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Anti-angiogenesis in colorectal cancer therapy

Zhenni Yang[1,2] | Xuqian Zhang[1,3] | Xiaozhe Bai[2] | Xiaonan Xi[4] | Wentian Liu[1] | Weilong Zhong[1]

[1]Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, Tianjin Institute of Digestive Diseases, Tianjin Key Laboratory of Digestive Diseases, Tianjin, China

[2]Department of Gastroenterology and Hepatology, Xing'an League People's Hospital, Xing'an League, China

[3]Department of Gastroenterology and Hepatology, China Aerospace Science and Industry Corporation, Beijing, China

[4]State Key Laboratory of Medicinal Chemical Biology and College of Pharmacy, Nankai University, Tianjin, China

Correspondence
Xiaonan Xi, State Key Laboratory of Medicinal Chemical Biology and College of Pharmacy, Nankai University, Tianjin 300071, China.
Email: 9820210009@nankai.edu.cn

Wentian Liu, Tianjin Key Laboratory of Digestive Diseases, Department of Gastroenterology and Hepatology, Tianjin Institute of Digestive Diseases, Tianjin Medical University General Hospital, Tianjin 300052, China.
Email: tliu01@tmu.edu.cn

Weilong Zhong, Tianjin Key Laboratory of Digestive Diseases, Department of Gastroenterology and Hepatology, Tianjin Institute of Digestive Diseases, Tianjin Medical University General Hospital, Tianjin 300052, China.
Email: zhongweilong@tmu.edu.cn

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Abstract

The morbidity of colorectal cancer (CRC) has risen to third place among malignant tumors worldwide. In addition, CRC is a common cancer in China whose incidence increases annually. Angiogenesis plays an important role in the development of tumors because it can bring the nutrients that cancer cells need and take away metabolic waste. Various mechanisms are involved in the formation of neovascularization, and vascular endothelial growth factor is a key mediator. Meanwhile, angiogenesis inhibitors and drug resistance (DR) are challenges to consider when formulating treatment strategies for patients with different conditions. Thus, this review will discuss the molecules, signaling pathways, microenvironment, treatment, and DR of angiogenesis in CRC.

KEYWORDS
angiogenesis, colorectal cancer, drug resistance, therapy, VEGF

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1 | INTRODUCTION

As the third most common malignancy worldwide, colorectal cancer (CRC) refers to the malignant transformation of colorectal cells. The global incidence of CRC has increased in recent decades.[1] The mortality rate of CRC ranks second next to lung cancer. When diagnosed, approximately one-quarter of patients present with metastatic disease.[2] Thus, a cure for cancer based on the mechanism of tumor formation is necessary. Complex networked systems are involved in tumor cell proliferation, survival, angiogenesis, invasion, and metastasis. Given that malignant tumor cells need nutrients, including oxygen and growth factors, to support their growth, they require sufficient blood circulation around them. Tumor vessel formation is an important promoter of tumor growth and metastasis. Folkman proposed that tumor angiogenesis is the beginning of tumor development.[3] However, tumor-promoting angiogenesis was not demonstrated until vascular endothelial growth factor (VEGF)-A was identified and its monoclonal antibody was manufactured, which ultimately clarified the preliminary mechanism between neovascularization and tumorigenesis.[3] Angiogenesis indicates that neonatal blood vessels take shape from existing blood vessels. This process is related to the proliferation, migration, and differentiation of endothelial cells (ECs), and multiple procedures during its process are rigorously regulated.[4] In addition, angiogenesis is primarily regulated by growth factors, cytokines, oncogenes, and other modulators.[5] Considering its key role in tumor formation and development, it might be a promising target in tumor treatment.[6] Although various successful studies have been conducted, its mechanism remains unclear, and the effects of targeted therapy are also controversial. These issues will be briefly discussed below.

2 | ANGIOGENESIS IN TUMORS

Angiogenesis is rather prominent in various aspects under normal physiological conditions, including tissue growth, wound healing, menstrual cycle, and placental implantation.[7] Regular occurrence of angiogenesis heavily depends on the dynamic equilibrium between the promoting and inhibiting function systems.[8] Angiogenesis is the process of new blood vessel formation. This process plays a key role in the progression of all types of cancers. Tumor masses have high nutritional requirements to support their need for growth; thus, new blood vessels are gradually formed around them to persistently supply oxygen and glucose.[9,10] In malignant tumors, angiogenic processes are sustainably maintained in a pro-angiogenic milieu,[11] similar to a wound that never heals.

2.1 | Characteristics of tumor vasculature

Tumor blood vessels are structurally and functionally abnormal compared with normal blood vessels. Besides being heterogeneous, the diameters of most tumor blood vessels are wide and their shapes are curved in different sizes, with few pericytes and defective basement membranes (BMs).[12] Tumor blood vessels are also hyp erpermeable, partly because of the overproduction of VEGF. The loose intercellular junction of tumor endothelial cells (TECs), lack of pericytes, and smooth muscle cells lead to extravasation of plasma fluid and proteins.[13] TECs with altered phenotypic release factors promote tumor progression and downregulate suppressing factors, finally promoting tumor formation adjacent to tumor cells in space.[14] Furthermore, tumor blood vessels are molecularly different because of their responses to environmental cues through transcriptional regulation.[15] In adenoma with dysplasia, premalignant lesions of the colon, VEGF ($p < 0.0005$), and microvessel density ($p < 0.0005$) significantly increase.[16] Thus, tumor blood vessels have different characteristics compared with normal blood vessels (Figure 1).

