Chapter 14
The Role of Inflammatory Cells in Tumor Angiogenesis

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Abstract Tumor growth depends on angiogenesis. The complex tissue environment surrounding tumor cells, which is composed of a variety of resident and infiltrating host cells, secreted factors and extracellular matrix proteins, influences tumor angiogenesis and progression. Moreover, the tumor microenvironment contributes to determining therapeutic responses and resistance to therapy. The ability to block tumor resistance is related to the understanding of the cellular and molecular pathways activated in the tumor microenvironment. Novel emerging targeted therapeutic strategies are based on the combination of different antitumor approaches with the aim of resolving refractory tumors and improving cancer treatment efficiency.

14.1 Tumor Angiogenesis

Healthy and pathologic tissue homeostasis requires an adequate supply of oxygen and nutrients that is connected to efficient development of the vascular system. Additionally, tumor cells to survive and proliferate need oxygen and nutrients and consequently the closeness to blood vessels. Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels (Carmeliet and Jain 2011). Generally, tumor development is an angiogenesis-dependent process, and the angiogenetic process depends on the temporal coordination of factors and related pathways needed for the establishment of stable channels to provide a supply to tumor cells (Weis and Cheresh 2011). It has been well established that during cancer progression, the interactions between tumor cells and inflammatory cells are closely associated with each other and with angiogenesis (Wang et al. 2019a).

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I. Kovalszky et al. (eds.), *The Extracellular Matrix and the Tumor Microenvironment*, Biology of Extracellular Matrix 11,
https://doi.org/10.1007/978-3-030-99708-3_14

The growth of solid tumor mass, its progression and the metastatic process, how it is widely described, are strongly influenced by angiogenesis (Folkman 1971). In 1966, Warren and collaborators implanted melanoma nodules in experimental animals and observed a rapid vessel sprout toward the mass, the formation of new capillaries, their penetration into the tumor, and the establishment of blood flow. This phenomenon was more evident during tumor growth than in inflammation processes (Warren and Shubik 1966). Research conducted by Folkman showed that without appropriate vascularization and therefore oxygen and nutrient supply, a tumor can grow limitedly to a size of a few millimeters and a cell content of approximately a few thousand cells (Folkman 1971; Nishida et al. 2006). Under these conditions, tumors induce a process recognized as an angiogenic switch in which tumor cells acquire angiogenic properties, leading to the transition from a quiescent to active endothelium and consequently the vascularization of the growing cell mass (Baeriswyl and Christofori 2009; Ribatti et al. 2007). In tumor murine models, this switch coincides with malignant transition of the growing mass and is needed for malignant tumor progression (Lin et al. 2006; Folkman et al. 1989). It became evident that some soluble factors released by the tumor induced the activation of angiogenesis. Folkman hypothesized that until the appropriate blood flow is created, the tumor mass stops its growth and enters a dormant state (Folkman et al. 1971). On this basis, in the last 50 years, research on mechanisms related to tumor angiogenesis has intensified to discover molecules usable as new targets in anticancer therapy. Tumor angiogenesis is a multiphasic process initiated directly by the tumor when it reaches a size that makes it hypoxic, which further leads to cancer development.

14.2 Tumor Microenvironment

It is well known that tumor cells develop in a complex tissue environment, the so-called tumor microenvironment (TME), which includes cancer cells, stromal cells, blood vessels, nerve fibers, extracellular matrix, and acellular components. The TME is involved in tumor initiation as well as during tumor progression and metastasis; furthermore, it also has important effects on therapeutic efficacy (Tamma et al. 2019a). It is believed that although cancer initiation is due to the acquisition of oncogenic mutations in cells, its progression depends on the surrounding cells that are recruited and subsequently release many cytokines and chemokines (Tysnes and Bjerkvig 2007). In 1863, Rudolf Virchow postulated the crosstalk between inflammation and cancer (Virchow 1989), and 20 years after Stephen Paget illustrated the "seed and soil" theory assuming that the choice of the target organ depends on the interactions between metastatic tumor cells (the "seed") and their organ microenvironment (the "soil") (Paget 1989). One hundred years later, Hanahan and Weinberg expanded from six to ten hallmarks of cancer and recognized the important role of the TME in cancer development (Hanahan and Weinberg 2011). The main cytokines and chemokines secreted by cells of the TME are involved in the regulation of

angiogenesis, including proangiogenic factors, such as the vascular endothelial growth factor (VEGF) family, fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), angiopoietins (Ang), and hypoxia-inducible factor (HIF), and angiostatic factors, such as angiostatin, endostatin, platelet factor 4 (PF4), and thrombospondin-1 (TSP1) (Ucuzian et al. 2010).

