17 from TAMs (141). The macrophages were then stimulated *in vitro* with GM-CSF or IL-4, and a decrease in the synthesis of CCL17 and CCL22 by the M2 macrophages was observed (141). This was associated with a decrease in the number of Tregs in a mouse model of syngeneic Lewis lung carcinoma (LLC) (141).

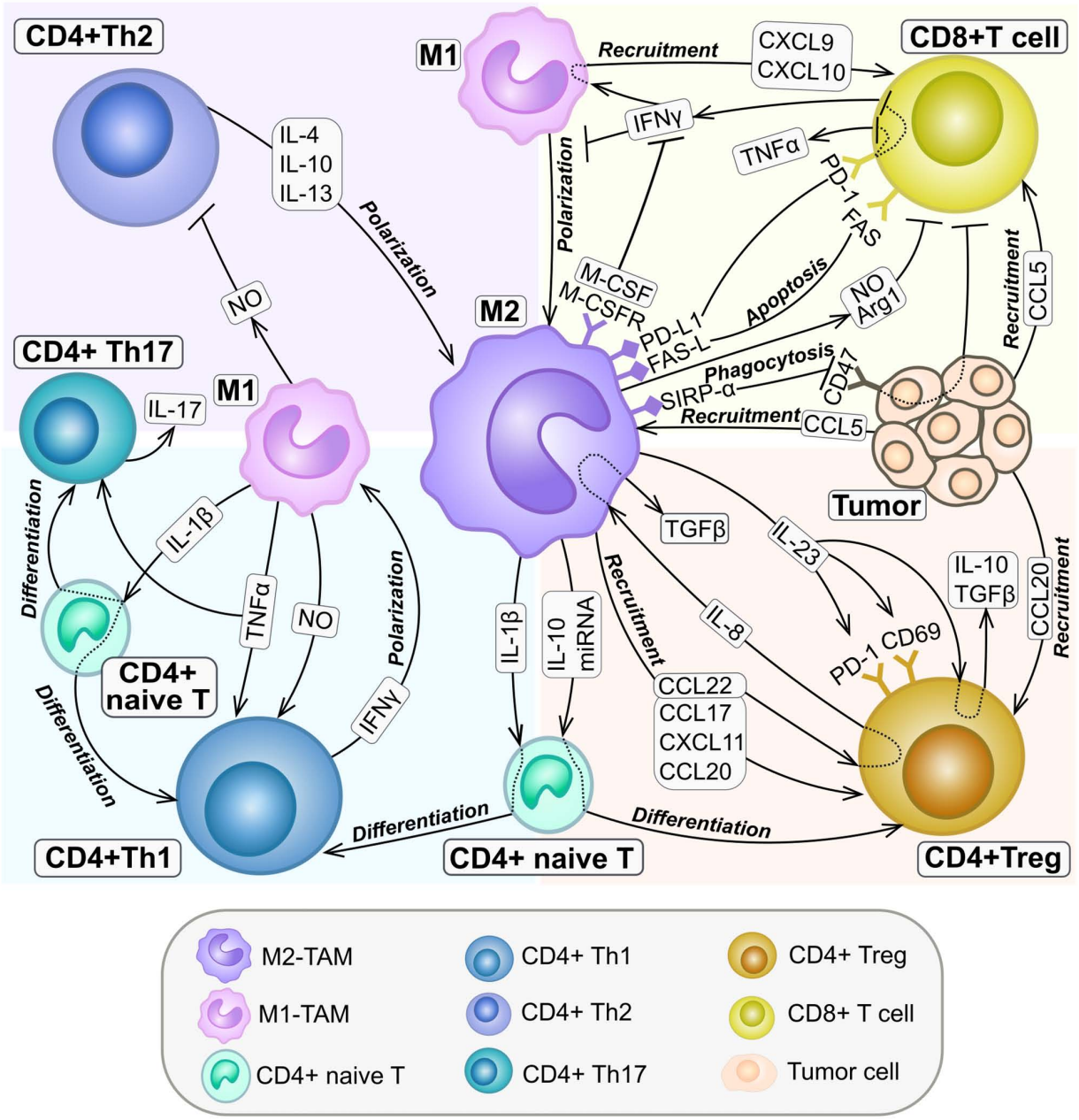

Figure 2. Functional interactions between TAMs and subpopulations of T cells. (Left upper panel) CD4+ Th2 cells promote M2 TAM polarization by expressing M2-polarization markers (IL-4, IL-10 and IL-13). (Right upper panel) M2 TAMs facilitate the immunosuppressive microenvironment by inhibiting the activity of CD8+ T cells. TAMs express PD-L1 and FAS-L, which induce suppression and apoptosis of CD8+ cells, as well as SIRP-α, which activates the 'do not eat me signal' for tumor cells and blocks CD8+ cells. (Left lower panel) M1 macrophages induce the differentiation and activation of pro-inflammatory CD4+ Th1 and CD4+ Th17 cells by expressing diverse pro-inflammatory stimuli (e.g., IL-1β, TNFα and NO). (Right lower panel) TAMs and Tregs reciprocally activate each other. TAMs promote the recruitment and pro-tumor activation of Tregs (via CCL22, CCL17, CXCL11, CCL20 and IL-23), which in turn mediate pro-tumor differentiation of TAMs (e.g., via IL-8). Arg1, arginase 1; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; FAS-L, Fas ligand; M-CSF, macrophage colony-stimulating factor; M-CSFR, M-CSF receptor; miRNA, microRNA; NO, nitric oxide; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SIRP-α, signal regulatory protein α; TAMs, tumor-associated macrophages; Th, T helper; Tregs, regulatory T cells.

In a mouse CRC model, it was found that the homing and migration of Tregs into the tumor depended on the interaction of CCR6 receptor with ligand CCL20 produced by both tumor cells and macrophages (142). Macrophages isolated from the tumor tissue of patients with CRC express high levels of CXCL11, which has an affinity to CXCR3 receptor expressed on Foxp3+IL-17+ Tregs (143). The depletion of macrophages by injection of diphtheria toxin into CD11b diphtheria toxin receptor (CD11b-DTR) mice decreased CCL20 mRNA and protein expression in the CRC tissue, indicating that TAMs are required for release of CCL20 from tumor cells and recruitment of Tregs (Fig. 2) (142). In mice injected with melanoma or colon adenocarcinoma cells, Tregs inhibited the activity of tumor-suppressing CD8+ T cells, which in turn led to an increase in the M2 macrophage phenotype (144).