2.2 | Types of vascular formation

Tumor blood vessels are formed in various patterns, such as vasculogenesis, sprouting angiogenesis, intussusceptive angiogenesis, and vascular mimicry. Vasculogenesis and angiogenesis are the two main types of vascular formation. In addition, tumor angiogenesis is the most extensively studied pattern of new vessel generation.[17] Vasculogenesis is the process in which endothelial and hematopoietic progenitor cells in the blood cycle are recruited by cytokines and chemokines to create new vessels.[18] Sprouting angiogenesis is the sprouting of neoplastic capillaries from existing ECs and tumor blood vessels; it might be the most characteristic way for the tumor to obtain oxygen and nutrients.[19,20] VEGF is the key player driving this process, which occurs in pathological situations in malignant tumors.[21] However, studies on intussusceptive angiogenesis are limited; in this type of angiogenesis, transluminal tissue pillars grow in pre-existing vessels and then integrate to recreate the vascular system.[22] It is also referred to as a "complementary method" to sprouting angiogenesis.[23] Contrary to canonical tumor angiogenesis, vasculogenic mimicry (VM) supplies independent blood perfusion to tumor cells.[20] The phenomenon of vascular mimicry exists in various kinds of tumor masses, including CRC.[24] The mechanism is a complex process and has not been distinctly distinguished. In particular, CRC stem cells (CRCSCs) are transdifferentiated to create vascular tube structures that assist tumor blood supply independent of tumor

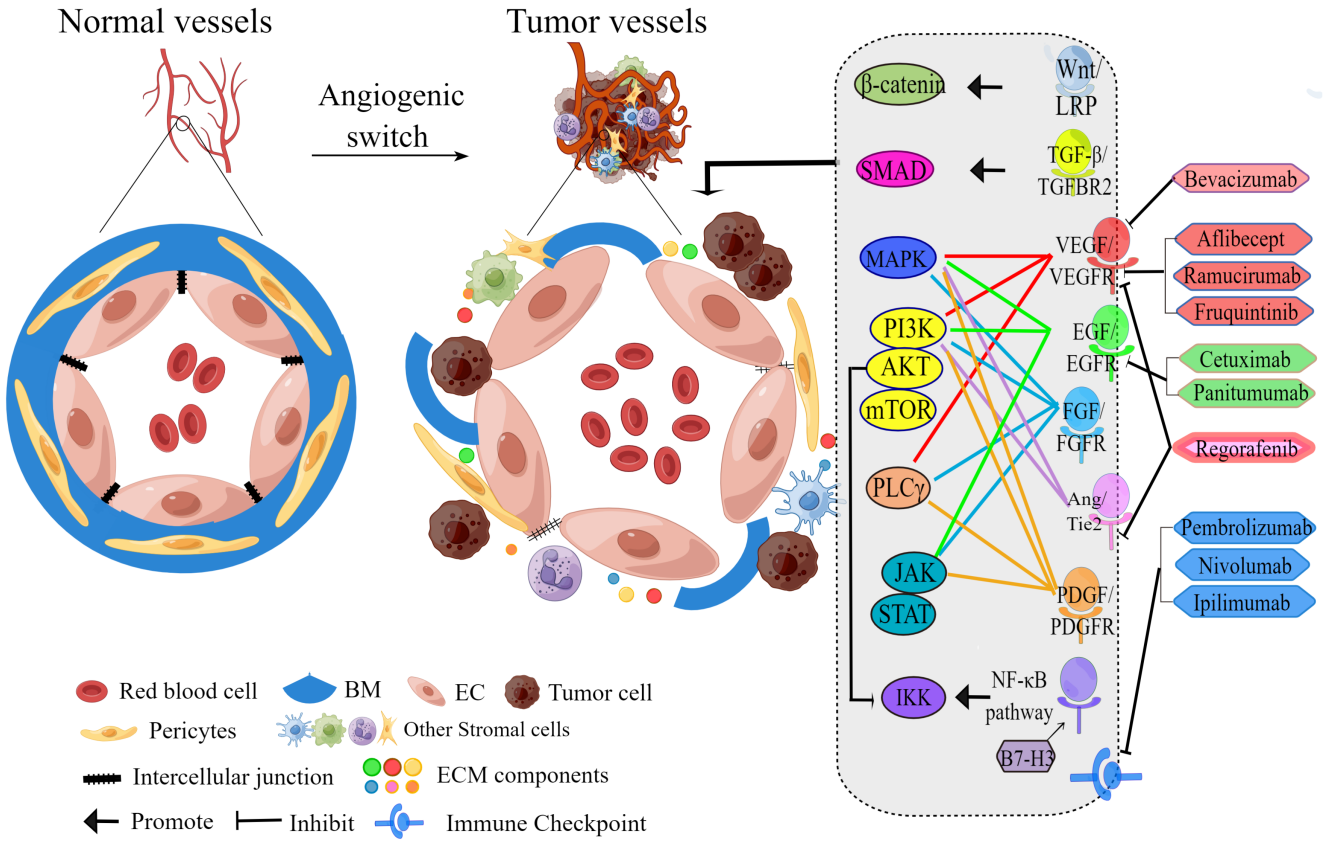

FIGURE 1 Full-text mechanism diagram. In normal blood vessels, endothelial cells have tight junctions with a normal number of surrounding pericytes and intact basement membranes (BMs). The diameters of most tumor blood vessels are wide, and their shapes are curved in different sizes, with few pericytes around and defective BMs. Tumor blood vessels are also hyperpermeable. The tumor microenvironment consists of stromal cells, ECM components, and exosomes. Many growth factors that promote angiogenesis and their signaling pathways are involved in these changes. Multiple anti-angiogenesis agents target different molecules. Drugs targeting immune checkpoints are also illustrated in this figure.