14.3 Pro-Angiogenic Factors

VEGF The human VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) originating from different genes (Melincovici et al. 2018). The VEGF family exerts its function by binding three transmembrane tyrosine kinase receptors (RTKs), VEGFR-1 (FLT1), VEGFR-2 (KDR, FLK1), and VEGFR-3 (FLT4). VEGFR-1 is expressed in monocytes, macrophages, hematopoietic stem cells, vascular smooth cells, and leukemic cells. VEGFR-2 is expressed in vascular endothelial cells, endothelial progenitor cells, and megakaryocytes, whereas VEGFR-3 is expressed in lymphatic endothelial cells. VEGFs can also interact with other proteins, integrins, cadherins, heparan sulfate proteoglycans, and with the coreceptors neuropilin-1 and -2 (NRP-1 and NRP-2), which enhance VEGFR-1 and VEGFR-2 action (Stuttfeld and Ballmer-Hofer 2009). VEGF-A is the main component of the VEGF family and is produced by endothelial and vascular smooth muscle cells, activated platelets, fibroblasts, lymphocytes, macrophages, and tumor cells. It is considered a crucial angiogenic stimulator involved in numerous pleiotropic effects, including the proliferation and inhibition of apoptosis of vascular endothelial cells (Ferrara and Davis-Smyth 1997; Gerber et al. 1998), permeability, chemotaxis and activation of monocytes and hematopoietic stem cells, and exerts neurotrophic and neuroprotective action (Storkebaum and Carmeliet 2004). Through alternative splicing, the VEGF-A transcript produces several isoforms with proangiogenic or antiangiogenic activities, including VEGF-A_{121}, VEGF-A_{145}, VEGF-A_{165}, VEGF-A_{189}, and VEGF-A_{206} (Yang et al. 2018a; Logue et al. 2016; Dehghani et al. 2018). $VEGFA_{165}$ is the most important both quantitatively and qualitatively. VEGF-B is involved in pulmonary angiogenesis after chronic hypoxia and has been found in cardiac and skeletal muscle. VEGF-C and VEGF-D are important lymphangiogenesis regulators (Rauniyar et al. 2018; Stacker and Achen 2018). PlGF, discovered in the human placenta, is highly expressed in trophoblast cells (Hang et al. 2013) and has also been found in the thyroid, lungs, heart, and skeletal muscle (Maglione et al. 1991). It includes four different subtypes that bind VEGFR-1, and the PlGF isoform also binds NRP-1 and NRP-2. PlGF regulates the growth, migration, and survival of endothelial cells directly through VEGFR-1 or indirectly through VEGFR-2/VEGF-A-mediated activation or formation of a PlGF/VEGF-A heterodimer (Autiero et al. 2003).

Fibroblast Growth Factors (FGFs) The human FGF family includes 22 members involved in the regulation of endothelial cell differentiation, proliferation, migration,

survival, and vessel maturation (Yun et al. 2010). FGF-1 and FGF-2, the first known as acid FGF and the latter as basic FGF, mostly mediate the angiogenic response (Motomura et al. 2008). FGF receptors (FGFRs) belong to the RTK superfamily. Upon activation, they undergo dimerization and internalization and initiate large-scale tyrosine phosphorylation responses and signaling cascades activating the Ras/MAP-kinase pathway (Mathew et al. 2016).

Platelet-Derived Growth Factor (PDGF) The PDGF family comprises four PDGF homodimers, namely, PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD, and one heterodimer, PDGF-AB (Fredriksson et al. 2004). PDGF was originally isolated from platelets, but it has been expressed by numerous other cell types, including epithelial and endothelial cells. PDGF receptors (PDGFRs) belong to the family of RTKs and include PDGFRα and PDGFRβ, which are encoded by two different genes (Gao et al. 2018). These receptors are expressed by fibroblasts, pericytes, vascular smooth muscle cells, monocytes, macrophages, lymphocytes, and mast cells and stimulate their proliferation and motility. PDGFs participate in vascular development by acting on the proliferation and survival of vascular mural cells (Olson and Soriano 2011).

Angiopoietins (Angs) The Ang protein family includes four members: Ang-1, Ang-2, Ang-3, and Ang-4 (Lee et al. 2004); the first two are the major members involved in vasculogenesis and vascular repair (Akwii et al. 2019). Angs bind to two receptors belonging to the family of RTKs named Tie1 and Tie2. Tie2 is expressed by endothelial and myeloid cells (Patan 1998). Tie1 is an orphan poorly characterized receptor that seems to be involved in the modulation of Ang/Tie-2 through the formation of heterodimers with Tie-2 (Eklund et al. 2017). Ang-1 is expressed by both mural cells and other nonvascular stromal and tumor cells. It is involved in the regulation of vessel stabilization during embryonic development, vessel remodeling, and maintenance of the normal vasculature (Brindle et al. 2006). Ang-2 is produced by the VEGF-stimulated endothelium, hypoxia, and shear stress, promoting blood vessel wall destabilization through competitive inhibition of Tie-2 and integrin activation. Furthermore, Ang-2 stimulates pericyte detachment, permeability, vascular regression, and lymphangiogenesis (Akwii et al. 2019).

