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Endothelial cells in colorectal cancer

Chen WZ *et al*. Endothelial cells in CRC

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**Abstract**

The dependence of tumor growth on neovascularization has become an important aspect of cancer biology. Tumor angiogenesis is one of the key mechanisms of tumorigenesis, growth and metastasis. The key events involved in this process are endothelial cell proliferation, migration, and vascular formation. Recent studies have revealed the importance of tumor-associated endothelial cells (TECs) in the development and progression of colorectal cancer (CRC), including epithelial proliferation, stem cell maintenance, angiogenesis, and immune remodeling. Decades of research have identified that the molecular basis of tumor angiogenesis includes vascular endothelial growth factors (VEGFs) and their receptor family, which are the main targets of antiangiogenesis therapy. VEGFs and their receptors play key roles in the pathology of angiogenesis, and their overexpression indicates poor prognosis in CRC. This article reviews the characteristics of the tumor vasculature and the role of TECs in different stages of CRC and immune remodeling. We also discuss the biological effects of VEGFs and their receptor family as angiogenesis regulators and emphasize the clinical implications of TECs in clinical treatment.

**Key words:** Colorectal cancer; Tumor-associated endothelial cells; Heterogeneity; Vascular endothelial growth factor; Immune remodeling

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**Core tip:** In 1971, Folkman highlighted the importance of angiogenesis in tumor growth. The key events involved in this process are endothelial cell proliferation, migration, and vascular formation. Recent studies have revealed the importance of tumor-associated endothelial cells (TECs) in the development and progression of colorectal cancer (CRC). However, few systematically reviewed the role of TECs in CRC. Our objective is to compare the characteristics of normal endothelial cells and TECs, review the role of TECs in the stages of CRC, and discuss the possibility of TECs to serve as a biomarker to predict the prognosis and a potential therapeutic target.

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**INTRODUCTION**

Colorectal cancer (CRC) is the leading cause of cancer death worldwide and is the second most common cancer in women and the third most common cancer in men[1,2]. A considerable number of patients have died from metastatic diseases, even after systemic therapy[3,4]. Although new drugs and treatments have emerged in recent years, the median overall survival of metastatic CRC remains less than 2 years[5].

In 1971, Folkman[6] highlighted the importance of angiogenesis in tumor growth. Targeting tumor blood vessels has been recognized as a promising strategy for cancer therapy. The tumor blood vessel unit includes endothelial cells, pericytes, endothelial progenitor cells, smooth muscle cells and extracellular matrix. Tumor blood vessels provide a vector to transport nutrition and oxygen and clear metabolite waste in tumor tissues. They also serve as gatekeepers to facilitate the metastasis of tumor cells[7]. The angiogenesis process is highly complex and dynamic and includes recruiting germinated blood vessels from existing blood vessels and incorporating endothelial progenitor cells into the growing vascular bed[8]. The main pathway involved in this process includes vascular endothelial growth factor (VEGF) and its receptor family (VEGF receptor, VEGFR)[9,10]. Studies have shown that the VEGF family is upregulated in the tumor vasculature and can activate downstream Akt signaling[10-12]. More importantly, the VEGF family promotes the transduction of tumor cells into endothelial cells[13]. Tumor-associated endothelial cells (TECs) could cause local immune remodeling. TECs promote tumor evasion by suppressing the response to inflammatory activation and downregulating leukocyte adhesion molecules[14]. VEGF overexpression has been proved to be associated with tumor progression and poor prognosis in CRC[15].

In this article, we compare the characteristics of normal endothelial cells (NECs) and TECs, review the role of TECs in the stages of carcinogenesis development and metastasis in CRC and highlight their effects on immune remodeling. We also discuss the biological effects of the VEGF/VEGFR family as angiogenesis regulators and emphasize the clinical implications of TECs in CRC treatment.

**TUMOR-ASSOCIATED ENDOTHELIAL CELL CHARACTERISTICS**

Endothelial cells line the innermost layer of the blood and lymphatic vessels and form a selectively permeable exchange barrier between the blood and tissue[16]. In normal tissues, endothelial cells arise from blast-like bipotential cells[17]. They form a uniform and continuous cell monolayer with few cytoplasmic processes. Endothelial cells are involved in a number of physiological processes, including the regulation of vasomotor tension, permeability, vascular tone and blood vessel growth, the transport of cells and nutrients, the maintenance of blood flow[18] and the quiescence of the inflammatory response[19]. These physiological functions of the endothelium are indispensable for body homeostasis. The dysfunction and activation of the endothelial cell response could cause many diseases, including peripheral vascular disease, stroke, heart disease, diabetes, insulin resistance, chronic kidney failure, tumor growth, metastasis, and venous thrombosis[20,21].

