A New Antitumor Direction: Tumor-Specific Endothelial Cells

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Targeting tumor blood vessels is an important strategy for tumor therapies. At present, antiangiogenic drugs are known to have significant clinical effects, but severe drug resistance and side effects also occur. Therefore, new specific targets for tumor and new treatment methods must be developed. Tumor-specific endothelial cells (TECs) are the main targets of antiangiogenic therapy. This review summarizes the differences between TECs and normal endothelial cells, assesses the heterogeneity of TECs, compares tumorigenesis and development between TECs and normal endothelial cells, and explains the interaction between TECs and the tumor microenvironment. A full and in-depth understanding of TECs may provide new insights for specific antitumor angiogenesis therapies.

Keywords: tumor-specific endothelial cells, tumor heterogeneity, tumor angiogenesis, tumor microenvironment, antiangiogenic therapy

1 INTRODUCTION

Tumor angiogenesis refers to the formation of new blood vessels in tumors. Tumor blood vessels provide oxygen and nutrients for tumor growth, remove waste from tumor tissues, and provide pathways for tumor metastasis. If a solid tumor has insufficient amounts of blood vessels, then it can only grow to a critical size of 1–2 mm (or approximately 10⁶ cells) (1). In recent years, many studies have identified significant differences in the structure and function between tumor vasculature and normal vasculature. Normal blood vessels have regular hierarchical structures that are responsible for blood flow throughout the body and maintain normal physiological activities, and these structures include arteries, veins, and capillaries. Tumor blood vessels, however, are highly irregular in shape, and they are swollen and twisting and have many blind ends, which results in abnormal vascular function, including increased vascular permeability, leakage and bleeding, and blood flow disorder (2, 3).

The specificity of tumor-specific endothelial cells (TECs) is one of the main reasons for tumor vascular anomalies. Blood vessels are composed of ECs and pericytes, which are responsible for the contraction and relaxation of blood vessels. In normal blood vessels, ECs are mostly in a static state. In tumors, hypoxia and chronic growth factor stimulation may cause endothelial dysfunction (4). Increasing evidence has shown that these abnormalities can lead to the development of cancer. Initial hypotheses suggested that TECs were genetically stable normal somatic cells that were not prone to mutation and drug resistance and remained consistent in various tumors, which would allow multiple types of cancer to be treated by a single antiangiogenic drug (5). However, in recent
years, many researchers have found that TECs are not ordinary somatic cells but rather are heterogeneous in many aspects relative to normal endothelial cells (NECs), which contradicts previous assumptions (6, 7). Therefore, the study of TECs will provide targets or directions for tumor therapy. Because most current antiangiogenic drugs are nonspecific, they cause damage to NECs, thus leading to fatal side effects, such as intestinal perforation and bleeding in the later stages (8, 9). Therefore, exploring specific targets for TECs have potential for antitumor therapy.

The tumor microenvironment (TME) is essential for tumor progression, which accelerates metastasis and increases tumor malignancy. TME refers to the local environment for tumor survival. A large number of tumor cells infiltrate in TME, includes stromal cells, TECs and immune cells (10). TME provides an acidic and hypoxic environment containing a large number of cytokines (11). TME plays an important role in the process that TECs promote tumor progression and drug resistance (12). Among them, tumor-associated macrophages (TAMs) and tumor-associated fibroblasts (CAFs) have been found to promote the proliferation, migration and tube formation of HUVECs (13–15). And Myeloid-Derived Suppressor Cells (MDSCs) and extracellular matrix (ECM) also regulate the function of ECs (16, 17). Therefore, to study the interaction between TECs and TME is necessary to target for TECs therapy.

2 ANTITUMOR ANGIOGENESIS THERAPY

Fifty years ago, Judah Folkman first emphasized that angiogenesis was an important process for the growth and proliferation of solid tumors (18) and proposed that antiangiogenesis may be a potential method for treatment various cancers. In recent years, many factors and related receptors that promote angiogenesis have been confirmed, including vascular endothelial growth factor (VEGF) (19), platelet-derived growth factor (PDGF) (20, 21) and angiopoietin (Ang) (22), and antitumor angiogenesis drugs have been developed.