Hypoxia-Inducible Factors (HIFs) HIFs are DNA-binding transcription factors that associate with specific nuclear cofactors under hypoxia (Palazon et al. 2014). They are heterodimers that include both the constitutively expressed HIF-1β subunit and oxygen-regulated HIF-1α or HIF-2α subunit (Hu et al. 2003). In humans, HIF-1α is ubiquitously expressed, while HIF-2α, although it is expressed mainly in the endothelium, in hypoxic conditions, is also expressed in the kidney, pancreas, brain, liver, intestine, and myocardium. When cells are in a hypoxic environment, the hydroxylation process is inhibited, and HIF-α escapes proteasomal degradation, dimerizes with HIF-1β, and associates with transcriptional coactivators (Berra et al. 2001). The latter recognizes hypoxia-responsive genes, resulting in physiological adaptation to hypoxia. Other stimuli, such as nitric oxide and reactive oxygen species (ROS), can also activate HIFs (Wellman et al. 2004).

Many human cancers are characterized by increased levels of HIF, and its expression correlates with mortality (Zhong et al. 1999; Talks et al. 2000). Hypoxic conditions contribute to increased HIF activity, which translates into the regulation of genes involved in angiogenesis, cell survival, metabolism, invasion, and metastasis. In solid tumors, the rapid proliferation of cancer cells limits oxygen diffusion within the tumor, decreasing its concentrations under physiological conditions. This leads to increased expression and activity of HIF, contributing to tumor angiogenesis (Huang et al. 2017; Shi and Fang 2004).

14.4 Angiogenic Inhibitors

Angiostatin Angiostatin is a 38 kDa internal fragment of plasminogen (Cao and Xue 2004; Ji et al. 1998). Angiostatin inhibits endothelial cell proliferation, migration, and tube formation (Pozzi et al. 2000) and induces apoptosis of endothelial cells (Ramirez-Moreno et al. 2020). Moreover, angiostatin inhibits the signaling induced by FGF-2 and VEGF in human microvascular endothelial cells (Redlitz et al. 1999) and inhibits primary tumor growth as well as angiogenesis-dependent growth of metastases (Dell'Eva et al. 2002).

Endostatin Endostatin is an angiostatic 20 kDa internal type XVIII collagen fragment released by proteolytic activity (Wenzel et al. 2006). The hinge region of endostatin contains several proteolytic cleavage sites where matrix metalloproteinases (MMPs), cathepsins, and elastases induce its release and consequently the interaction with cell membrane receptors, including α5β1, αvβ3, and αvβ5 integrin receptors, on endothelial cells (Zatterstrom et al. 2000). Endostatin inhibits the mitogen-activated protein kinase pathway in endothelial cells, leading to the inhibition of angiogenesis (Wickstrom et al. 2005). Endostatin affects VEGF to VEGFR-2 binding and tyrosine phosphorylation (Jia et al. 2004) and inhibits the activities of matrix metalloproteinases-2, -9, and -13 (MMP-2, MMP-9, and MMP-13) (Kim et al. 2000).

Platelet Factor 4 (PF4) PF4 is the most abundant chemokine member of the C-X-C family found in platelets and megakaryocytes. It exhibits antiangiogenic effects both in vivo and in vitro and directly interacts with VEGF-A_{165} (Hang et al. 2013; Maurer et al. 2006).

Thrombospondin-1 (TSP-1) TSP-1 belongs to a family of extracellular matrix (ECM) glycoproteins. TSP-1, initially discovered in platelet granules, is also produced by endothelial cells, monocytes/macrophages, and smooth muscle cells. TSP-1 interacts with numerous ECM proteins, modulates extracellular protease levels, and activates transforming growth factor beta (TGF-β) (Lawler 2002). TSP-1 inhibits angiogenesis by inhibiting the growth, sprouting, and motility of endothelial cells. High concentrations of TSP-1 have the opposite effect, promoting angiogenesis (Lawler and Lawler 2012).

14.5 TME Infiltrating Cells

Macrophages Tumor-associated macrophages (TAMs) are one of the major tumor-infiltrating innate immune cells and play an important role in the TME because they are involved in promoting tumor growth, invasion, metastasis, and therapeutic resistance (Chanmee et al. 2014). TAMs are described in two different polarization states: M1 CD68-positive and M2, CD-163 and CD-206-positive (Medbury et al. 2013). It is generally believed that M1 macrophages are involved in proinflammatory processes by migrating to inflamed tissues and targeting pathogens directly or activating cells of the adaptive immune system. It has been demonstrated that the M1 subpopulation has antitumor function because of its ability to kill tumor cells and recruit cytotoxic T lymphocytes to activate adaptive immune responses (Chanmee et al. 2014). The M2 subpopulation, on the other hand, has the functions of debris removal, angiogenesis stimulation, and tissue reconstruction and promotes tumorigenesis. They induce immune tolerance and attract T regulatory cells and Th2 T cells. It is believed that M2 TAMs have protumor activity because they stimulate angiogenesis and tumor growth (Jayasingam et al. 2019). Usually, TAM recruitment is correlated with the induction of angiogenic switching and is associated with a poor prognosis in most cancer types. Many cytokines and chemokines are secreted by vascular and perivascular cells, stromal cells, and cancer cells that recruit TAMs in the TME and include C-C motif ligand 2 (CCL2), CCL5, CCL7, Ang-2, colony-stimulating factor-1 (CSF1), VEGF, interleukin-33 (IL-33), semaphorin 3D (Sema 3D), endothelial monocyte-activating polypeptide-II (EMAP-II), endothelin (ET)-1 and 2, stromal cell-derived factor 1α (SDF1α/CXCL12), eotaxin, and oncostatin (Wang et al. 2019a).