In contrast to NECs, TECs originate not only from endothelial progenitor cells but also from the differentiation of cancer stem cells (CSCs). It has been reported that poorly differentiated HCT116 CRC cells can be converted into TECs under specific hypoxia conditions *via* VEGFR-2[22]. In addition, similar somatic mutations are found in both ECs and tumor cells. This evidence indicates that TECs may be derived from tumor cells. Moreover, it has been demonstrated that CSCs may also generate pericytes to support vessel function and tumor growth[23]. Compared to NECs, TECs have abnormal structural and functional characteristics. In tumor tissues, tumor vessels often have a tortuous appearance, with uneven blood vessel diameters due to immature vessel wall compression by tumor cells[24]. Abnormalities in tumor blood vessels are attributed to paramorphic TECs and unbalanced expression of angiogenic factors and inhibitors. Irregular TECs with fragile cytoplasmic protrusions could penetrate the vessel lumen and create openings on the vessel wall[24]. Therefore, TECs do not form a regular single layer and have normal barrier function[25]. Pericytes are also present on TECs, which physically surround the blood vessels, establish tight junctions with ECs and participate in the regulation of ECs survival. However, tumor polarized pericytes form impaired electronic coupling and abnormally loose associations with TECs[26]. Basement membrane of tumor vessels also has a loose association with ECs, and consists of abnormal focal holes. Owing to these abnormal structure of tumor vascular vessels, tumor cells could infiltrate through the blood vessels, which is the first step in metastasis[27]. Due to the extravasation of intravascular fluids and plasma proteins, a remarkable increase occurs in the interstitial tissue pressure[28]. High interstitial fluid pressure impair endothelial monolayer function, causes the blood vessels to collapse and reduces blood flow, resulting in the irregular blood flow or even no perfusion in tumor vessels[29]. In addition, tumor blood vessels are unevenly distributed in tissues, and there are many areas where blood vessels are insufficiently supplied, resulting in a local hypoxic environment[30]. Hypoxia then promotes angiogenesis by supporting the expression of multiple angiogenic factors *via* hypoxia inducible factor (HIF) activation, which could contribute to tumor growth and metastasis[31,32]. The angiogenic growth factors triggered by insufficient local perfusion and chronic hypoxia in tumor tissue can also result in reduced leukocytes recruitment, a lack of immune activation and resistance to chemotherapy and radiotherapy, which is called “endothelial cell energy”[14]. In a mouse model of human LS174T colon carcinoma, researchers found that leukocyte adhesion was diminished in vessels inside the tumor, which was related to lower intercellular adhesion molecule 1 (ICAM1) expression on TECs, while anti-VEGF antibody prevented rescued this result[33].

Heterogeneity can be found in the cell morphology, function and gene expression of TECs. A study from Japan suggested that phenotypic heterogeneity may be induced by different tumor microenvironment (TMEs). The researchers isolated two types of TECs from high-metastatic (HM) and low-metastatic (LM) tumors, and compared their characteristics. The HM-TECs were more proliferative, motile, sensitive to VEGF, and invasive to the ECM than the LM-TECs. In addition, HM-TECs showed upregulation of the angiogenesis-related genes VEGFR-1, VEGFR-2 and VEGF. Akt phosphorylation levels were higher in HM-TECs than in LMTECs. The researchers also reported that a Stem-like phenotype existed in HM-TECs[34]. In addition, a recent study of human patients with CRC investigated the impact on TEC heterogeneity in different TME and discovered that TEC heterogeneity is regulated by SPARCL1. SPARCL1 in TECs promotes cell quiescence and vessel homeostasis, thus contributing to a favorable prognosis[35]. Recent studies have revealed the importance of TECs in the different stages of CRC, including carcinogenesis, development, metastasis, and immune remodeling (Figure 1).

**TUMOR-ASSOCIATED ENDOTHELIAL CELLS AND COLORECTAL CANCER CARCINOGENESIS**

CRC carcinogenesis is affected by many genetic and environmental factors[36]. Many studies have shown that CSCs exist in CRC. Although they account for a small proportion, CSCs play an important role in carcinogenesis, development and metastasis. These cells not only initiate and maintain tumor growth but also mediate chemical resistance and promote CRC recurrence[37,38]. TECs can release soluble factors by paracrine action to increase the CSC ratio, clonal sphere formation, tumorigenicity, and chemical resistance. These effects are caused by the activation of Notch signaling in CRC cells and changes in the CSC phenotype[39]. In addition, endothelial cells can regulate the CSC phenotype and chemoresistance *via* the Akt-mediated induction of the NANOGP8 pathway in a paracrine fashion[40].