VEGF is considered a key factor in inducing tumor angiogenesis and is research hotspot as a key target for antitumor vascular therapy. VEGF activates MAPK, PI3K and other signals in ECs by binding to VEGF receptors (VEGFR1-3) to promote the formation of new blood vessels, increase vascular permeability, and regulate tumor angiogenesis (23–25). In recent decades, VEGF has been used as a therapeutic target to inhibit angiogenesis and promote the normalization of tumor blood vessels, and has achieved great success. Bevacizumab is the first approved antitumor angiogenesis therapy monoclonal antibody, and it can specifically bind to VEGF to inhibit tumor angiogenesis (26). But, the effect of bevacizumab treatment alone is limited. Minjian et al. observed that a significant upregulation of VEGF and downregulation of β-FGF and ANG1 in colon cancer-derived endothelial cells treated with bevacizumab alone, which might activate a potential self-regulating mechanism of angiogenic growth factors and also explained why current antiangiogenic therapy with bevacizumab alone has limited effects in prolonging the survival of colon cancer patients (27). Clinical studies have confirmed that a combination of bevacizumab and chemotherapy drugs can significantly prolong the survival period of tumor patients and achieve antitumor effects (28–30). Nadine et al. found that telomerase regulates VEGF expression and secretion through its catalytic subunit hTERT in gastrointestinal cancer cells, and VEGF inhibition with bevacizumab increased hTERT expression which further increased VEGFR1 and VEGFR2 expression. They suggested the combination of bevacizumab with telomerase inhibitors could improve tumor cell response to anti-VEGF treatment (31). The VEGF pathway coordinates with many other signaling pathways, such as Ang/Tie receptor and PDGF/PDGF signaling targeted by specific inhibitors nesvacumab and olaratumab, participates in tumor angiogenesis. Tyrosine kinase inhibitors (TKIs) are small molecule drugs that can inhibit the kinase activity of different receptors and their downstream signal transduction. Several studies revealed sunitinib, a TKI, not only targets VEGFR (32) but also inhibits PDGFR (33) and FGFR (34). Sunitinib has been used to treat a variety of cancers. Similarly, studies have reported that sunitinib treatment alone can cause ECs senescence, loose ECs connections, and promote tumor cell migration through the endothelial barrier (35). Based on the above research reports, treatment with one antitumor angiogenesis drug alone have great limit effects on cancer therapy (Figure 1).

Previously, antiangiogenic drugs were thought to be less toxic than other cytotoxic drugs; however, they subsequently been found have serious side effects (hypertension (36), bleeding (37), gastrointestinal perforation (8), etc.), with vascular toxicity particularly prominent. Theseside effects are associated with the inhibitory role of most current antiangiogenic drugs on cell signaling pathways, such as VEGF/VGFR, which has a negative impact on the survival of NECs (38). Antiangiogenic drugs and their side effects are shown in (Table 1) (39–49). An important goal of cancer treatment is to develop new and safer tumor-specific antiangiogenic drugs.

3 TUMOR-SPECIFIC ENDOTHELIAL CELLS

At present, tumor angiogenesis research and antiangiogenic drug development use cultured ECs, such as human umbilical vein ECs (HUVECs). A number of studies have clarified the molecular differences between TECs and NECs through global analysis and compare TECs with NECs to try to find specific molecules for TECs. For example, Alam et al. conducted a DNA chip analysis and found that suprabasin might be a new marker for TECs. Compared with NECs, suprabasin, the upstream factor of the AKT pathway, was highly expressed in TECs and positively correlated with the migration and tube formation ability of TECs (50). Microarray and immunohistochemical analyses revealed that biglycan was a specific marker and an autocrine angiogenic factor of TECs (51). Goveia et al. performed single-cell RNA (scRNA) sequencing on 56,771 ECs from human/mouse tumor in lungs and cultured human lung TECs, and detected 17 known and 16 previously unrecognized phenotypes. And found that collagen modification was a
candidate pathway for angiogenesis (52). Among the abovementioned studies, a few have focused on the function of TECs because human primary TECs culture have several limits, including small amounts from surgical specimens, difficult to separate, a short life span in vitro, easily lose their specificity and cannot be cultured in large quantities. In 2019, NakoMaishi and others established immortalized human TECs (h-imTECs) and their normal counterparts (h-imNECs) by transfecting with a lentivirus that produces simian virus 40 large T antigens and human telomerase reverse transcriptase to overcome replication barriers. These ECs exhibited an extended life span and retained their characteristic endothelial morphology, endothelial marker expression, and tube formation ability. Hence, these h-imTECs could be a valuable tool for drug screening to develop novel therapeutic agents specific to TECs or functional biological assays in tumor angiogenesis research (53).

3.1 Heterogeneity of Tumor-Specific Endothelial Cells

As a component of blood vessels, TECs are also different from NECs in many aspects (54). The whole tumor can be heterogeneous and biopsy may not be representative of the whole tumor. Angiogenesis contributes to the development of pathological conditions, such as tumor progression and metastasis, diabetic retinopathy, psoriasis, atherosclerosis, and rheumatoid arthritis (55).