M2 macrophages derived from human peripheral blood monocytes induce T cell differentiation towards Tregs via IL-10 secretion (136). In patients with EOC, an increased number of TAMs and Tregs, and elevated levels of IL-10 were found in tissue samples, and these were associated with decreased

survival time (136). In a mouse model of ovarian cancer, TAMs secreted exosomes containing microRNAs, which affected the differentiation of $CD4^+$ T cells and increased the number of immunosuppressive Tregs via the STAT3 mechanism (127). *In vitro*, recombinant human IL-23 secreted predominantly by TAMs enhanced the immunosuppressive activity of Tregs, as indicated by increased expression levels of PD-1 and CD69, as well as the secretion of IL-10 and TGFβ (Fig. 2) (145).

Co-cultivation of $CD4^+CD25^-Foxp3^-$ T cells with M2 macrophages stimulated by the supernatant of a laryngeal carcinoma cell line resulted in the change of phenotype of T cells towards $CD4^+CD25^+Foxp3^+$ Tregs (146). In turn, the cultivation of Tregs with tumor cells and human peripheral blood-derived monocytes stimulated the expression of M2-specific markers in monocytes (146). Tregs can express an increased level of ligand-activated aryl hydrocarbon receptor transcription factor (AHR) (147). AHR-expressing Tregs exhibit increased secretion of immunosuppressive factors [IL-10, VEGF and cytotoxic T-lymphocyte associated protein 4 (CTLA-4)] (147). Co-cultivation of Tregs pretreated with kynurenine, which activates AHR, resulted in the predominance of the M2 macrophage phenotype (147).

6. $CD8^+$ T lymphocytes

$CD8^+$ T lymphocytes are one of the key elements of adaptive immunity in infectious and oncological diseases (148,149). $CD8^+$ cells are activated by interacting with major histocompatibility complex-1 molecules and various costimulatory signals and cytokines (148). Cytotoxic $CD8^+$ T cells are able to recognize and directly participate in the destruction of transformed pathogenic carrier cells, in particular tumor cells (149). An increased amount of $CD8^+$ T lymphocytes is associated with improved patient survival (150).