Angiogenesis, a process guided by proliferation of TECs, is also a key factor in carcinogenesis. For one thing, abundant blood vessels can provide nutrients and oxygen for tumor cells and remove toxic metabolic products. Besides, proliferative factors such as RAS signaling also participate in the initiation of neovascularization as well as TME[41]. A significant increase in VEGF and microvessel density was found in the colon pre-malignant lesions such as adenoma with dysplasia[42,43]. The VEGF-related gene family of angiogenic and lymphangiogenic growth factors comprises six secreted glycoproteins called VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placenta growth factors (PlGF)-1 and PlGF-2[44-46]. VEGFs mediate multiple functions *via* the stimulation of cognate receptors on TECs. TECs were found to overexpress specific genes, such as VEGFR, tumor endothelium markers (TEMs) and EGFR, thereby promoting angiogenesis and carcinogenesis. TEMs are specific genes of TECs that are involved in tumor-specific angiogenesis[47], and they include TEM1, TEM5, TEM7, TEM7R and TEM8[48]. Moreover, in several experimental models, the expression of VEGF and VEGFR were associated with the progression of adenoma, indicating that both of them could be targeted to reduce the risk of carcinogenesis[49,50].

**TUMOR-ASSOCIATED ENDOTHELIAL CELLS AND COLORECTAL CANCER DEVELOPMENT**

The development of neo-vasculature promoting tumor growth is now a well-known aspect of cancer biology. The vital regulator of this process is VEGF, which is overexpressed in approximate 40% to 60% of CRC cases and correlated with disease progression. As we have described above, hypoxia is developed in the solid tumor and further induce the activation of HIF1, which increases the expression of pro-angiogenic factors such as VEGF-A, angiopoietin2 and CXCL12[51]. Activation of the VEGF receptor and CXCL12-CXCR4 pathway polarizes the TME towards more pro-angiogenic state[52]. Besides immunosuppressive cells such as M2-macrophages, myeloid derived suppressor cells, granulocytes, cancer-associated fibroblasts and pericytes are polarized as well and play crucial role in angiogenesis and tumor development. Moreover, VEGFs play an important role in the mobilization of endothelial progenitor cells from the bone marrow to distant neovascularization sites. VEGFs could also enhance vascular permeability and is involved in the angiogenetic function of platelet-derived growth factor (PDGF) family in several model systems[53].

In addition to angiogenesis, TECs have been demonstrated to promote cancer cell growth and chemo-resistance by releasing soluble factors *via* a paracrine way in multiple solid tumors such as lung cancer and gastric cancer, which is referred as “angiocrine”[54,55]. Angiocrine factors mainly consist of growing factors such as VEGF-A, PGF, PDGF, Jagged 1/2 and NO, and adhesion molecules such as E-selectins, ICAM1 and vascular cell adhesion molecule 1 (VCAM-1). A recent study used a transgenic mouse model (EndoIRKO-Min) to detect the role of insulin in TECs during tumor development[56]. The authors suggested that insulin decreased the expression of VCAM-1 and leukocyte adhesion in TECs with intact insulin receptors. Knocking out insulin receptors in endothelial cells promotes intestinal tumor formation. Human hepatic sinusoidal endothelial cells could secrete macrophage migration inhibitory factor, to promote the chemotaxis and outgrowth of CRC in liver pro-metastasis.

**TUMOR-ASSOCIATED ENDOTHELIAL CELLS AND COLORECTAL CANCER METASTASIS**

The formation of remote CRC metastasis is the main cause of death in patients. A great of researches have shown that TECs play critical role in CRC metastasis. TECs in metastatic tumors express higher levels of vascular secretion factors than TECs in non-metastatic tumors, suggesting that TECs may affect the behavior of tumor cells[57]. This phenomenon is further confirmed by the result that TEC apoptosis could inhibit liver metastasis and improve the survival rate of a liver metastasis CRC animal model[58]. TEC proliferation, migration and differentiation are the key steps during the neovascularization and spreading of CRC cells promoted by tumor-derived interleukin-33 (IL-33) in the liver[59,60]. Blocking IL-33 signaling could inhibit angiogenesis and reduce liver metastasis[59,60]. TECs could also promote the formation of CRC-CSCs by secreting Jagged-1, which activates NOTCH signaling in tumor cells and serves as an important factor in CRC metastasis[39,61-63]. It has also been reported that miR-497 can inhibit CRC metastasis and invasion *in vitro* and *in vivo* by mediating the VEGF-A/ERK/MMP-9 signaling pathway[64]. In addition, VEGF-C signaling *via* VEGFR3 promotes lymphangiogenesis and metastasis by orthotopic colorectal tumors in mice and reduces lymphatic endothelial barrier integrity[65].