angiogenesis.[25] Nevertheless, epithelial–mesenchymal transition (EMT) and tumor microenvironment (TME) are related to sprouting angiogenesis.[20] As VM cells directly come into contact with blood flow, shed cells can be easily transported. Therefore, VM is related to advanced malignant tumors with high invasion and high metastasis, which are indicators of poor patient prognosis.[26] Moreover, vessel co-option indicates that tumor tissue receives oxygen and nutrients from pre-existing vessels rather than creating new vascellums.[27–29] Vessel co-option is a possible cause of anti-angiogenic drug resistance (DR). Frentzas showed that vessel co-option might be involved in an undesirable response to anti-angiogenic agents in patients with CRC and hepatic metastases.[28] Utilization of numerous angiogenesis types, together with some normal physiological balance disruptions, can eventually lead to the unbridled growth of tumor cells.

3 | ANGIOGENESIS AND COLORECTAL CANCER

Similar to other observed solid tumors, CRC development, progression, and metastasis depend heavily on angiogenesis.[30,31] Numerous molecules participate in the process, such as growth factors (VEGF and epidermal growth factors [EGFs]), fibroblast growth factor (FGF)-2, transforming growth factor (TGF)-α and TGF-β, angiopoietins (Angs), platelet-derived growth factor (PDGF), membrane-bound factors (integrins, ephrins, cadherins, matrix metalloproteinases [MMPs], and hypoxia-inducible factor-1 [HIF-1]).[32] Figure 1 illustrates some prominent pro-angiogenic factors.

3.1 | Molecules in angiogenesis

Vascular endothelial growth factor plays a crucial role in all forms of solid tumor growth and development, including CRC, by causing the formation of new blood vessels. Its high serum level is closely associated with CRC and its clinical stages.[33] Derived from tumor cells and the surrounding microenvironment, it is upregulated by hypoxia, growth factors, and cytokines such as IL-1, EGFs, PDGFs, and tumor necrosis factor (TNF)-α.[34–36] Furthermore, VEGF-mediated pathogenic effects on vascular permeability are primarily caused by junction remodeling, fenestra induction, and vesiculo-vascular organelles (VVOs).[37] As a survival factor, VEGF can accelerate the growth and prevent apoptosis of vascular ECs.[38] The seven

members of the VEGF family are VEGF-A to VEGF-F and placenta growth factor (PlGF).[35] Among them, VEGF-A, VEGF-B, and PlGF stimulate angiogenesis, whereas VEGF-C and VEGF-D are responsible for lymphangiogenesis.[39] VEGF-A undergoes alternative splicing of pre-mRNA from eight exons that leads to multiple isoforms, including VEGF121, VEGF165, VEGF189, and VEGF206.[34,40] The overexpressed VEGF165 increases the expansion of the tumor by promoting the recruitment of smooth muscle cells and vessel maturation in CRC.[41] Three VEGF receptors exist in CRC: VEGFR-1, VEGFR-2, and VEGFR-3. VEGFR-1 is related to tumor grade, Dukes' stage, and lymph node involvement; VEGFR-2 is correlated with lymph node involvement; and VEGFR-3 is not associated with any of the clinicopathological variables.[42] Activated VEGFR-2 leads to the activation of various signaling pathways, including the PLCγ and RAS/RAF/MEK/ERK (MAPK) pathways, by which the growth of EC is promoted, and the PI3K/AKT pathway, by which cells might avoid apoptosis.[43] VEGF might suggest metastasis and poor prognosis of CRC.[44] Overexpressed VEGF was detected in 70% of the cases in a study where 50 patients with CRC were enrolled, thereby revealing patients' poor prognosis as its tight relationship with tumor size, grade, and advanced tumor stage ($p=0.006$, $p<0.001$, $p<0.001$, respectively).[45] Meanwhile, overexpression of VEGF-A can reverse the inhibition of CRC cell proliferation, migration, invasion, and angiogenesis caused by HIF-1miR-150-5p.[46] Moreover, VEGF-VEGFR activity might be altered by HIF-1, COX-2, mutated K-RAS, and p53, which can promote the malignant phenotype of tumor cells such as proliferation and migration.[47]

Binding with EGFR and EGF can activate several crucial downstream signaling pathways, including PI3K/AKT/mTOR, MAPK, and Janus kinase (JAK)/Signal Transducer and Activator of Transcription 3 (STAT3), in regulating cell growth survival, invasion, and migration.[48–50] Dysregulation of the EGFR signaling pathway often occurs in human cancers, including CRC.[51] The erythroblastosis oncogene B (ErbB)/human epidermal growth factor receptor (HER) family is composed of tyrosine kinase receptors (RTKs), which contain ErbB1 (EGFR/HER1), ErbB2 (Neu/HER2), ErbB3 (HER3), and ErbB4 (HER4).[52,53] HER2 is a special member of the EGFR family, which is activated by heterodimerizing with other ligand-bound receptors but not ligands.[54] Gene amplification and missense mutation are the most common alterations in HER2 in 7%–8% CRC.[55] Approximately 5% of metastatic CRC tumors are facilitated by amplification or mutation of HER2, which might be a cancer-promoting factor, a prognostic and diagnostic biomarker, and a promising treatment target in CRC.[56] EGFR was found to be highly expressed in 85.2% of the 54 patients with cancer and correlated with tumor sizes and invasion depth ($p=0.043$ and $p=0.05$, respectively).[57] In addition, angiogenic-associated cytokines including VEGFA and IL-8, produced by the EGFR/Akt/NF-κB pathway, can be activated by highly dry human CRC cells, thereby inducing angiogenesis.[58] Heparin-binding EGF-like growth factor (HB-EGF), a member of the EGF family, and EGF are both pro-angiogenesis mediators that work by activating signaling pathways including PI3K, MAPK, and eNOS.[59]