During tumor development, M2-polarized macrophages can affect $CD8^+$ T lymphocytes by suppressing their cytotoxic activity, while M1 TAMs are associated with a higher density of $CD8^+$ T cells (151). The antitumor immune response is mediated by T cell-dependent reprogramming of TAMs towards the M1 phenotype in tumor tissue, which has been demonstrated in a mouse model of LLC (152). Direct contact of $CD8^+$ cells with stromal $CD11c^+CD206^+$ TAMs decreased T cell motility followed by their exhaustion in human lung squamous-cell carcinoma (150). In a mouse model of lung adenocarcinoma, the depletion of tissue-resident macrophages by injection of diphtheria toxin into CD169-DTR mice contributed to the active accumulation of $CD8^+$ T cells in tumor tissues, reducing tumor invasiveness and growth (153). In mouse model of HCC, a CCR2 antagonist inhibited tumor infiltration by macrophages, which was associated with an increase in the number and cytotoxicity of $CD8^+$ T cells and a decrease in tumor size (154).

TAMs regulate the recruitment of $CD8^+$ T cells to the tumor site. $CD8^+$ T lymphocytes are recruited to the tumor by both tumor cells themselves and macrophages (155-158). The chemokines CCL5, CXCL9 and CXCL10 are critical for attracting $CD8^+$ T cells, which has been demonstrated in various cancer types: Breast, colon, ovarian, lung and uterus cancer (155-158). The chemokine receptors CCR5 (specific to CCL5) and CXCR3 (specific to CXCL9) have been found on the surface of T cells (155,156). TAM-derived CCL2 does not directly affect the activity of $CD8^+$ T cells; however, its overexpression reduces the synthesis of CXCL9, one of the key $CD8^+$ T cell chemoattracting cytokines (159). The effect of CCL5 is lower than that of CXCL9 since CXCR3 is predominantly expressed on stem PD-1^{low} $CD8^+$ T cells, while CCR5 is increased on exhausted PD-1^{high} $CD8^+$ T cells (155). The expression of CCL5 and CXCL9 is associated with the expression of CD8A, a cytotoxic T cell glycoprotein involved in intercellular interaction (156). In the tumor tissue of patients with lung cancer, M1 macrophages are the main source of CXCL9 (151). In a mouse model of HCC, high expression of the Sonic hedgehog protein activated the 'hedgehog' pathway associated with an increase in the number of M2 macrophages and a decrease in the expression of the chemoattracting cytokines CXCL9 and CXCL10, followed by the inhibition of $CD8^+$ T cell migration (158).

CCL5 is predominantly expressed by tumor cells and stimulates macrophages to synthesize CXCL9 (155). Tumor-infiltrating lymphocytes express IFNγ, which in turn stimulates CXCL9 synthesis in macrophages (Fig. 2) (156). In a mouse model of HCC, CXCL10 together with CXCL9 affected the cytotoxic index of $CD8^+$ T cells (158). The decrease in the expression of these cytokines was associated with an increase in tumor infiltration by $CD163^+$ TAMs (158).

TAMs induce apoptosis in $CD8^+$ cells. In a mouse liver metastasis model, hepatic monocyte-derived $CD11b^+F4/80^+$ macrophages could induce immunosuppression of $CD8^+$ T lymphocytes via Fas-Fas ligand (FasL) interaction (160). Binding of FasL, expressed by macrophages, to Fas on the surface of $CD8^+$ T cells leads to the activation of the apoptotic pathways in $CD8^+$ T cells (160). In mouse colon carcinoma, fibrosarcoma, methylcholanthrene-induced sarcoma and lymphoma models, $F4/80^+$ macrophages isolated from tumor tissue had higher levels of iNOS and arginase I inhibited T cell activity and activated their apoptosis (161).

TAMs suppress the cytotoxicity of $CD8^+$ T cells. M-CSF affects the proliferation and differentiation of macrophages via M-CSFR receptor (162). The M-CSF/M-CSFR axis is able to suppress the cytotoxicity of $CD8^+$ T cells (163). The use of antibodies blocking M-CSFR reduced the infiltration of TAMs and increased $CD8^+$ T cell activation in a mouse colon carcinoma model (163). A decrease in M-CSF expression increases the expression of IFN-γ by T cells (164). The IFNγ-IFNγ receptor 1 axis between $CD8^+$ T cells and TAMs reduces macrophage polarization into the M2 phenotype (Fig. 2) (144).

In subcutaneous mouse breast and colon tumor models, monoacylglycerol lipase deficiency resulted in lipid accumulation in TAMs and their polarization into M2 phenotype, resulting in reduced $CD8^+$ T cell activity (165). The decreased expression of COX-2 increased the number of TAMs, which was associated with an increase in $CD8^+$ T cell infiltration and improved survival of mice in a mammary carcinoma model (166). Blockage of COX-2 reduced the expression of macrophage pro-tumor markers (arginase-1, IL-10 and iNOS), which reversed the suppression of tumor-infiltrating lymphocytes (166).