As a component of blood vessels, TECs are also different from NECs in many aspects. Compared with most normal ECs, TECs have a higher proliferation rate and do not form a regular monolayer; the tumor vascular basement membrane is discontinuous or nonexistent, and the tumor endothelium is variably covered by pericytes with abnormal morphology (56, 57). Due to the phenotypic difference between tumor blood vessels and normal blood vessels, studies have concluded that may also exist genotype changes. Kyoko Hida found that the nucleus of TECs was larger than that of NECs and showed increased aneuploidy, abnormal centrosomes, and abnormalities, such as chromosome deletion, markers of unknown origin, and double microchromosomes (58). Chromosomal aberrations are also found in human renal carcinoma ECs and human B-cell lymphoma microvascular ECs (59, 60). These findings can be used as evidence of genetic instability of TECs. High-throughput expression profiles reveal changes in gene and protein expression profiles in the tumor endothelium. Li C et al. analyzed the expression differences between cervical cancer-derived ECs and NECs by scRNA-seq, and found several marker genes such as
| Type                          | Drug         | Target   | Manufacturer | Approval | Indication                                                                 | Side Effects                                                                 |
|-------------------------------|--------------|----------|--------------|----------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Monoclonal antibodies         | Bevacizumab  | VEGF     | Genentech    | 2004     | Colorectal cancer, Lung cancer, Cervical cancer, Glioblastoma, Ovarian cancer | Fatigue, pain, headache, abdominal pain, constipation, diarrhea, nausea, vomiting, anorexia, hemorrhage, dyspnea, Hypertension |
|                               | Cetuximab    | EGFR     | ImClone      | 2004     | Colorectal cancer, Head and neck cancers                                   | Fatigue, weakness, pain, headache, insomnia, weight loss, skin toxicities, GI toxicities, cough, dyspnea, fever, pharyngitis |
|                               | Panitumumab  (Vectibix) | EGFR     | Amgen        | 2005     | Colorectal cancer                                                         | Fatigue, ocular toxicity, nausea, diarrhea, vomiting, skin toxicity, dyspnea reactions |
|                               | Ramucirumab  | VEGFR2   | Imclone      | 2014     | Colorectal cancer, Lung cancer, Gastric cancer                            | Hypertension, diarrhea                                                                 |
|                               | Necitumumab  | EGFR     | Eli Lilly    | 2015     | Lung cancer                                                               | Acne, diarrhea, vomiting, mouth sores, vision changes, tearing or itching, red and swollen nails, itching |
|                               | Olaratumab   | PDGFR    | Eli Lilly    | 2016     | Sarcoma                                                                   | Nausea, fatigue, anorexia, skin discoloration, rash, hand-foot syndrome, edema, muscle cramps, joint pain, headache, abdominal discomfort, anemia, cough and itching, heart failure, neuropathy, headache |
| Tyrosine kinase inhibitors    | Imatinib     | PDGFR, SCFR | Novartis Abl | 2001     | Chronic myelocytic leukemia, Gastrointestinal Stromal Tumors               | Diarrhea, rash, itching, dry skin, acne                                                                 |
|                               | Gefitinib    | EGFR     | AstraZeneca  | 2003     | Nonsmall-cell lung cancer                                                  | Fatigue, diarrhea, anorexia, skin discoloration, rash, hand-foot syndrome, edema, muscle cramps, joint pain, headache, abdominal discomfort, anemia, cough and itching, heart failure, neuropathy, headache |
|                               | Nilotinib    | PDGFR    | Novartis Bcr-Abl | 2004 | Chronic myelocytic leukemia                                                | Diarrhea, rash, itching, dry skin, acne                                                                 |
|                               | Sorafenib    | VEGFR, PDGER | Bayer Raf    | 2005     | Renal cell carcinoma                                                      | Diarrhea, fatigue, hair loss, constipation, skin rash, high blood pressure |
|                               | Sunitinib    | PDGFR, VEGFR | Pfizer       | 2006     | Renal cell carcinoma                                                      | Hand and foot skin reactions, rash, diarrhea, fatigue, increased blood pressure, mucositis, fever, yellow skin, edema |
|                               | Dasatinib    | SRC, PDGFR | Bristol-Myers Squibb Bcr-Abl | 2006 | Chronic myelocytic leukemia                                               | Diarrhea, headache, nausea, rash, dyspnea, bleeding, fatigue, musculoskeletal pain, infection, vomiting, cough, abdominal pain, fever |
|                               | Lapatinib    | EGFR     | GlaxoSmithKline | 2007 | Breast cancer                                                             | Nausea, diarrhea, stomatitis and indigestion, dry skin, rash, breathing difficulties and insomnia |
|                               | Pazopanib    | VEGFR, PDGR, FGFR | GlaxoSmithKline | 2009 | Renal cell carcinoma, soft tissue sarcoma, Nonsmall-cell lung cancer      | Diarrhea, high blood pressure, hair color changes, nausea, anorexia, vomiting |
|                               | Crizotinib   | ALK      | Pfizer       | 2011     | Nonsmall-cell lung cancer                                                 | Abnormal vision, nausea, diarrhea, vomiting, constipation, edema, fatigue |
|                               | Vandetanib   | VEGFR, EGFR | AstraZeneca  | 2011     | Thyroid cancer                                                            | Diarrhea, skin rash, acne, nausea, high blood pressure, headache, fatigue, loss of appetite, abdominal pain |
|                               | Axitinib     | VEGFR     | Pfizer       | 2012     | Renal cell carcinoma                                                      | Diarrhea, high blood pressure, fatigue, loss of appetite, nausea, dysphonia, weight loss, vomiting, fatigue, constipation |
|                               | Afatinib     | EGFR      | Boehringer   | 2013     | Nonsmall-cell lung cancer                                                 | Diarrhea, skin rash, stomatitis, paronychia, loss of appetite, nose bleeding, dry skin |
|                               | Erlotinib    | EGFR      | Roche        | 2013     | Nonsmall-cell lung cancer                                                 | Skin rash, diarrhea, loss of appetite, fatigue, dyspnea, cough, nausea, infection, vomiting, stomatitis, itching, dry skin, conjunctivitis, keratoconjunctivitis, abdominal pain |
|                               | Ceritinib    | ALK       | Novartis     | 2014     | Nonsmall-cell lung cancer                                                 | Diarrhea, nausea, vomiting, abdominal pain, fatigue, loss of appetite, constipation |
|                               | Osimertinib  | EGFR      | AstraZeneca  | 2015     | Nonsmall-cell lung cancer                                                 | Skin rash, mouth ulcers, paronychia                                                                 |
|                               | Regorafenib  | VEGFR, EGFR | Bayer        | 2017     | Colorectal cancer, Hepatocellular carcinoma, Gastrointestinal Stromal Tumors | Fatigue, loss of appetite, diarrhea, oral mucositis, weight loss, high blood pressure, dysphonia |
|                               | Lorbrrena    | ALK       | Pfizer       | 2018     | Nonsmall-cell lung cancer                                                 | Edema, cognitive effects, dyspnea, fatigue, weight gain, joint pain, diarrhea |
|                               | Dacomitinib  | ALK       | Pfizer       | 2018     | Nonsmall-cell lung cancer                                                 | Diarrhea, skin rash, paronychia, stomatitis |