Twenty-three small heparin-binding growth factor members contained in the FGF family are highly conserved and bind to one or more of the four highly affine FGFRs (FGFR1–FGFR4).[6] FGF2 is also a basic FGF (bFGF) that plays dual roles not only as a stimulator of VEGF-A expression in ECs or stromal cells but also as a regulator of VEGFR-2 signaling; thus, it is the most distinctive mediator in regulating angiogenesis.[60] In addition, high expression of FGFs and FGFRs in cancers including CRC and its pathway functional mechanism is related to tumor growth and invasion.[61] The MAPK, PI3K, PLCγ, or STAT pathways, activated by the binding of FGFs and FGFRs, participate in regulating cell proliferation, survival, differentiation, migration, and angiogenesis.[62] Knuchel et al. showed that fibroblasts induce cell contact-dependent CRC cell migration and invasion in vitro under 2D and 3D conditions by FGF-2. They are located on the fibroblast cell surface, activate SRC, and are mediated by FGFR, and the adhesion of cancer cell to fibroblast is dependent on αvβ5 integrin.[63]

The PDGF family harbors four heparin-binding polypeptide growth factors: A, B, C, and D. PDGF has a wide range of sources, such as activated platelets, ECs, epithelial cells, inflammatory cells, and glial cells. Moreover, its targets contain a broad category of cell types, including fibroblasts, pericytes, and smooth muscle cells.[64] All members in the PDGF family show strong angiogenic capacity in vivo, but the PDGF-B/PDGFRβ axis is the most representative.[65] PDGFs and PDGFRs are expressed in a large range of malignant tumors, and their activation is relevant to tumor growth, metastasis, invasion, and angiogenesis by stimulating downstream signaling pathways.[66] Pericytes and vascular smooth muscle cells (VSMCs) are the major targets of the PDGF/PDGFR signaling pathway, and they are known to promote angiogenesis. Higher preoperative intraplatelet VEGF and PDGF levels were detected in patients with CRC than in controls.[67] Higher expression of PDGF-BB was found in patients with CRC than in patients with adenoma. Consistently, the high levels of PDGFR α/β in patients with CRC were related to tumor invasion and metastasis.[68] PDGF-BB can elicit different downstream cascade pathways, including PI3K, PLCγ, MAPK, and JAK/STAT.[69]

Similar to VEGFs, Angs are one of the growth factors that can regulate vascular homeostasis and tissue repair. Three members are included in the human Angs family (Ang-1, Ang-2, and Ang-4), whereas their receptors are Tie-1 and -2, which are highly expressed transmembrane tyrosine kinases in ECs. Ang-1 and -2 are the main ligands of Tie-2; upon their activation, several downstream signaling pathways are stimulated, including PI3K/AKT, MARK, caspase-9, eNOS, Bad, and survivin.[70–72] Ang-1 promotes the recruitment of smooth muscle cells and pericytes to maintain the stabilization of mature vasculature.[73] However, as a prognostic factor in metastatic CRC,[74] Ang-2 guides vasculature conversion to an unstable state, which is easier to induce under the effect of VEGF.[75] Thus, Ang-2 might be highly expressed in tumor cells, whereas Ang-1 is the opposite. This deduction was verified by Ahmad et al. [76] Ang-2 was found to be an oncogene, whose malignant biological functions were investigated with shRNA in the LoVo CRC cell line, and its expression was convoluted with clinicopathological parameters in CRC.[77] Similar to VEGF, Ang-2 expression is induced by hypoxia in CRC.[78]

3.2 | Signaling pathway in angiogenesis

The phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway overexpression has been identified in various malignant tumors, including primary and metastatic CRCs.[79] Common in CRC, overactivation of mTOR signaling is strongly related to cancer progression, initiation, and DR. In CRC, mTOR significantly regulates proliferation, survival, growth, differentiation, and autophagy.[80] The PI3K/AKT/mTOR pathway is an intracellular signaling pathway composed of different kinases. Dysregulation of the PI3K signaling pathway is caused by the amplification and genetic mutation of the PI3K gene, encoding a catalytic and regulatory subunit of PI3K isoforms, and various protein mutations described in this pathway, which is responsible for cell growth, proliferation, survival, and angiogenesis.[81,82] For angiogenesis, mTOR is important for energy metabolism in ECs. It receives signals from PI3K-Akt, which can be upregulated by growth factors (VEGF, insulin-like growth factor-1 [IGF-1], and EGF) and their respective receptors.[83,84] PI3K/Akt signal transduction, which is essential for proliferation, metastasis, and survival, is one of the classic ways to increase blood vessel quantity and vascular permeability. Blood vessel reconstruction can be achieved by VSMC phenotype transformation.[13,85] Increased EGF upregulates hydrogen peroxide (H_2O_2) synthesis, which stimulates ribosomal protein S6 kinase beta-1 (S6K1) or p70S6K1 via the PI3K/AKT/mTOR pathway, eventually activating VEGF.[86] In CRC, other angiogenic factors can also be regulated by the PI3K/AKT pathway, including angiopoietins and nitric oxide (NO).[84]