P65 is one of the proteins of the NF-κB family, and its activation leads to increased expression of T-cell inhibitory molecule B7x (also referred to as B7-H4 or B7S1) on the TAM surface and a decrease in IL-10 in TAMs, suppressing the activation of tumor-infiltrating $CD8^+$ T lymphocytes during lung tumorigenesis (167). However, inactivation of macrophage PI(3) kinase, which is an inhibitor of NF-κB, promoted $CD8^+$ T cell activation in tumors in mouse models of implanted human papillomavirus $(HPV)^+$ and HPV^- head and neck squamous cell, lung and breast carcinoma (168).

Antigen presentation to $CD8^+$ T lymphocytes. Macrophages and DCs are antigen-presenting cells (169). The ability of macrophages to present antigens to T lymphocytes can lead to exhaustion of T cells; however, this property can be used in therapy to stimulate T cell cytotoxicity (170-172). Interferon regulatory factor 8, as a transcription factor, controls DC-like properties in TAMs and induces antigen acquisition and presentation by macrophages (170). Furthermore, macrophages presenting tumor cell antigens depleted $CD8^+$ T cells in a mouse BC model (170). Macrophages express signal regulatory protein α interacting with the CD47 'do not eat me' signal on tumor cells, which leads to the termination of phagocytosis of tumor cells by TAMs (Fig. 2) (171). The use of anti-CD47 antibodies promotes efficient phagocytosis of cancer cells, antigen presentation to $CD8^+$ T cells and stimulation of $CD8^+$ T cell activity by TAMs *in vivo* and *in vitro* (171). DCs interacting with macrophages also regulate the cytotoxic response in $CD8^+$ T cells (172). In BC, macrophages produce IL-10, which suppresses the production of IL-12 by DCs (172). IL-12 is required for the cytotoxic response of $CD8^+$ T cells but its blockade inhibits the T cell response (172).

Interaction between macrophages and $CD8^+$ T cells via programmed death-ligand 1 (PD-L1)/PD-1. Inside the tumor, TAMs and DCs are the main sources of PD-L1 (173,174), while $CD8^+$ T cells express the PD-1 receptor (150,159). The PD-L1/PD-1 interaction axis inhibits the cytotoxic activity of T lymphocytes (173), which reduces the effectiveness of the use of immune checkpoint blockade agents (155). An increased amount of progranulin, which is expressed in a number of tumors, could lead to the upregulation of PD-L1 in macrophages, followed by their polarization towards the M2 phenotype and suppression of the activity of $CD8^+$ T cells in a mouse BC model (173).

Blockade of PD-1 enhances $CD8^+$ T cell activity via increased production of IFN-γ and TNFα (Fig. 2) (174,175). One of the key markers of the anti-PD-1-induced antitumor response is CXCL9, which is a chemoattracting and activating cytokine for $CD8^+$ T cells (175). In tumor samples from patients with recurrent glioblastoma who received neoadjuvant anti-PD-1 therapy, the possibility of enhancing the interaction between the $CD8^+$ receptor CXCR3 and CXCL9/10 was confirmed using a bioinformatic interactome analysis based on single-cell data (176).

Several studies have demonstrated that anti-PD-1 therapy combined with macrophage inhibitors is more efficient in terms of increasing the immune response and suppression of TAM activity compared with mono-immunotherapy (150,159,163). In mouse models of glioblastoma and ovarian cancer, anti-PD-1 therapy in combination with the blockade of LIF (anti-IL-6 class cytokine that affects cell proliferation) increased survival and promoted tumor regression more effectively than mono-therapy (159). The use of a M-CSF inhibitor in combination with anti-PD-1 therapy increased the migration and infiltration of $CD8^+$ T cells in a mouse BC model (150). Another macrophage inhibitor, lenvatinib, in combination with an anti-PD-1 agent, increased the percentage of $CD8^+$ T cells, followed by a decrease in tumor growth and vascular invasion in a mouse colon carcinoma model (163).

7. B cells

B cells are important components of the immune defense against cancer. Opinions on the role of B cells in tumor carcinogenesis vary based on collected evidence on both pro-tumor and antitumor activity of B cells (177-181). For example, pro-tumor activity of B cells can be mediated by the recruitment of TAMs via immune complexes and Fcγ receptor interactions, whereas the beneficial effect of B cells is related to the activation of antitumor immunity through antigen presentation or direct cytotoxicity towards tumor cells via secretion of granzyme B and TNF-related apoptosis-inducing ligand (179,181). The complexity of studying B cells in carcinogenesis is associated with difficulties in isolating and purifying B cells (180). Furthermore, there are several functional phenotypes depending on the TME (177).