(Continued)
TAGLN2, KLF5, STAT1 and STAT2 (7). ScRNA sequencing revealed that 2590 genes were differentially expressed between TECs isolated from human hepatocellular carcinoma and NECs isolated from normal liver tissues (61). Proteomics analysis identified 127 highly expressed proteins in ECs isolated from human renal cancer, colon cancer, and lung cancer compared with NECs, among which CD146, CD31, and VWF might be tumor endothelial cell markers (62). In addition to expressing common vascular endothelial markers, TECs also show upregulated expression of VEGFR-2, VEGFR-3, e-selectin, ICAM-1, CD44, integrin and MUC-18 (63) and the nontraditional angiogenic factors biglycan, lysyl oxidase and pentraxin 3, which together promote tumor angiogenesis (64). These data indicate that the huge differences between TECs and NECs can be exploited to specifically target TECs for tumor treatment.

In addition to differing from NECs, different TECs also show heterogeneity. TECs have long been regarded as normal somatic cells without tumor characteristics, such as susceptibility to mutation and drug resistance. However, in glioblastoma, some ECs were found to originate from the glioblastoma stem cell population (65). In lymphoma and neuroblastoma, ECs derived from tumor cells were also confirmed (60, 66). In recent years, bone marrow-derived endothelial progenitor cells have been found to be involved in the formation of tumor pathological blood vessels, although the mechanism of action is still unclear (67). These findings provide new targets and directions for antitumor therapies that specifically target TECs but also increase the difficulty of developing such therapies.