TAMs can transdifferentiate into vessel-like structures by vasculogenic mimicry. In gliomas, the areas where vascular mimicry is found are characterized by high TAM infiltration and correlated with M2 density (Rong et al. 2016). The angiogenic factors secreted by TAMs include EGF-A, TGF-β, FGF-2, CCL18, Sema4D, adrenomedullin (ADM), and PlGF (Riabov et al. 2014). TAMs express the MCT1-lactate transporter. Furthermore, TAMs express VEGF-A when exposed to hypoxia or in the presence of lactate produced by tumor cells following aerobic or anaerobic glycolysis (Zhang et al. 2020). This effect is mediated by HIF1α, and lactate seems to lead to M2-like polarization of TAMs (Colegio et al. 2014). TAMs have been found to localize frequently in avascular and hypoxic areas of invasive carcinoma of the breast, where the expression of VEGF-A is upregulated (Lewis and Pollard 2006). Fra-1 and the IL-6/JAK/Stat3 signaling pathway in TAMs are involved in the secretion of proangiogenic factors (Choi et al. 2018). TAMs produce CCL18, which stimulates angiogenesis in synergy with VEGF-A (Lin et al. 2015). ADM is a potent vasodilator belonging to the calcitonin superfamily whose secretion by macrophages is upregulated by inflammatory factors and hypoxia. In melanoma, TAM-derived ADM induces angiogenesis in a paracrine manner via the endothelial nitric oxide synthase (eNOS) signaling pathway (Chen et al. 2011). MMP-9, which is highly expressed by M2 macrophages, triggers the angiogenic switch during

carcinogenesis by the release of VEGF-A from the ECM in colorectal cancer (Deryugina and Quigley 2015; Yahaya et al. 2019).

Mast Cells (MCs) MCs are involved in a large spectrum of biological processes, ranging from inflammation and immune modulation to angiogenesis, tissue repair, remodeling, and cancer (Welker et al. 2000). MC precursors complete their differentiation and maturation in target tissues under the control of local growth factors, including IL-9, IL-10, IL-3, IL-4, IL-33, CXCL12, nerve growth factor (NGF), and TGF-β (Hu et al. 2007). MCs are traditionally classified based on the production of tryptase and chymase, and resident MCs of various organs are characterized by the expression and release of peculiar factors related to their tissue-specific functions (Krystel-Whittemore et al. 2015). MCs can be recruited to the tumor microenvironment by tumor cell-released chemoattractants, including stem cell factor (SCF) or CCL-15 (Yu et al. 2018). In the TME, MCs release proangiogenic factors such as FGF2, VEGFA, tumor necrosis factor alpha (TNFα), and CXCL8 (Norrby 2002). Furthermore, they produce MMPs and chymase, and tryptase activates pro-MMPs (Kanbe et al. 1999; Johnson et al. 1998). The localization of MCs in the TME is determined by interactions of CCR2, CXCR2, and CXCR3 with their respective ligands CCL2, CXCL1, and CXCL10. In this way, MCs facilitate tumor angiogenesis and promote tumor invasiveness (Ramirez-Moreno et al. 2020; Komi and Redegeld 2020). On the other hand, numerous cytokines released by MCs contribute to inflammation, inhibiting tumor cell growth and inducing tumor cell apoptosis (Ribatti and Crivellato 2012). MC tryptase activates the Ang-1 pathway and induces endothelial cell proliferation in pancreatic cancer (Guo et al. 2016). MC inactivation delayed the angiogenic switch and malignant progression in early preneoplastic lesion experimental squamous epithelial, intestinal, and pancreatic islet cancer models (Maciel et al. 2015).

Neutrophils Neutrophils release large amounts of soluble factors, including cytokines and chemokines, through which they recruit and activate other immune cells (Malech et al. 2014). Moreover, they are involved in chronic inflammation regulation and in various steps of tumor progression and angiogenesis, exerting both pro-(tumor-associated neutrophil, TAN-N2) and antitumor (TAN-N1) roles. Normal density neutrophils (NDNs) have been associated with cytotoxic antitumor activities, while immature low-density neutrophils (LDNs) exert immunosuppressive protumor activities (Cerecedo et al. 2021). The TME is infiltrated with $CD66b^{+}$ neutrophils, and their number is correlated with poor clinical outcome (Carus et al. 2013). TGFβ reduces endothelial adhesiveness of neutrophils and neutrophil transmigration through the endothelium as well as the number of antitumor neutrophils in the TME (Granot 2019). In a Nod Scid mouse model of human prostate cancer, TANs are the major source of MMP-9 (Li et al. 2020a). In gliomas, the high TME infiltration of neutrophils was correlated with the tumor grade as well as resistance to anti-VEGF therapy (Liang et al. 2014). Neutrophils produce low amounts of tissue inhibitors of metalloproteinases-1 (TIMP-1), thus enhancing the angiogenic effect of MMP-9 (Wang et al. 2019b). In a RIP-Tag murine model, granulocyte-CSF (G-CSF) stimulates neutrophils to release the proangiogenic molecule Bv8, which is critical

for VEGF-independent tumor angiogenesis (Bjornmalm et al. 2017). Resistance to anti-VEGF therapy in tumors has been correlated with the infiltration of neutrophils and associated with Bv8 neutrophil expression (Shojaei et al. 2008). On the other hand, neutrophils are also involved in the inhibition of angiogenesis through the release of antiangiogenic factors, such as affecting neutrophil migration toward CXCL1 and CXCL8 (Jeronimo et al. 2017).