Evidence indicates that B cells and macrophages can have a common bipotential progenitor in bone marrow (182). In the early stages of development, pre-B cells co-expressing B-cell and myeloid markers can differentiate into macrophages, due to the receptors of B cells not being rearranged, which indicates the plasticity of B cells (182).

When studying the cross-talk of Bruton's tyrosine kinase (BTK)-expressing immune cells in a mouse model of pancreatic carcinoma and *in vitro*, the important role of the interaction between B cells and macrophages was noted (179). Activation of macrophage Fc receptors initiates BTK signaling via the PI3K-dependent signaling pathway and activates macrophage repolarization towards the M2 phenotype and promotes tumor development (179). Tumor B cells enhance the change in macrophage phenotype in favor of type 2 by influencing macrophage Fc receptors (179).

The antitumor or pro-tumor function of B cells can be mediated by antibody synthesis (179). B-cell-expressed IgG binds to macrophages and induces macrophage-mediated phagocytosis of tumor cells through antibody-dependent cellular cytotoxicity in breast, pancreatic and gastric cancer but not in clear cell renal cell cancer, squamous cell carcinoma and non-small cell lung cancer (179). IgG secretion by B cells is associated with poor prognosis (183).

Despite these findings, to the best of our knowledge, the direct mechanisms of the interaction of TAMs and B cells in the TME remain unknown (Fig. 3).

8. NK cells

NK cells are part of the innate immune system (184). Together with macrophages, they are among the first cells recruited to the site of infection (185). NK cells have cytotoxic activity