In addition to the different origins of TECs, TEC phenotypes are affected by TME. Comparing the TECs stimulated by two different metastatic tumor supernatants, found that the treatment of highly metastatic tumor conditioned medium increased the resistance of TECs to 5-fluorouracil (5-FU) (68). After coculture with lung cancer cells, human umbilical vein ECs showed enhanced cell motility and microvascular formation and a decrease in the percentage of apoptosis (69). Conditional culture can also cause epigenetic changes in gene expression in cultured ECs (70). This evidence reveals the influence of the tumor microenvironment on the characteristics of TECs and leads to heterogeneity among TECs. Therefore, studying the heterogeneity and diversity of TECs in the development of tumors will contribute to the development of antitumor angiogenesis drugs. Antitumor research about specifically targeting TECs has become a trend (Figure 2).

### 3.2 Function of Tumor-Specific Endothelial Cells in Cancer Progression

#### 3.2.1 Tumorigenesis

The cellular origin of cancer and the nature of cells responsible for the maintenance and progression of tumors are still unsolved challenges for cancer therapy (71). Predictably, cancer originating from a single cell expands with the development of the cancer (72). Cancer stem cells (CSCs) have stem cell-like properties and can renew themselves. A number of studies have found that CSCs may cause cancer (73), thus leading to tumor recurrence (74). In melanoma, ECs can interact with CD133+ cancer stem cells to promote the occurrence and development of tumors (75). Targeting Cxcl12+ECs can inhibit the formation of the niche of gastric stem cells around blood vessels and inhibit the occurrence of diffuse gastric cancer (76). The specific regulatory mechanism of TECs on tumor stem cells is not very clear. In vitro experiments found that HUVECs co-cultured with human liver cancer cells (MHCC97H) enhanced the spheroidizing ability of MHCC97H cells and the expression of CD133 (77). Jia et al. found that TECs could release soluble factors through paracrine action and increased the CSCs ratio, in TECs and changes in the CSCs phenotype (78, 79). Knocking down the Notch ligand Dll4 in ECs inhibits Epithelial-Mesenchymal Transition (EMT) and results in a reduction in the number of CSCs and decreased tumor metastasis (80). The above evidence shows that TEC may regulate cancer stem cells through the Notch signaling pathway. In addition, studies have found that TECs may also regulate the phenotype and chemotherapy resistance of CSCs through the AKT, Src, and FAK signaling pathways (81, 82).

The transcriptional regulator YAP/TAZ has strong activity in malignant tumors and has been found to promote the occurrence of many tumors, including gastric cancer, colorectal cancer, liver cancer, and neuroblastoma. The YAP/TAZ signaling could influence the function of ECs to promote the tumor progression (83). Up-regulation of the tumor suppressor gene DLC1 in ECs activated YAP signal and ECs lost the contact inhibition function, which led to the occurrence and proliferation of angiosarcoma (84, 85). YAP also controls the activation of ECs and regulates tumorigenesis and angiogenesis (86). Thus, interference with the YAP/TAZ signaling pathway is expected to suppress tumorigenesis and tumor angiogenesis (Figure 3).
3.2.2 Tumor Transendothelial Migration

Metastasis is the main cause of cancer patient death, which has not yet been resolved by current tumor treatments. Tumor cell migration across the endothelium is an important step in the process of tumor invasion and metastasis. Tumor cells cross the basement membrane and enter peripheral blood circulation to reach distant organs, then adhere to vascular ECs through cell adhesion molecules, and migrate through vascular endodermis to colonize these organs. Endothelial-to-mesenchymal transition (EndoMT) is considered a necessary process for tumor migration across the endothelium. EndoMT is a complex cell differentiation process in which ECs break away from the cell population and migrate, which reduces the characteristics of ECs to varying degrees, and these cells then acquire mesenchymal characteristics. The main hallmark of EndoMT is that TGF-β induces ECs to transform into CAF-like cells, thus leading to the loss of endothelial adhesion molecules and endothelial cytoskeleton reorganization through the Rho and Rac-1 signaling pathway (87) (Figure 4). EndoMT helps to destroy the endothelial barrier, which leads to tumor extravasation and increase metastasis. Studies have confirmed that EndoMT increases the transendothelial migration of melanoma (88). Similarly, EndoMT, which is mediated by osteopontin (OPN) through the PI3K/Akt/TSC2 and mTORC1 signaling pathways, promotes the growth and metastasis of colorectal cancer (89). EndoMT caused by endoglin deficiency causes increased liver and lung metastasis in pancreatic cancer model mice (90). Therefore, it is feasible to use EndoMT as a target to inhibit tumor metastasis. Moreover, some studies have pointed out that EndoMT may be the cause of drug resistance in antitumor therapy (91). Therefore, the role of EndoMT needs to be explored and fully understood.