TECs could promote the transendothelial migration of CRC cells by expressing E-selectin. Studies have shown that in mouse models with E-selectin overexpression in the liver, more metastases are observed in the liver than at other sites, suggesting that E-selectin present on activated TECs promotes tumor cell metastasis[66,67]. The binding of death receptor-3 (DR-3) to E-selectin could activate the mitogen-activated protein kinases p38 and ERK, thus inducing signaling in endothelial cells and increasing endothelial permeability, which allows the trans-endothelial migration of cancer cells[68,69]. The binding of human CRC cells to E-selectin-expressing TECs or a recombinant E-selectin/Fc chimera leads to the activation of SAPK2/p38, and blocking the activation of SAPK2/p38 in these CRC cells inhibits their transendothelial migration[70]. In addition, the selectin-mediated interaction between circulating tumor cells with blood components such as platelets and leukocytes causes endothelial cell activation, induces C-C chemokine ligand 5 (CCL5) production and promotes metastasis[71,72]. A study found that an anti-P-selectin monoclonal antibody inhibited the metastasis of gastric cancer in mouse models without adversely affecting immune function[73]. The use of glycometabolic inhibitors to inhibit the O-glycosylation of mucin and fucosyltransferase, which indirectly reduced the production of selectin ligands, suggests that cancer cell metastasis is attenuated after treatment with glycometabolic inhibitors[74-76].

**TUMOR-ASSOCIATED ENDOTHELIAL CELLS AND IMMUNE REMODELING**

TECs can remodel the local immune system and help tumor cells escape immunity in many ways. NECs can express adhesion molecules to promote peripheral leukocyte capture and release chemokines to facilitate leukocyte migration into tissues[77]. Integrins bind to immunoglobulin superfamily members on endothelial cells, resulting in the adhesion of leukocytes to endothelial cells[78]. TECs lack a response to inflammatory activation (endothelial anergy) and downregulate leukocyte adhesion molecules. TECs can also inhibit the chemotaxis and activation of immune cells and regulate the expression of immune co-stimulatory and inhibitory molecules to promote immune tolerance[6,79]. TECs also show increased expression of PD-L1, which in turn can bind to PD-1 in activated lymphocytes to inhibit T cell activation[80-82]. In addition, FasL expression in TECs promotes their ability to kill effector CD8+ T cells, causing TEC-associated immune cell death and enhanced tumor escape[83,84]. Activated or damaged endothelial cells could release E-selectin, which is chemotactic to neutrophils and contributes to the migration of neutrophils[85,86]. Leukocytes then migrate out of the blood vessels and into the tissue through the endothelial cell layer and underlying basement membrane. The maturation and normalization of tumor blood vessels restore the potential of tumor endothelial cells to recruit and direct circulating immune cells into tumor tissues[87,88].

Researches have proved that angiogenesis inhibitors can promote tumor vascular stability and vascular bed normalization, as well as restore immune surveillance[89,90]. Endothelial cell activation can usually be induced by a variety of factors, including circulating inflammatory cytokines, such as tumor necrosis factor and IL, and reactive oxygen species[87,91,92]. Antiangiogenic therapy corrects structural abnormalities and dysfunction in tumor blood vessels[24,93,94], promotes lymphocyte infiltration and enhanced cytotoxic T cell activity, thus reflecting the successful activation of anti-tumor T cell immunity[95,96]. In addition, antiangiogenic therapy enhanced the efficacy of anti-PD-L1 therapy in preclinical studies using mouse breast and pancreatic neuroendocrine tumor models, and anti-PD-L1 therapy sensitized tumors to antiangiogenic therapy and prolonged their efficacy as well[95].