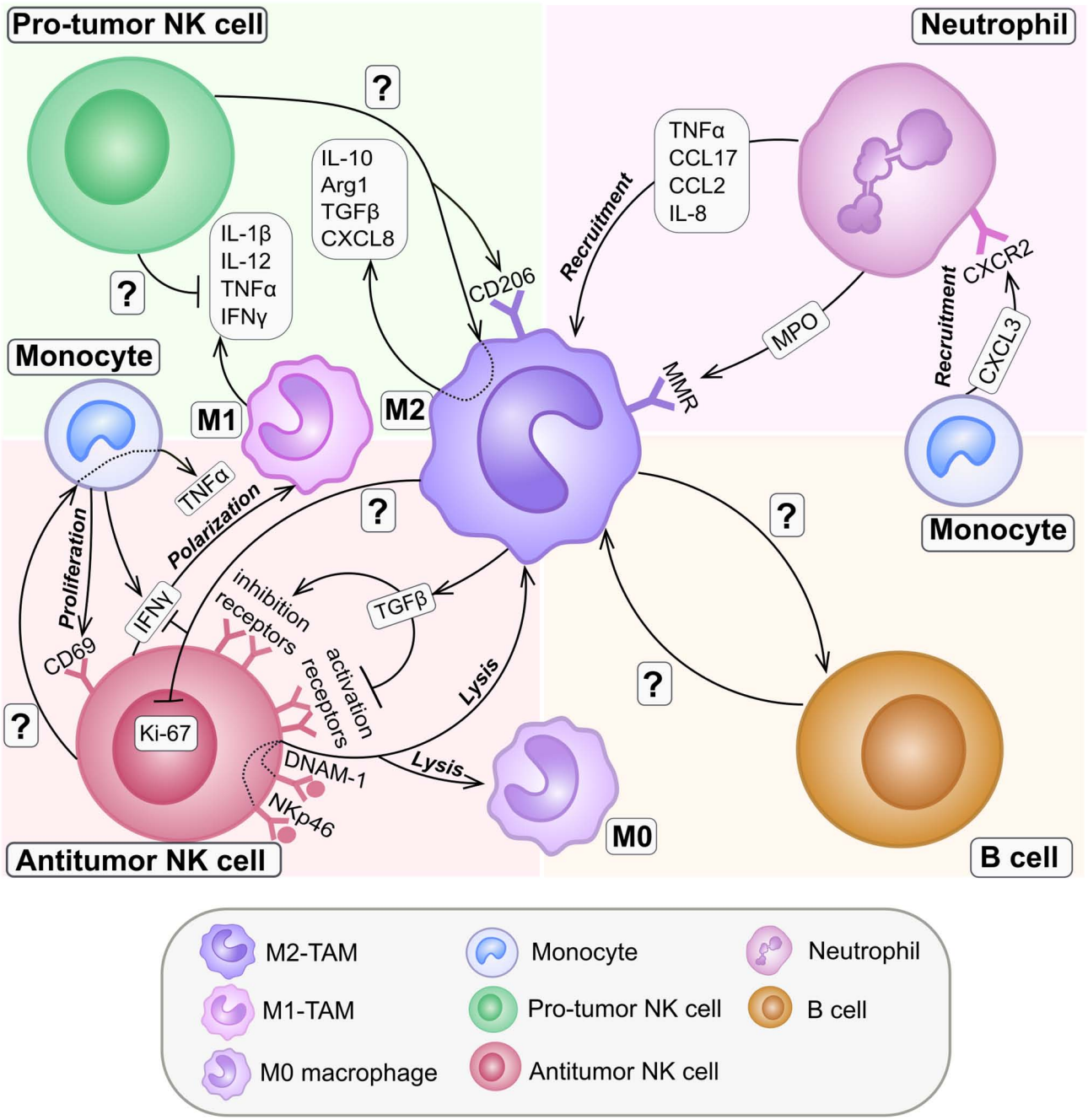

Figure 3. Functional interactions between TAMs and other immune cells. (Left upper and lower panels) M1 and M2 TAMs exist in reciprocal cross-talk with NK cells. TAMs are able to regulate the activity of antitumor NK cells through activation or inhibition of NK cell receptors. Activation receptors include NKp30, NKG2D and CD27, and inhibition receptors include CD56, CD9 and CD107a. Antitumor NK cells induce M1 polarization and lysing of M2 TAMs. Pro-tumor NK cells promote M2 polarization of TAMs through unknown mechanisms. (Right upper panel) M2 TAMs are recruited to the tumor by neutrophil-derived factors. (Right lower panel) TAMs can interact with B cells; however, to the best of our knowledge, the mechanisms of these interactions remain unknown. Arg1, arginase 1; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor; DNAM-1, DNAX accessory molecule-1; MMR, macrophage mannose receptor; MPO, myeloperoxidase; NK, natural killer; NKp46, natural cytotoxicity receptors 46; TAMs, tumor-associated macrophages.

against infected or transformed cells that helps to kill tumor cells even when the latter do not express major histocompatibility complex class 1 or its expression is reduced (184,186).

In turn, the TME can reduce the cytotoxic activity of NK cells against tumor cells and inhibit the expression of NK receptors responsible for the recognition and killing of tumor cells (187,188). Macrophages are able to change the expression of activating and inhibiting NK cell receptors (187,189-192). M2 TAMs suppress the cytotoxic activity of NK cells (193). Co-culture of NK cells isolated from the murine spleen and peritoneal or bone marrow M2 macrophages revealed suppression of the expression of CD27 activation marker, while co-culture with M1-like macrophages under similar conditions did not suppress the cytotoxicity of NK cells (187).

In patients with stage II and III esophageal cancer, high tumor infiltration by TAMs and low infiltration by NK cells are associated with poor prognosis (194). Macrophages/monocytes isolated from autologous nontumor and tumor tissues of

patients with gastric cancer cultured together with allogeneic peripheral blood NK cells reduced the expression of IFNγ and TNFα in NK cells co-cultured with tumor-associated monocytes/macrophages (190). In addition, a decrease in the expression of cell proliferation marker Ki-67 by NK cells was observed, which together indicated a decrease in the functional activity of NK cells (190). MARCO-expressing TAMs exhibited immunosuppressive properties against NK cells in a mouse melanoma model (195).

One of the mechanisms by which TAMs interact with NK cells is the secretion of TGFβ1 by macrophages/monocytes, which, in a gastric cancer *ex vivo* model, induced functional impairment of NK cells (190). *In vitro*, TGFβ1 affected the expression of activation receptors, natural cytotoxicity triggering receptor 3 (NKp30) and killer cell lectin like receptor K1 (NKG2D), in NK cells isolated from human peripheral blood mononuclear cells (191). A decrease in the expression of NKp30 and NKG2D suppresses the cytotoxic activity of NK cells against a melanoma cell line (191). In peripheral blood NK cells from patients with prostate cancer, TGFβ is able to increase the surface expression of CD56 and CD9 receptors, which decrease the cytotoxic activity of NK cells, and reduce the expression of NK cell activation receptor NKG2D *in vitro* (192). Similarly, in a mouse lymphoma model, M2-like macrophages suppressed the activity of NK cells by secreting TGF-β, which decreased the expression of degranulation factor CD107a by NK cells (187).