Cell adhesion molecules are essential for tumor migration across the endothelium. Laferriere et al. found that E-selectin expressed by TECs ensured that colon cancer cells adhered to ECs and activated the SAPK2/P38 signaling pathway (92). In addition, the activation of ERK by E-selectin regulates the opening of the endothelial space by initiating the activation of Src kinase activity and the dissociation of the VE-cadherin/β-catenin complex (93).
In melanoma, ICAM-1 expressed in TECs interacts with its receptor integrin LFA-1 to promote tumor cell migration across the endothelium in vitro (94). The VE-cadherin binding domain of fibrinogen induces the permeability of the endothelial barrier and enhances the transendothelial migration of malignant breast epithelial cells (95). Therefore, blocking the production of cell adhesion molecules or inhibiting their function has great potential to inhibit tumor metastasis.
Studies have confirmed that anti-cell adhesion molecule antibodies can inhibit tumor growth and metastasis. For example, after treatment with an anti-L1CAM antibody, the cancer growth (up to 75%) of SKOV3ip ovarian cancer cells was significantly reduced (96). Unfortunately, such treatment cannot effectively eliminate highly malignant tumors. In view of this situation, additional in-depth research is required to find more effective treatment strategies that target cell adhesion molecules (Figure 4).

3.2.3 Tumor Resistance

Drug resistance is an obstacle that impairs the success of cancer therapies. In some cases, relapse occurs in initially responsive patients after repeated cycles of chemotherapy due to the acquisition of tumor resistance (97). In the early stage, TECs were considered to be homogenous, these genetic stable cell populations did not cause drug resistance. With the progression of tumor, as we previously mentioned, TECs occurred considerable heterogeneity and genetic instability which might lead to drug resistance (98). A number of experiments have proven that ECs show resistance to some drugs. For example, kidney cancer ECs are resistant to vincristine (63) while liver cancer ECs are resistant to adriamycin (99) and 5-fluorouracil (100). However, it is not clear whether this resistance is related to the genomic characteristics of TECs. The resistance of ECs to antiangiogenic treatment appears to be related to the increased expression of multidrug resistance proteins, such as P-glycoprotein (Pgp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2), which serve as cellular efflux pumps (101, 102). In addition, Ca2+ transporters are also changed in stromal cancer cells, including ECs and endothelial colony forming cells (103). The remodeling of the endothelial Ca2+ toolkit may enhance the resistance of anticancer treatments by supporting tumor angiogenesis and reducing the sensitivity to proapoptotic stimuli (104). VEGF is an important target for antitumor angiogenesis. Studies have found that the failure of anti-VEGF drugs in anticancer treatment may be due to the recruitment of endothelial progenitor cells. VEGF inhibitors can induce the expression of placental growth factor, IL-6 and stem cell factors in nontumor tissues, and these cytokines can recruit bone marrow-derived ECs and myeloid progenitor cells to promote the formation of a premetastatic environment. Some of these recruited cells express VEGFR-1 and are resistant to VEGF inhibitors that target VEGFR-2 (105).
3.3 Interaction of Tumor-Specific Endothelial Cells and the Tumor Microenvironment

The interaction between a tumor and mesenchymal cells may be the reason for the abnormal structure of mesenchymal cells. The TME consists of stromal cells (including fibroblasts, macrophages, regulatory T cells, myeloid suppressor cells, ECs, pericytes and platelets) and extracellular matrix components (including inflammatory cytokines, chemokines and Matrix metalloproteinases), which enhance invasion and metastasis of cancer cells through mutual signal transduction. The TME induces gene expression in ECs to develop in a direction that is conducive to angiogenesis (Figure 5).