**CLINICAL IMPLICATIONS**

***Therapy targets***

Tumor cells produce several angiogenic factors that promote neovascularization, including VEGF, basic fibroblast growth factor, angiopoietins, hepatocyte growth factor, chemokines, and PDGF[97]. As we have reviewed above, VEGF is the most important identified regulator of angiogenesis, and its expression is significantly increased in metastatic colorectal tumors[18]. The VEGF-VEGFR axis consists of multiple ligands and receptors with different and overlapping ligand-receptor binding specificities. The VEGF family is consisting of VEGFA, VEGFB, VEGFC, VEGFD and PGF, among which VEGFA is studied more than other members and is usually simplified as VEGF. VEGFRs are ligands binding to the tyrosine kinases (RTKs) of these VEGFs, such as VEGFR1, VEGFR2 and VEGFR3. VEGF-VEGFR activation can trigger a network of signaling processes that promote endothelial cell survival, growth and migration from the pre-existing vasculature. In addition, VEGFs expression are related to increased vascular density, mediate vascular permeability and are associated with malignant exudation[98,99]. Thus, the role of VEGF in promoting tumor pathogenesis and angiogenesis has led to the development of agents that selectively target the VEGF-VEGFR axis. Studies of various anti-VEGF/VEGFR therapies have shown that these drugs can effectively inhibit angiogenesis and tumor growth in preclinical models. Recently, several anticancer therapies, such as neutralizing antibodies to VEGF, low molecular weight VEGFR tyrosine kinase inhibitors, and soluble VEGF constructs (VEGF-Trap), have been developed to block this factor[100,101]. Bevacizumab, a recombinant humanized monoclonal IgG1 antibody that neutralizes VEGF-A, has been shown to increase survival in stage IV CRC patients in combination with chemotherapy[36,102,103]. Aﬂibercept is a fully humanized recombinant fusion protein consisting of a VEGF-binding segment (VEGFR-1 and VEGFR-2) fused to the Fc segment of human immunoglobulin G1. This fusion protein has been associated with survival benefits in metastatic CRC patients when combined with FOLFIRI chemotherapy[104]. Regorafenib, an orally active inhibitor of angiogenic tyrosine kinases (VEGFR-1 and VEGFR-3), appears to be active in patients with metastatic CRC who experience disease progression after standard treatment[63,105].

***Prognostic markers***

Progressive survival and overall survival could be marginally improved when metastatic CRC patients receive an antiangiogenic mediator combined with chemotherapy[106]. There are no clear clinical or biological tools available to select patients who may benefit from VEGF pathway inhibitors or to exclude those who may experience specific adverse events[107,108].Current evidence suggests that some specific markers in the peripheral blood have some predictive value, such as increased VEGF expression, decreased circulating endothelial cells, decreased VEGFR-2 expression, KRAS and BRAF mutations, polymorphisms in VEGF pathway components, and microvascular density[62]. Circulating endothelial cells (CECs) have been reported to serve as a potential surrogate biomarker for angiogenesis. A study including 140 patients with metastatic CRC suggested that CECs were independent predictors of poor survival (HR = 1.81; *P* = 0.03)[109]. The clinical value of CECs and their subpopulations [total CECs (tCECs) and resting CECs (rCECs)] as biomarkers in antiangiogenic therapy has been introduced[101]. Patients who achieved a radiological response showed a significant decrease in rCECs and a decreasing trend for tCECs in comparison with patients not achieving a response[110]. However, the vascular structures of specific cancers at different clinical stages and under different treatment regimens are still unknown[62,111].

**FUTURE DIRECTIONS AND CONCLUSION**

Despite the limitations of our review, TECs have been shown to have positive effects on the development of tumor cells and play a key role in cancer progression. TECs play an important role in the carcinogenesis, development and metastasis of CRC and participate in TME immune remodeling. Studies on the molecular events and animal models of TECs have increased our understanding of TEC-related signaling pathways and cellular biology. Clinically, antiangiogenic (anti-VEGF) therapy for metastatic CRC has become the standard therapy. Despite the increasing evidence that has been reported in this field, antiangiogenic therapy resistance is still a challenging issue. Several mechanisms can account for this therapeutic failure, such as the heterogeneity of TECs. Understanding the interaction between TECs and the TME would help to improve existing treatment options and discover new molecular targets. How to identify TEC-specific biological targets for anti-angiogenesis therapy in clinical decision-making remains a challenge in the near future. In addition, it is necessary to further understand the VEGF-VEGFR family and its role in tumor angiogenesis. For example, is there a certain VEGF-VEGFR pair more important than others in tumor angiogenesis? Which VEGF-VEGFRs are the key for targeting TECs in tumor angiogenesis? What is the role of VEGF-VEGFRs in tumor cell growth and survival? We await in-depth studies to answer these questions. A next step would be to design biomarker-based anti-VEGF trials for identifying patients who could benefit from this therapy and to develop new treatment strategies to overcome anti-VEGF resistance. A comprehensive and continuous understanding of the biological effects of TECs and VEGF-VEGFRs in angiogenesis remains challenging, but there is potential for promising breakthroughs.

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**Figure 1 The role of tumor-associated endothelial cells in the different stages of colorectal cancer.** TECs: Tumor-associated endothelial cells; CSCs: Cancer stem cells.