The human TGF-β family consists of 33 identified members, including three TGF-β isoforms, three activins, growth and differentiation factors, and nodal and bone morphogenetic protein.[87] In addition, the SMAD family is the downstream effector of this signaling pathway.[88] Nevertheless, the absence of SMAD4 upregulates VEGF expression, increases the vascular quantity, and promotes tumor metastasis in the CRC HCT116 cell line.[89] The combination of TGF-β and its type II TGF-β receptors (TGFBR2) initially activates the TGF-β signaling pathway.[90] Under normal conditions, TGF-β suppresses normal intestinal epithelial cell proliferation and induces apoptosis and differentiation.[91] However, highly expressed TGF-β plays a pro-tumor role in the late stage of CRC, thereby increasing the production of several mitogenic growth factors, including TGF-α, FGF, and EGF.[92] Recently, CRC was suggested to be classified into four consensus molecular subtypes (CMS) based on transcriptomic properties and the following molecular characteristics: CMS1 (microsatellite instability [MSI] immune), with DNA damage repair and defective DNA mismatch repair, BRAF mutations, and diffuse immune infiltrate; CMS2 (canonical), with more oncogene expression with absent tumor suppressor gene expression, epithelial differentiation, Wnt and MYC pathway upregulation; CMS3 (metabolic), with KRAS activating mutations and metabolic dysregulation; and CMS4 (mesenchymal), with angiogenesis, EMT, TGF-β signaling activating, and matrix remodeling.[93] The TGFBR2 gene, containing microsatellite sequence, accumulates MSI mutations to a high level in nearly all CRC cells. Nonetheless, TGF-β signaling activation remains functional to promote the tumor–stromal interaction, which has a positive correlation with malignant cell phenotype and poor prognosis.[94,95] Secreted by TGF-β-stimulated cancer-associated fibroblasts (CAFs), IL11 acts on GP130/STAT3 signaling in tumor cells.[96]

The NF-κB family contains five members that interact with one another to homodimerize or heterodimerize: NF-κB1 (p50), NF-κB1 (p52), RelA (p65), RelB, and c-Rel.[97] The IKK kinase complex consisting of catalytic subunits IKKα and IKKβ and regulatory subunit NF-κB (an essential modulator) is the key element of the NF-κB signaling cascade.[98] NF-κB signaling has two different but interactive pathways: the canonical (activated by TNF-α, lipopolysaccharide, and IL-1) and non-canonical (activated by BAFF, CD40, receptor-activated NF-κB ligand, and lymphotoxin β) pathways.[99] Their activation is positively associated with cell survival, angiogenesis, apoptosis, and metastasis in CRC.[100] Moreover, in CRC, the expression of NF-κB (p65) is directly associated with the expression level of HIF-1α, VEGF, and vascular invasion.[101] The NF-κB pathway promotes the expression of multiple angiogenic factors, including VEGF, PDGF-BB, CXCL1, CXCL8, MMP-2, MMP-9, COX-2, and IL-8, ulteriorly inducing tumor angiogenesis. Highly expressed B7-H3 in the tissues of patients with CRC promotes VEGFA expression through the NF-κB pathway. In other words, the B7-H3/NF-κB/VEGFA axis plays a role in CRC angiogenesis.[102] As one of the immune checkpoint proteins, such as star molecules CD80 and CD86, B7-H3 (CD276) was detected in various malignant masses, including CRC.[103] B7-H3 has immunomodulating effects and participates in regulating angiogenesis.[104] In the study of tumor-bearing mice, highly expressed B7-H3 was found to be correlated with increases in TGF-β and interleukin 10 (IL-10).[105] This phenomenon might activate the JAK–STAT pathway and promote VEGF expression, thereby inducing angiogenesis.[106]

As another critical signaling pathway, JAK/STAT occupies a place in the list of regulating angiogenesis and other pathological processes in CRC. JAK and STAT are two key tyrosine kinase-associated receptors in this pathway. They become activated after being coupled. Four proteins constitute the JAK family: JAK1, 2, 3, and TYK2.[107] Meanwhile, the STAT family has seven members: STAT1 to STAT7.[108] Binding to their ligands, RTK, cytokine receptors, or G-protein-coupled receptors (GPCRs) recruit JAK, which facilitates signal transduction and STAT3 phosphorylation and homodimerization.[109] By promoting gene expression and release of inflammatory mediators to activate the STAT3 signaling pathway, STAT2 is considered a factor in promoting the development of CRC.[110] In a hypoxia micro-environment, activated by reactive oxygen species (ROS), a mechanistic target of rapamycin complex 1, and/or IL-6 in cancer cells, STAT3 finally induces HIF-1a expression. This transcription factor promotes the transcription of VEGF. These events act on surrounding ECs to reactivate STAT3 via VEGFR. In ECs, together with HIF-1a and specificity protein 1 (sp1), STAT3 upregulates gene expression that induces EC growth, survival, and migration, resulting in angiogenesis.[111] Otherwise, several promoting factors have been reported, including IL-6, EGF, IL-11, and solute carrier family 6 member 14 (SLC6A14).[112–115]