Lymphocytes The role of lymphocytes in tumor progression and angiogenesis remains to be further explored, and conflicting data about their function in the TME are emerging (Paijens et al. 2021). B cells are often present in the TME, and it is believed that they may contribute to tumor angiogenesis via STAT3 activation. STAT3 activation in cancer promotes tumor cell survival and proliferation, and a positive correlation has been established between its expression and VEGF release (Yang et al. 2013). It is thought that although only a subset of B cells infiltrating the tumor express STAT3, this might be enough to potentiate and maintain persistent STAT3 activation. Transplantation of STAT3-expressing B cells in tumor mouse models increased tumor growth and angiogenesis through the production of VEGF (Wang et al. 2019c). Another way by which B cells contribute to tumor angiogenesis is the antibody-mediated activation of Fcγ receptors on TAMs. This mechanism induces the secretion of IL-1, leading to the recruitment of myofibroblasts and promotion of tumor angiogenesis (Voronov et al. 2014). Tumor-infiltrating T cells play an important role in the antitumor response by the production of many cytokines, such as TNF-α, interferon gamma (IFN-γ), IL-2, IL-17, IL-22, and IL-36. TAMs inhibit $CD8^+$ T-cell infiltration and antitumor function (de Ruiter et al. 2017; Lan et al. 2021). Regulatory T (Treg) cells are immunosuppressive cells that affect the specialization and function of antigen-presenting cells (APCs), decrease their interactions with T cells, and subsequently inhibit effector T-cell function (Maimela et al. 2019). In addition, Tregs suppress natural killer (NK) cell activities (Li et al. 2020b). Cytotoxic T cells in the TME release IL-2, IL-12, and IFN-γ, improving the cytotoxic functions of $CD8^+$ T cells through the production of TNF-related apoptosis-inducing ligands (TRAILs), ROS, and perforin (Grossman et al. 2004). Tumor cells express coinhibitory receptors such as programmed death ligand-1 (PD-L1) and CD80 that interact with the inhibitory molecules programmed death-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) expressed by $CD8^+$ T cells. These interactions may inhibit $CD8^+$ T-cell activation and function (Cai et al. 2019). $CD4^+$ and $CD8^+$ T cells produce FGF-2 and heparin-binding epidermal-like growth factor (HB-EGF), which are both proangiogenic factors (Blotnick et al. 1994). On the other hand, T cells are also involved in the antiangiogenic response through TNFα, TGFβ, and IFNs. IFNs induce the expression of CXCL-9, CXCL-10, and CXCL-11 with angiostatic activities that can directly bind CXCR3 on endothelial cells (Blotnick et al. 1994; Beatty and Paterson 2001). NK cells are able to control tumor growth through their cytotoxic activity (Wu and Lanier 2003). Intratumor NK cells display phenotypic and/or functional alterations compared with peripheral NK cells depending on the influence of local factors and/or the interaction with other cell types of the TME (Larsen et al. 2014). The presence of TGF-β inhibits CD16,

perforins, granzymes, and IFN-γ secretion, reverting NK cells to a proangiogenic phenotype characterized by the secretion of VEGF. Furthermore, the interaction between the immunoregulatory class I MHC molecule HLA-G and the KIR2DL4, ILT-4, and ILT-2 inhibitory NK cell receptors induces NK cells to acquire proangiogenic activities. Prostaglandin E2 (PGE2) is believed to contribute to the NK cell angiogenic switch (Bassani et al. 2019). Tumor-infiltrating NK cells express high levels of CD56, but low levels or none of CD16 produce several factors, such as VEGF, angiogenin, Ang-1, PIGF, CXCL8, and MMPs, which stimulate endothelial cell growth and angiogenesis (Bruno et al. 2018).

Cancer-Associated Fibroblasts (CAFs) CAFs are able to interact with tumor cells and form a myofibroblastic microenvironment that supports tumor progression and angiogenesis via secretion of various growth factors, cytokines, chemokines, and the degradation of ECM (Liu et al. 2019). A significant percentage of CAFs may share endothelial markers such as PECAM/CD31, and this allows us to suppose that they originate from an endothelial subpopulation through endothelial-to-mesenchymal transition (Potenta et al. 2008). Regarding their influence on angiogenesis, several studies have shown that their secretome is rich in several cytokines with proangiogenic effects, including VEGF, CXCL-8, and FGFs (Linares et al. 2020). Furthermore, CAF release is able to form capillary-like structures through vasculogenic mimicry by TGF-β and SDF-1 paracrine action (Yang et al. 2016a). Moreover, SDF-1 recruits endothelial precursor cells (EPCs), which may transdifferentiate into endothelial cells and stimulate the formation of novel vasculature at the tumor-host cell interface (Orimo et al. 2005). CAFs express podoplanin, which promotes angiogenesis in breast cancer via upregulation of VEGF-C rather than VEGF-A or VEGF-D (Kubouchi et al. 2018). The galectin family of glycan-binding proteins displays important functions in cancer development and progression. In gastric cancer, CAF expression of Galectin-1 is upregulated, leading to enhanced VEGF expression. Under hypoxic conditions, G-protein-coupled estrogen receptor (GPER) downregulation in CAFs reduces VEGF expression (Ham et al. 2019). In human pancreatic adenocarcinoma, VEGF expression by CAFs may be regulated by fibroblast activation protein α (FAP α), which is involved in affecting the balance of pro- and anti-angiogenic mediators (Higashino et al. 2019).