Activation of the natural cytotoxicity receptors 46 and DNAX accessory molecule-1 receptors on NK cells results in the lysis of human peripheral blood monocyte-derived M2 macrophages (196,197). Resting NK cells do not exhibit cytolytic activity against macrophages; however, activated NK cells lyse M0 and M2 macrophages (Fig. 3) (197). In co-culture, monocytes obtained from peripheral blood and synovial fluid of patients with inflammatory arthritis could activate NK cells via increased expression of the proliferation marker CD69 and elevated secretion of IFN-γ by NK cells (198). Additionally, NK cells increased the secretion of the pro-inflammatory cytokine TNFα by monocytes (198). IFN-γ secreted by NK cells altered macrophage polarization to an M1 phenotype in a mouse model of sarcoma (199).

In addition to antitumor activity, NK cells can be involved in pro-tumor polarization of TAMs (192). Co-cultivation of human MDMs with NK cells isolated from the blood of patients with prostate cancer revealed a decrease in the expression of M1-like factors (IL-12, TNFα, IFNγ and IL-1β) and an increase in the expression of M2-like factors (CD206, Arg1, IL-10, TGFβ and CXCL8) (Fig. 3) (192).

9. Neutrophils

Neutrophils are immune cells that serve an important role in the development of inflammation (200). Similar to macrophages, neutrophils are classified into N1 and N2: Antitumor and pro-tumor, respectively (201). Activated neutrophils are able to secrete IL-8 and TNFα, which recruit macrophages into the inflammation site (202). The interaction of macrophages with neutrophils likely occurs through the macrophage mannose receptor highly expressed by macrophages and through neutrophil-secreted myeloperoxidase (Fig. 3) (202). Neutrophil-derived CCL2 and CCL17 affected the migration of macrophages into the tumor in a mouse model of HCC (203). In another study, granulocyte colony-stimulating factor receptor-depleted mice had neutropenia, which was associated with increased tumor progression, compared with wild-type mice in a 3-methylcholanthrene-induced sarcoma model (200). An increase in neutropenia was associated with an increase in the expression of the M2 macrophage genes and was associated with poor prognosis (200). Tumor monocytes derived from patients with non-small cell lung cancer are also able to affect the migration of neutrophils via CXCL3, a ligand for the neutrophil receptor CXCR2 (204).

The co-cultivation of tumor cells simultaneously with macrophages and neutrophils resulted in increased proliferation, invasion and colony formation of tumor cells compared with those of tumor cells cultured with a monoculture of macrophages or neutrophils (205). The data were confirmed in three intrahepatic cholangiocarcinoma cell lines: SG231, RBE and HuCCT1 (205).

10. Combined therapeutic approaches based on TAMs and other cells of the TME

Anti-CAF and anti-TAM combined therapy can be a promising option in antitumor immunotherapy (206-208). In murine models of lung cancer, melanoma and colon cancer, immune modifying poly(lactic-co-glycolic acid) nanoparticles (referred to as ONP-302) were used to target CAFs and TAMs (209). The authors of the previous study suggested that ONP-302 was able to alter the polarization of TAMs and MDSCs from pro-tumor to antitumor state. The same mechanism was described for CAFs (209).

Combined anti-VEGFA/Ang2 and anti-CD40 therapy led to vascular pruning and normalization of blood vessels, myeloid cell activation, including M1-like TAM skewing in colon cancer, melanoma and BC models *in vivo* (210). Tie2 expression in TAMs and ECs could be another possible target for combined therapy (211). The Tie2-targeting antitumor hydrophobic peptide T4 was modified to generate self-assembly nanoparticles (P-T4) (211). T4 interacted with Tie2 and inhibited signal transduction, cell migration and angiogenesis (211). P-T4 exerted an inhibitory effect on the viability of Tie2-positive RAW264.7 cells and ECs *in vitro*, and reduced vessel density and distant metastasis formation *in vivo* (211). SAR131675 is a dose-dependent selective inhibitor of VEGFR-3 tyrosine kinase activity (212). In a murine BC model, SAR131675 inhibited primary human lymphatic cells *in vitro* and reduced the migration of cancer cells into lymph nodes and lungs in tumor-bearing mice (212). IHC staining of tumor tissues isolated from murine mammary tumors revealed reduced macrophage infiltration, suggesting that reduction of tumor growth might be associated with decreased TAM infiltration (212).