The aberrant activation of the Wnt signaling pathway is another major molecular mechanism in CRC development and progression.[116] Humans have 19 Wnts, suggesting it is a complicated signaling and biological process.[117] The Wnt signaling pathway has two branches: canonical and non-canonical pathways.[100] β-catenin is a crucial member of the canonical pathway as a switch, and its expression is promoted by activated Wnt signaling.[118] Mutations of the β-catenin gene associated with nuclear localization of the protein have been mainly detected in microsatellite unstable CRC.[116] Wnt/β-catenin signaling upregulates angiogenic factors such as VEGFs, chemokines, and MMPs.[116] Wnt2 is primarily produced by CAFs, thereby inducing invasive and metastatic CRC cell phenotypes.[119] Wnt2 levels are closely correlated with the expression of angiogenesis-associated regulators, including Ang-2, PlGF, granulocyte colony-stimulating factor (G-CSF), IL-6, and extracellular matrix components.[120] The expression levels of transglutaminase 2 (TGM2) and transmembrane-4 L-six family member-1 (TM4SF1) are both higher in CRC tissues than in normal tissues. TGM2 upregulates the expression of Wnt3a and β-catenin, whereas TM4SF1 activates the Wnt/β-catenin/c-Myc/SOX2 signaling pathway, thereby promoting angiogenesis in CRC.[100]

Moreover, the COX-2/PGE2/EP4 axis,[121] notch signaling pathway,[100] c-MET/hepatocyte growth factor (HGF) signaling pathway,[122] and EPH/ephrin signaling system[123] are all related to angiogenesis in CRC. These various factors and pathways are connected and cross each other like points and lines. Therefore, angiogenesis is stimulated by multiple points to achieve promotion. The complex network they form is like a map but with landmarks, which can be inferred as targets for diagnosis, prediction, or treatment.

3.3 | Tumor microenvironment

The TME is a complex system formed by the interaction of different cells and their products, which can be described as "soil" cultivating tumor cells.[124] It is important for tumor progression and metastasis and is functionally immunosuppressive.[125,126] It is a compound comprising stromal cells (including pericytes, ECs, fibroblasts, macrophages, regulatory T cells, myeloid-derived suppressor cells, and platelets), ECM components (including inflammatory cytokines, chemokines, MMPs, integrins, and other secreted molecules), and exosomes.[127] TECs are the innermost cells of tumor blood vessels, which are mostly derived from normal vascular ECs or directly differentiated from tumor cells. Their irregular cell morphology and phenotype lead to the defective barrier function of blood vessels, which can be beneficial for tumor survival.[125,128] In the processes of tumorigenesis and angiogenesis, multifunctional pericytes, together with ECs, play a key role in BM remodeling in the TME.[12,129] Immune functions of pericytes might be involved in the exit of innate leukocytes in inducing angiogenesis, regulating lymphocyte activation, and controlling phagocytic activity.[130] CAFs, including fibroblasts or myofibroblasts, take effect in the ECM through intercellular contact, soluble growth factor (FGF2 and VEGFA) secretion, and promotion of ECs' malignant phenotype transformation.[131] Autophagy of CAFs induced by oxidative stress has a positive effect on tumor proliferation and metabolism.[132] Exosomes secreted by CAFs promote CRC metastasis and chemotherapy resistance.[133] Expressed in CAFs, endoglin is involved in CAF-mediated invasion and metastasis through TGF-b signaling pathway activation.[134] Tumor-associated macrophages (TAMs) are indispensable in TME and control angiogenesis.[135] TAMs were detected both in vivo and in human tissues as a main source of multiple kinds of pro-angiogenic and ECM remodeling regulators, including VEGF, EGF, PDGF, TGF-α, TGF-β, Ang-1 and 2, and MMPs (e.g., MMP2, MMP9, and MMP12).[136] The interaction between TAMs and CRC cells mediated by cytokines or exosomes can jointly promote the metastasis of CRC by regulating the EMT of tumor cells and the M2-type polarization of TAMs.[137] Tumor-associated neutrophils (TANs) promote tumor invasion and angiogenesis by upregulating MMP9, VEGF, and HGF in the primary and metastatic sites. The neutrophil-to-lymphocyte ratio is a promising predictive marker of CRC.[138] As a member of various proteases, the MMP family plays a fundamental role in angiogenesis.[116] It is pivotal in degrading ECM, which makes the blood vessel permeable and allows cancer cells to dissociate from the tumor mass and be easily transferred.[139] In colon cancer, the upregulated MMPs are correlated with tumor progression, and some of them influence tumor invasion, metastasis, or poor outcomes. In Buttacavoli et al., MMP2 and MMP9 were found to be expressed more in colon cancer tissues than in normal adjacent tissues.[140] Moreover, the MMP family is regulated by circRNAs in ECM remodeling.[141] Citrullination of ECM, expression of peptidylarginine deiminase 4 (PAD4, a member of the PAD family), and expression of tenascin C (TNC, a glycoprotein in ECM) were found to promote liver metastasis in human CRC.[142]

Inflammation has been well established as a hallmark of CRC. Pro-inflammatory factors promote tumor growth and angiogenesis while inhibiting apoptosis and suppressing antitumor activities.[143] Myeloid-derived suppressor cells (MDSCs) in the TME have dual functions. They promote the metastasis of tumor cells by infiltrating primary tumors and promoting tumor angiogenesis. MDSCs also inhibit the immune response to accelerate tumor progression. MDSCs maintain the survival and proliferation of tumor cells by releasing inflammatory cytokines (IL-1, IL-6, IL-23, and IL-17A) or possibly induce adaptive anti-tumoral immunity by IL-12, interferon-gamma (IFN-γ).[144] Overexpressed $CD33^+$ $CD11b^+$ $HLA\text{-}DR^-$MDSCs were found in primary CRC tissues, which suggested advanced TNM stage and lymph node metastasis.[145] IL-1α is one of the dominant inflammatory mediators influencing the pathogenesis of inflammation-associated CRC. It enhances angiogenesis, metastasis, DR, and inhibition of tumor-suppressive genes in CRC.[146] IL-17A is a pro-inflammatory cytokine that contributes to the pathogenesis of inflammatory and autoimmune diseases.[147] High levels of IL-17 in serum and tissues of patients with CRC are important in the metastasis and prognosis of CRC.[148] IL-17A activates the ERK, p38 MAPK, and NF-κB signaling pathways within transformed enterocytes, thereby inducing early tumor development in mice.[149] As a tumor prompter, IL-17A also relies on stromal cells in the microenvironment. In murine models,