14.6 TME Inflammatory Cells and Angiogenesis. Our Experience in the Study of Human Lymphomas

We studied the inflammatory cell infiltrate and its role in tumor angiogenesis in diffuse large B-cell lymphoma (DLBCL) by comparing activated B-cell-like (ABC) patients to germinal center B-cell-like (GCB) patients. We demonstrated that increased ABC expression of STAT3 was correlated with poor prognosis in DLBCL and was associated with higher M2 TAM (Fig. 14.1a, b) and $CD8^+$ (Fig. 14.1c, d) cell infiltration into the TME, which, in turn, induced a strong

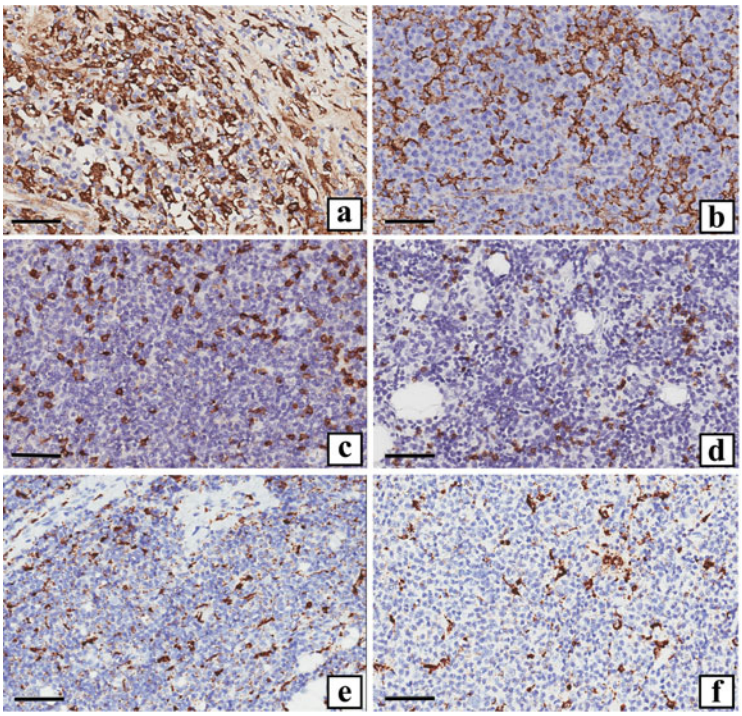

Fig. 14.1 Immunohistochemical staining of $CD163^+$ macrophages in ABC (**a**) and GCB (**b**) DLBCL samples; $CD8^+$ T cells in ABC (**c**) and GCB (**d**) DLBCL samples; $CD68^+$ macrophages in MALT lymphoma (**e**) and control (**f**) samples. Scale bar 60 mm

angiogenic response in the ABC group (Tamma et al. 2020). Moreover, tumor vessels appeared lined by endothelial cells expressing both FVIII and STAT3 (Tamma et al. 2019b). Regarding the morphological distribution of the different TME cells in DLBCL, we established that cell patterns generated by $CD4^+$, $CD8^+$, $CD68^+$, $CD163^+$, and $tryptase^+$ mast cell profiles have a higher uniformity index in the ABC, indicating a tendency of the cells to assume a more uniform distribution in the tissues in this more aggressive DLBCL subtype (Guidolin et al. 2021). Recently, Laddaga and coworkers suggested that the number of tumor infiltrating lymphocytes in the DLBCL TME is connected to a pre-existing antitumor immune response and then to an improved therapy response (Laddaga et al. 2021).

In a further study, we demonstrated that mucosa-associated lymphoid tissue (MALT)-type lymphoma and the tumor inflammatory TME included a high number of $CD3^+$, $CD4^+$ and $CD8^+$ lymphocytes, $CD68^+$ (Fig. 14.1e, f), $CD163^+$ macrophages, and $tryptase^+$ mast cells. Interestingly, $CD8^+$ cell content positively correlated with both $CD34^+$ vessels, remarking on the important role of these cells in tumor angiogenesis and with $CD163^+$ TAMs. Moreover, $tryptase^+$ mast cells correlated with $CD4^+$ lymphocytes (Tamma et al. 2021).

14.7 Targeting Angiogenesis and Inflammatory Cells in TME

Chemotherapy associated with surgery and/or radiotherapy is the principal cancer therapy worldwide (Bjornmalm et al. 2017). The TME has been gradually recognized as a crucial contributor to cancer progression and drug resistance (Heinrich et al. 2012), so the study of the components of the TME was deepened to identify new therapeutic targets.