3.3.1 Tumor-Associated Macrophages

TAMs are the key cells that control tumor angiogenesis and the main source of angiogenic factors. TAMs can secrete angiogenesis factors, such as VEGF (106–108), basic fibroblast growth factor (Fgf2) (109), insulin-like growth factor-1 (Igf1) (110), chemokine ligand 2 (Ccl2) (111, 112) and placental growth factor (Pgf) (113)ect. These factors can stimulate ECs and promote proliferation rapidly of cells, which leads to tumor angiogenesis (14). Recent studies have found that TAMs highly express certain cytokines in gastric cancer, such as VEGF-A, VEGF-C, matrix metalloproteinase 1 (MMP-1) and amphiregulin (114), and induces capillary morphogenesis in human gastric cancer lymphatic ECs (115). Another study showed that CCL18 released...
by TAMs cooperated with VEGF to promote the migration of ECs, induce EndoMT, and activate ERK and Akt/GSK-3β/Snail signals in HUVECs, thereby promoting breast cancer angiogenesis (116). The latest breakthrough study found that an M1-like macrophage subtype might keep vascular cells quiescent, and at the same time, Matrix-remodeling macrophages might assist invasive cancer cells to co-opt vessels (117). Therefore, TAMs regulate the phenotype and function of ECs in the process of tumor angiogenesis and vascular remodeling. There is no doubt that TECs can also act on TAMs. First, TECs can recruit TAMs to tumor sites, which are mediated by several signaling pathways including the Ang-2/TIE2 signaling (118, 119). Second, changes in the permeability of ECs will also increase the infiltration of TAMs, thereby promoting the development of tumors (120). In addition, studies have found that ECs could selectively activate the differentiation of tumor-promoting M2 macrophages and promoted tumor angiogenesis (121). The latest research confirms that TECs may induce M2 polarization of macrophages by secreting HSPA12B to activate the PI3K/Akt/mTOR signal pathway (122). The above evidence shows that ECs play a key role in inducing the differentiation of macrophages and promoting further polarization to a pro-angiogenic phenotype. Therefore, studying the interaction between TECs and TAMs may provide a novel therapeutic approach on specifically targeting TECs.

3.3.2 Tumor-Associated Fibroblasts

In the TME, CAFs are a major matrix component that helps build the extracellular matrix and provides necessary growth factors for tumor cell growth and development. There are various sources of CAFs, such as activated tissue cells, transdifferentiated pericytes and adipocytes. However, CAFs can also be generated from transdifferentiated ECs through EndoMT (123). Studies have speculated that approximately 40% of CAFs are formed from ECs (124). As mentioned above, this process is mainly mediated by TGF-β. TGF-β secreted by tumor cells stimulates the phosphorylation of TGF-β receptors on the surface of ECs and activates Smad, which in turn activates the downstream signal transduction cascade, then leads to the occurrence of EndoMT and to generate CAFs (125, 126). A study found that exosomes secreted by tumors may also mediate the differentiation of ECs into CAFs and promote tumor invasion (123). Another study confirmed that melanoma-derived exosomes increased the number of CAFs differentiated from HUVECs by promoting EndoMT, which showed obvious morphological, molecular changes and motility (127). It is worth mentioning that the generated CAFs secrete a large number of cytokines, which can react with TECs and promote tumor angiogenesis. For example, CAFs release a large amount of angiogenic factors, such as VEGF-A (128) and FGF2 (129), in the TME to activate ECs and promote tumor angiogenesis. Interestingly, CAFs can also recruit endothelial progenitor cells by secreting CXCL12 to accelerate tumor growth and increase angiogenesis (130). In addition, early studies have found that platelet-derived growth factor C (PDGF-C) produced by CAFs can act on ECs and enhance the resistance to anti-angiogenesis and anti-VEGF treatments (131). Later studies showed that CAFs enhanced the motility and permeability of ECs by upregulating the LPP gene and promoted chemotherapy resistance in ovarian cancer (132). Overall, studies on the relationship between TECs and CAFs will provide a deeper understanding of tumor angiogenesis and chemotherapy drug resistance. Inhibiting the generation of CAFs or killing existing CAFs might represent effective therapeutic targets for antitumor angiogenesis.