tumor-infiltrating Th17 cells and IL-17 can stimulate TAF to release G-CSF, which, in turn, recruits MDSCs to the tumor parenchyma.[150] MDSCs produce VEGF, prokineticin 2/Bv8, MMP9, and pro-inflammatory S100A8/9 molecules (calprotectin).[151] Chemokines are GPCRs binding small peptides, which mediate angiogenesis, inflammation, and chemoattraction.[152] Tumor cells often secrete a few inflammatory chemokines, such as neutrophil-attracting CXC-chemokines. After combining with CXCR1 and/or CXCR2, CXC-chemokines can induce the migration of TANs. In the background of the TME, increasing evidence has revealed that by infiltrating into tumor tissues, neutrophils play a prominent role in promoting tumors and embracing growth, invasion, angiogenesis, and metastasis in various cancers, including CRC, although they were originally thought to be antitumor cells.[138]

Continuously driven by cancer-promoting factors in the tumor, novel vascular networks might be incapable of maturing and pruning, vascular diameters are not of uniform size, and blood flow through the poorly organized and malformed vessels is possibly chaotic.[153] Along with high tumor cell density, hypoxia is induced within the tumor mass. Hypoxia is not only a hallmark of cancer that influences cancer cells' function but also an important component in the TME because it alters the extracellular matrix, modulates the tumor-immune response (immune cell infiltration, immune checkpoint [IC] expression, and secretion of immune molecules) in the TME[154] and increases angiogenesis. Tumor hypoxia promotes the recruitment of ECs and pericytes to stimulate angiogenesis by inducing VEGF, particularly VEGF-A,[155] and hastens the recruitment of bone marrow-derived cells (BMDCs). Recruited stromal cells heighten tumorigenesis through extracellular matrix remodeling, growth factor signaling, and evasion of the antitumor immune response.[126] A hypoxic environment inhibits immune response by promoting ICs such as PD-L1 expression, stimulating immunosuppressive cells including TAMs, MDSCs, and regulatory T cells (Treg cells), as well as inhibiting tumor-infiltrating lymphocyte (TIL) infiltration.[156,157]

Tumor hypoxia is primarily attuned by a transcription factor family, described as HIFs.[158] HIFs are heterodimeric transcription factors consisting of one of three possible isoforms of an O2-labile α subunit (HIF-1α, 2α, and 3α) and a HIF-1β subunit. Expression of HIF-1α induced by hypoxia promotes abnormal angiogenesis formation and enhances CRC metastasis.[154] Evidence from Arabsorkhi et al. showed that the level of HIF-1α expression in CRC is related to different MSI classifications.[159] Overexpressed HIF-1 acts as a master regulator of oxygen-regulated gene expression; in addition, its target genes are particularly relevant to cancer-encoding angiogenic factors, proliferation/survival factors, glucose transporters, and glycolytic enzymes.[160] In the hypoxic environment, ubiquitin-mediated HIF-1 degradation is disabled, leading to the accumulation of HIF-1,[161] which plays an active role in promoting the expression of angiogenesis-associated target genes, including HIF1, VEGF, PLGF, Ang-2, TGF-β, and hypoxaMIRs.[162] The supposed Warburg effect indicates that regardless of oxygen level, tumor cells preferentially utilize glycolysis to produce lactic acid for energy supply. This process has extremely high efficiency in energy generation to meet the nutritional needs of tumor cells' rapid growth.[163] The increased HIF-1α can augment the Warburg effect.[162]

As a gaseous free radical, NO acts as a signal that is relatively stable in biological systems.[164] It is involved in angiogenesis and stimulates the EGF-R signaling pathway. NO mediates stimulatory effects on tyrosine phosphorylation of EGF-R. BK-mediated angiogenesis in ECs involves the induction of the expression of VEGF associated with the activation of the NO/EGF-R/p21Ras/ERK1/2 MAP kinase signaling pathway, which indicates that NO generation plays a role in the expression of VEGF.[165] Nearly all cells, whether normal or malignant, produce NO by taking advantage of heme enzymes from the family of NADPH cytochrome P450 reductases, referred to as NO synthase (NOS).[166] Three isoforms have been identified in mammals: NOS1 (neuronal) and NOS3 (endothelial), which are persistently expressed, and NOS2, which needs to be induced and was initially characterized in macrophages. All isoforms require l-arginine as a substrate for NO synthesis. NOS2 and NOS3 play key roles in angiogenesis with the regulation of VEGF.[164] Endogenous NO promotes colon neoplasms. Moreover, NO is a crucial factor in many signaling pathways in CRC, including the Wnt/β-catenin and ERK pathway, which are relevant to cancer initiation, metastasis, inflammation, and chemoresistance/radioresistance. Thus, NO/NOS is expected to be a promising target for the treatment of CRC.[167]