Targeting Angiogenesis Bevacizumab was the first anti-VEGF antibody Food and Drug Administration (FDA) approved and actually used in different cancers, including metastatic colorectal cancer, lung cancer, kidney cancer, glioblastoma metastasis, and HER2-negative breast cancer, with response rates and durations highly variable (Jang et al. 2017). The addition of bevacizumab to chemotherapy has shown improvements in progression-free and overall survival with respect to chemotherapy alone (Jang et al. 2017; Yang et al. 2017). Another strategy consists of the inhibition of VEGF binding to its receptors by soluble decoy receptors (Holash et al. 2002). Aflibercept is a recombinant fusion protein containing portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human immunoglobulin G1 able to bind with high-affinity VEGF and PlGF, inhibiting the activation of cognate VEGFRs (Holash et al. 2002). Experimental data about the use of aflibercept in cancer xenograft models demonstrated greater antitumor activity than bevacizumab (Chiron et al. 2014). Ramucirumab is a monoclonal anti-VEGFR-2 antibody used as monotherapy or in combination with paclitaxel for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma, metastatic non-small cell lung cancer (NSCLC), and colorectal cancer (Singh and Parmar 2015; Aprile et al. 2014). Tyrosine kinase inhibitors (TKIs) are used for the inhibition of VEGFRs, PDGF-A and PDGF-BRs, and c-Kit (Hamberg et al. 2010; Wang et al. 2016). Among TKIs, pazopanib is commonly used for the treatment of advanced renal cell carcinoma and soft tissue sarcoma (Hamberg et al. 2010; Nakano et al. 2019) and sunitinib is used in metastatic renal cell carcinoma (Roma-Rodrigues et al. 2019). Sunitinib has more benefits than sorafenib as a first-line therapy, although sunitinib has higher toxicity than sorafenib (Deng et al. 2019). M-TOR inhibitors decrease endothelial cell proliferation through the mTOR/AP-1/VEGF pathway, among which everolimus (Wang et al. 2016). Patients treated with antiangiogenic agents have a reduced response to therapies for the acquisition of drug resistance. Two mechanisms of this resistance are the activation of alternative signaling pathways and the upregulation of alternative angiogenic factors and cytokines. Deepening these pathways would allow us to elaborate new treatments and the development of combination regimens with more durable clinical benefits (Philips and Atkins 2014). Anti-VEGF treatment in pancreatic cancer induces increased expression of FGF-1 and -2 and Ang-1 (Zhuang et al. 2010). In patients affected by colorectal cancer treated with bevacizumab, high levels of Ang-2 were detectable (Goede et al. 2010). In glioblastoma multiforme, anti-VEGFR therapy

leads to increased levels of FGF-2 and SDF-1. Similar results have been found in lung cancer models resistant to angiogenesis inhibitors in which epidermal growth factor receptors (EGFRs) and FGFRs are overexpressed (Cascone et al. 2011). In colorectal and renal cancer patients treated with TKIs, increased levels of PIGF and VEGF were detectable (Motzer and Bukowski 2006). Vanucizumab, a bispecific anti-Ang-2/anti-VEGF-A antibody, revealed an acceptable safety profile and promising antitumor activity (Hidalgo et al. 2018). FGFR inhibitors restore the sensitivity to bevacizumab in tumor mouse models (Gyanchandani et al. 2013), but further research failed to determine the relevance of this association (Norden et al. 2015; Semrad et al. 2017). The VEGFR, FGFR, and PDGFR multiple receptor TKI lenvatinib showed promising effects in several tumors and should be considered for counteracting resistance to antiangiogenic agents (Suyama and Iwase 2018).

Anti-angiogenic therapies induce the production of cytokines, such as SDF1, IL-8, and G-CSF, involved in the recruitment of bone marrow-derived cells (BMDCs), which contributes negatively to the anti-angiogenic effect (Montemagno and Pages 2020). An increase in $CD11b^{+}$ $Gr1^{+}$ myeloid-derived suppressor cells (MDSCs) has been observed in tumors not sensitive to anti-VEGF-A treatment (Shojaei et al. 2007). Th-17 cells induce the expression of G-CSF by CAFs and consequently the recruitment of MDSCs (Shojaei et al. 2009). Hypoxia has been related to sunitinib resistance in glioblastoma and breast and metastatic renal cell carcinoma as a consequence of the increased recruitment of MDSCs to the tumor niche (Piao et al. 2012).