3.3.3 Myeloid-Derived Suppressor Cells

MDSCs are immature myeloid cells that are normally produced and secreted by the bone marrow in the state of local inflammation. They have strong immunosuppressive activity, which can inhibit excessive inflammation and protect the host from autoimmune diseases (133). In the tumor state, MDSCs are abnormally produced and recruited to the TME to help establish an immunosuppressive TME and promote tumor angiogenesis and metastasis to support tumor progression. There are two main types of MDSCs, mononuclear MDSCs (M-MDSCs) and polymorphonuclear MDSCs (PMN-MDSCs) (134). In tumors, M-MDSC can quickly differentiate into TAMs (135, 136), and the relationship between TAMs and ECs and the promotion of tumors have been discussed above. However, evidence has shown that PMN-MDSCs are mainly recruited to tumor tissues by chemokines to play a pro-tumor effect. Sushil et al. found that CXCL2 and CCL22 promoted MDSC recruitment to primary tumors and metastatic sites in triple-negative breast cancer (137). However, inhibiting the expression of CXCL1 and CXCL2 reduces the recruitment of MDSCs in ovarian cancer (138). ECs are the main sources of chemokines. Studies have shown that in a variety of tumors, TECs can secrete a large number of chemokines, such as CCL2, CXCL8 and CXCL12 (139, 140). Chemokine receptors are distributed on the cell membrane of MDSCs, and chemokine recruit MDSCs to the tumor site by binding these chemokine receptors and promote tumor progression (141). After knocking down the chemokine receptor (CXCR2) in myeloid cells, the recruitment of MDSCs is reduced and vascular remodeling is inhibited (142). The above studies show that TECs play a key role in MDSCs recruitment and tumor progression. Similarly, MDSCs can also regulate TECs. A study found that MDSCs may interact with lysosomal acid lipase to cause dysfunction of ECs (16). Moreover, in vitro experiments have shown that the culture supernatant of PMN-MDSCs can significantly promote the tube formation of HUVECs (143). This finding indicates that PMN-MDSCs may secrete some pro-angiogenic factors. Later studies confirmed that MDSCs might promote endothelial cell angiogenesis through the production of VEGF-A, Ang2 and HIF-1α and unregulated angiogenesis by activating the STAT3 signaling pathway (144). In summary, TECs play key roles in the pro-tumor effect of MDSCs and exploring the mechanisms involved in MDSCs-induced tumor angiogenesis will provide new insights for anti-angiogenesis therapy.

3.3.4 Extracellular Matrix

Along with stromal cells, the extracellular matrix is another important part of the TME. The extracellular matrix (ECM) is a noncellular three-dimensional polymer network composed of
collagen, elastin, fibronectin, laminin and other proteins. It can regulate a variety of cellular functions and is essential for maintaining normal homeostasis. The production and maintenance of the ECM is an important aspect of endothelial cell function. The ECM provides mechanical support to ECs and mediates signaling (145) via secreted molecules (146) and mechanical strain (147) between cells. In the absence of angiogenesis stimulation, ECM helps ECs to maintain in a quiescent state. In the tumor growth stage, the ECM is degraded in the TME and the basement membrane is destroyed, which cause ECs migrate from existing blood vessels to newly formed blood vessels. In this progress, MMPs play a major role. MMPs are the main enzyme in degrading extracellular matrix proteins, and can participate in the occurrence and development of tumors in different ways. On the one hand, MMPs can regulate the expression of VEGF to promote formation of neovascularization and increase blood vessel permeability (148). Moreover, MMPs can also degrade collagen to promote the migration of ECs, which adhere to the temporary ECM through specific integrins to form a tubular structure and obtain a continuous lumen (149). On the other hand, it can degrade a variety of extracellular matrix components to promote tumor progression. For example, MMP-2 promotes the transendothelial migration of breast cancer cells by degrading the laminin component of the ECM (150). MMP9 can bind to CD44 to degrade fibronectin, which leads to the active form of TGF-β releasing (151), then TGF-β enhances the conversion of ECs to endothelial mesenchyme and increases the quantity of CAFs to promote tumor progression (152). In short, the ECM is the main regulator of angiogenesis and vascular stability. However, it is not a stable component and will undergo tremendous changes under a variety of pathological conditions including tumors. Therefore, promoting the normalization of ECM composition can be used as a new therapy for antitumor angiogenesis.

4 CONCLUSION

This review summarizes the tissue differences between tumor blood vessels and normal blood vessels. Tumor blood vessels are highly irregular in shape with increased vascular permeability and leakage, which contributes to the tumor metastasis. Contrary to previous ideas, recent studies suggest that TECs differ from NECs in many aspects. Different studies have revealed TECs originate from various cell types, for example bone marrow-derived endothelial progenitor cells and tumor cells. The development of TECs and angiogenesis are affected by the intricate TME including infiltrated various cells and inflammatory cytokines, growth factors and so on. All the above described factors can contribute to the different gene expression profile between TECs and NECs, which affects the formation and function of tumor blood vessels. Moreover, identification of relevant factors influencing the structural and functional differences between TECs and NECs are also imminent to provide clues for target therapies of angiogenesis. Taken together, this review summarizes the most recent research developments in the field of the molecular and cellular features of angiogenesis of cancer biology. Importantly, this review systematically introduces the current knowledge on TECs, and provides new insights into the potential of targeted therapies.

AUTHOR CONTRIBUTIONS

JL drafted the manuscript, SW and GZ drew the figures, BH contributed equally to plot the table, BZ and QB revised the review. All authors contributed to the article and approved the submitted version.

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