The use of immunotherapy against both macrophages and Tregs can help improve the prognosis of patients with cancer, since there is a positive association between TAMs and Tregs (146). Mono-immunotherapy against TAMs or Tregs was not efficient in a colon cancer *in vivo* model (213). Deletion of the *CSF1* gene in colon adenocarcinoma cells (MC38 line) led to a decrease in the population of M2 macrophages *in vivo* but

an increase in the number of Foxp3$^+$ Tregs followed by slight tumor growth in mice (213). In turn, depletion of Foxp3$^+$ Tregs in tumor-bearing mice upon administration of diphtheria toxin resulted in an increase in colony-stimulating factor 1 receptor (CSF1R)$^+$ TAMs and slight tumor growth (213). In a mouse model of head and neck cancer, radiotherapy in combination with anti-CD25 depletion of Tregs resulted in reduced tumor growth and an increase in the M1/M2 ratio (214). Notably, the use of radiotherapy alone led to an increase in the proportion of M2 macrophages (214).

In a mouse pancreatic cancer model, a CSF1R blockade and PD-1/CTLA-4 antagonist combination therapy reduced tumor progression more effectively than single therapy (215). In a mouse melanoma model, the use of the CSF1R inhibitor in combination with the transfer of naive CD8$^+$ T cells activated with a synthetic peptide vaccine resulted in a reduction in tumor growth (216). The use of regorafenib (an inhibitor of protein kinases, including VEGFR, CSF1R and others) in combination with anti-PD1 therapy inhibited tumor development due to a decrease in M2 macrophages and Tregs, and an increase in CD8$^+$ T cells and M1 macrophages inside the tumor in a mouse colon cancer model (217). In mice with gastrointestinal stromal tumors, anti-CD40 therapy activated TAMs against tumor cells and recruited more monocytes from the bone marrow (218). Additionally, the efficacy of treatment with the combination of anti-CD40 with imatinib (affects the KIT mutation characteristic of this type of cancer) was completely dependent on the presence of macrophages in the tumor and partially on the presence of CD8$^+$ T cells (218).

Various interleukins are widely used in cancer immunotherapy (195,219,220). Pro-inflammatory cytokines such as IL-12, IL-15 and IL-18 are involved in the regulation of activity, proliferation and cytotoxicity of NK cells and other cells of myeloid origin (221). In a mouse model of melanoma, combination therapy with a DNA vaccine based on endoglin and IL-12 gene therapy was applied (220). Combination therapy resulted in the re-polarization of TAMs from M2 phenotype to M1 phenotype, which was associated with an increase in the number of NK cells by >3 times compared with the control group (220). Treatment of mouse macrophages with polyinosinic:polycytidylic acid (stimulator of type I IFN) revealed an increase in the synthesis of ligands for NKG2D NK cell receptor, which increased NK cell cytotoxic activity against lymphoma tumor cells *in vitro* (222). In a mouse model of melanoma treated with AIP therapy that included a combination of an antitumor antibody ('A'), an extended half-life IL-2 ('I'), and an anti-PD-1 ('P'), the therapeutic effect was dependent on the presence of NK cells and macrophages in the tumor, which, under the influence of therapy, were reprogrammed into an antitumor phenotype (223).

During the development of methods of therapy for pancreatic adenocarcinoma, it was revealed that the simultaneous inhibition of CCR2$^+$ macrophages and CXCR2$^+$ neutrophils enhanced antitumor immunity (224).

11. Conclusions

The present review demonstrates the broad network of TAM interactions with stromal and immune components of the TME via cell-to-cell and extracellular mechanisms. The collected data indicate that CAFs are an essential source in the TME for monocyte recruitment and M2 TAM polarization. Despite the involvement of TAMs in ECM remodeling, they have a minor impact on CAF activity, only inducing MMT. After polarization, TAMs are able to interact with naive fibroblasts and promote their differentiation into functional CAFs, creating a self-sustaining loop.

TAMs are also involved in tumor angiogenesis and lympangiogenesis via reciprocal interaction with blood ECs and LECs, respectively. ECs are able to recruit TAMs to the tumor site, where the latter are differentiated toward perivascular and lymphatic vessel-associated macrophage subpopulations promoting proliferation and migration of ECs, as well as growth of novel vessels.

The crosstalk between TAMs and other immune cells can be crucial for the balance between the pro-tumor and anti-tumor immune state and regulation of immunosuppression.

Finally, combined targeting of TAMs and other cells of the TME can be decisive to achieve advanced efficacy of anticancer treatment. Most studies have focused on targeting stromal or immune cells alone (225-228). However, it is critical to not exclude cell-cell crosstalk within the TME and future studies should aim to identify possible targets in these interactions in order to increase the effectiveness of antitumor therapy. Combined therapeutic approaches should be considered to prevent distant metastasis and reduce the risk of tumor recurrence.

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Authors' contributions

The research project was designed, organized and reviewed by IL, and reviewed and critiqued by JK. AK, TS, OK and IL performed the literature research, wrote the first draft of manuscript and prepared the figures. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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