Vessel co-option is believed to be correlated with refractoriness to anti-VEGF drug treatment of colorectal cancer liver metastases (Frentzas et al. 2016) and has been observed following anti-VEGFR-2 inhibition in cerebral melanoma metastases (Frentzas et al. 2016). Moreover, vessel co-option has been evidenced in human breast cancer liver metastases, NSCLC, and lung metastases (Kuczynski et al. 2016). The blockade of both VEGF-A and ARP2/3, VEGFA and c-MET or VEGF-A and ZEB2 suppresses vessel co-option and tumor invasion (Sennino et al. 2012; Depner et al. 2016). Vasculogenic mimicry is deeply associated with poor patient survival (Sun et al. 2004). In ovarian cancer models, bevacizumab may induce the progression of metastatic disease, which would correlate with a hypoxic response and vasculogenic mimicry (Xu et al. 2012). Studies on the TME in everolimus-resistant renal carcinoma demonstrated that the antiangiogenic drug stimulates vasculogenic mimicry by differentiating tumor cells into endothelial-like cells (Serova et al. 2016). Moreover, everolimus induces triple-negative breast cancer invasion via vasculogenic mimicry; thus, its evaluation could be helpful in predicting the efficacy of antiangiogenic therapy in these patients (Sun et al. 2017).

Targeting TAMs Targeting TAM-recruiting mediators, which include chemokines, complement components, CSF-1, and VEGF, is being studied (Liu et al. 2020). It has been reported that the inhibition of CSF1R in glioblastoma and cervical and breast cancer murine models induces a dramatic reduction in tumor volume and survival of mice (Pyonteck et al. 2013). This inhibition seems to reprogram TAMs by GM-CSF to induce their repolarization to an antitumoral

state (Quail and Joyce 2013; DeNardo et al. 2011). The monoclonal antibody RG7155 in human patients led to a remarkable reduction in CSF-1R$^+$ CD163$^+$ macrophages in diffuse-type giant cell tumor patients (Ackermann et al. 2013). TAM reduction improves antiangiogenic treatments. Treatment with vascular-disrupting agents such as combretastatin-A4-phosphate has been reported to markedly increase its efficacy when TIE2$^+$ TAM recruitment is blocked (Welford et al. 2011). The reduction in TAMs augmented the effects of sorafenib (Zhang et al. 2010). In addition, TAMs improved the antiangiogenic and antitumor effects of VEGF/VEGFR2 antibodies in subcutaneous tumor models (Priceman et al. 2010). TAMs limit the cytotoxic activity of CD8+ cytotoxic T cells during tumor progression, mainly in the M2 polarization state. Inhibiting TAM recruitment or blocking TAM polarization to the M2 phenotype may enhance T-cell-mediated antitumor responses and improve the efficacy of immunotherapies (Coussens et al. 2013). Moreover, some immunotherapies may also depend on the reprogramming of TAMs toward an M1 phenotype. One method used to reprogram TAMs is histidine-rich glycoprotein (HRG) treatment, which induces macrophage downregulation of PlGF and stimulates the normalization of blood vessels and the efficiency of chemotherapy in mouse tumor models (Rolny et al. 2011). Other strategies include the suppression of nuclear factor-kB signaling (Hagemann et al. 2008) or exposure to anti-IL-10R antibodies combined with the TLR9 ligand CpG (Guiducci et al. 2005).

Targeting TANs Inhibition of the protumor functions of TANs (Hsu et al. 2020) may be combined with conventional or new anticancer therapies to improve the antitumor effects (Khan et al. 2020). CXCR2 inhibitors are also used in combination with other therapies in clinical evaluation in patients with different tumors (Li et al. 2019; Timaxian et al. 2021; Groth et al. 2021; Cabrero-de Las Heras and Martinez-Balibrea 2018). The neutrophil-derived enzyme elastase promotes tumor growth and invasiveness. The elastase inhibitor ONO-5046 reduced tumor growth in NSCLC (Houghton et al. 2010). Another approach has been to reprogram neutrophil function in the TME through the inhibition of TGFβ (Qin et al. 2020). The inhibition of angiotensin-converting enzyme and the angiotensin II type 1 receptor nicotinamide phosphoribosyltransferase (NAMPT) or CXCR4 is another approach to reprogram neutrophils to an antitumor state (Shrestha et al. 2016; Yang et al. 2018b).

Targeting CAFs The protein FAP is considered a candidate for targeting CAFs because it is expressed in tumors but not in healthy tissues and is considered a predictor of poor survival (Liao et al. 2013). Nevertheless, both sibrotuzumab, an antibody targeting FAP, and inhibitors of FAP activity induced lower survival rates (Liu et al. 2019; Yang et al. 2016b). An IL-2 variant targeting FAP, RO6874281, is under investigation (Joshi 2020; Koustoulidou et al. 2021).

14.8 Concluding Remarks

Cytokines and chemokines secreted by cells of the TME are involved in the regulation of tumor angiogenesis based on the balance of pro- and antiangiogenic factors. Deepening the mechanisms underlying the crosstalk between the TME and tumor cells has allowed the discovery of numerous molecular-targeted drugs that control diverse elements of the TME. Different approaches varying from traditional and emerging inhibitors of angiogenic cytokines and their receptors to the modulation of TME cell activities and novel immune checkpoint inhibitors proved to be promising in tumor progression. Despite the promising results of these new therapeutic approaches, their efficacy is often limited by evasion, and resistance mechanisms have emerged. Overcoming resistance to antitumor therapies is a great challenge but might lead to the improvement of the clinical outcome of patients and, for this reason, currently constitutes a major focus of research.

Acknowledgments This work was supported by Associazione "Il Sorriso di Antonio," Corato, Italy.

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