Exosomes are membrane-bound extracellular vehicles (EVs) that can transmit bioactive molecules between different cells in vivo.[168] These signaling molecules have been identified as miRNAs, mRNAs, lncRNAs, and proteins.[169] Exosomes released by various cell types perform various biological functions, primarily mediating communication between different cells, particularly those active in cancer, including CRC.[170] The ncRNAs released from exosomes play a pivotal role in multiple processes of tumor formation and development, including proliferation, differentiation, angiogenesis, migration, and apoptosis.[171,172] The quantity and contents of exosomes are significantly different in tumors or normal tissues; thus, exosomes might be diagnostic indicators of CRC.[168] Numerous EV-miRNAs are not only possible diagnostic markers in CRC, including miR-1246, miR-21, miR-92A, and various others,[173] but also useful prognostic markers, such as miR-27a and miR-130a, which indicate poor prognosis.[174] Exosomal miR-21 derived from transformed cells regulates VEGF and angiogenesis in recipient cells.[175] In addition, cancer-derived exosomes activate the angiogenic properties of macrophages, such as producing VEGF. Meanwhile, exosomes from macrophages are thought to disturb the adhesion, morphology, and apoptosis of tumor cells, thereby contributing to their migration, invasion, and metastasis.[176]

3.4 | RNA: Long non-coding RNAs, miRNA, and circRNA

Long non-coding RNAs (lncRNAs), miRNA, and circRNA belong to the family of non-coding RNAs (ncRNAs). Acting as oncogenes or tumor suppressor genes in CRC, they might be potential diagnostic biomarkers.[177]

Long non-coding RNAs are longer than 200 nts non-coding transcripts, which recently became one of the largest and most significantly diverse RNA families. As small and long evolutionarily conserved ncRNA families, lncRNAs activate and repress genes through various mechanisms at both transcriptional and translational levels.[172] They have dual effects on tumor cell proliferation, angiogenesis, and DR by promoting or inhibiting them. Thus, DR affected by lncRNA appears in various aspects of tumor treatment strategies involving chemotherapy, targeted therapy, and immunotherapy.[178,179] Recently discovered lncRNA SET binding factor 2 antisense RNA 1 (lncRNA SBF2-AS1), an oncogenic antisense RNA to SBF2, is located at 11p15.1 locus and is 2708 nt long. Furthermore, lncRNA SBF2-AS1 participates in the progression of various tumors, including CRC.[180] lncRNA and miRNA interact with each other. On the one hand, lncRNA can regulate diverse functions and expression levels of miRNA as endogenous regulators. On the other hand, miRNA affects the stability of lncRNA after combining with it. lncRNA can competitively bind to the target mRNA of miRNA to isolate it, thereby inhibiting its function. Multiple pairs of interacting lncRNA and miRNA have been identified in angiogenesis, such as H19/miR-let-7 and NFIA/miR-382-5p.[181,182] Interactions among lncRNA/miRNA/mRNA have been found in liver metastasis, EMT, inflammation formation, and chemoresistance/radioresistance in CRC. In summary, lncRNAs play an important role in CRC growth and metastasis.[183]

miRNAs are highly conserved short single-stranded ncRNAs (18–22 nucleotides). They promote regulatory effects via the 3′-untranslated binding region (3′-UTR) of target messenger RNA in the posttranscriptional regulation of genes,[184] which indicates that miRNAs modulate protein-coding gene expression primarily through mRNA degradation or silencing.[172] In addition, miRNAs have two contradictory functions in regulating angiogenesis in CRC. Some miRNAs directly affect VEGF or inhibit angiogenesis through certain signaling pathways (PI3K/AKT and HIF-1a). By contrast, some other RNAs, particularly exocrine-derived ones, can promote angiogenesis. Along with angiogenesis, miRNAs also have effects on cancer genesis, invasion, and metastasis as diverse functions.[182,185] miRNAs that promote or inhibit angiogenesis are shown in Table 1.

Previous studies showed that circRNAs also play multiple roles in regulating the TME.[187] circRNAs are a family of single-stranded closed-circle molecules that lack 5′ and 3′ ends and poly(A) tails, which make them capable of resisting RNase R, leading to high stability.[188] As an indispensable factor inhibiting angiogenesis, circRNAs can conversely promote VEGFA and the expression of other pro-angiogenic molecules to positively regulate angiogenesis.[187] For example, the high expression of circ-Erbin was found in CRC, thereby promoting the miR-125a-5p-5p/miR-138-5p/4E binding protein 1 axis to elevate the expression of HIF-1α and finally inducing angiogenesis.[189] By contrast, in glioblastoma multiforme cells, circSMARCA5 was confirmed to downregulate the expression of VEGFA through alternative splicing of its pre-mRNA to limit the increase of blood vessel density.[190] Several studies showed similar results; the expression levels of different circRNAs might be upregulated or downregulated in CRC. Collectively, these research findings revealed that circRNA is related to the progression and pathogenesis of CRC.[191] As they can be both oncogenic and anti-oncogenic, circRNAs can potentially be utilized in the treatment and prognosis of CRC.[192]

Therefore, by enlarging our perspective to the level of the microenvironment, the participation of different functions of various cells and the specific release of different types of signals make this mixture similar to soil with abundant nutrients, which is greatly different from the normal tissue environment. Such an environment is more conducive to the growth and development of tumors than a normal tissue environment.

3.5 | Gut microbiota

Being parasitic in the human intestinal tract, the microflora is a huge organism that can interact with the host. As for CRC, the gut microbiota plays a special role. Gut microflora is important for host

TABLE 1 miRNAs that regulate angiogenesis in colorectal cancer[185,186]

miRNA	Function	Targets	Result
miR-145, miR-206, miR-148a, miR-195-5p, miR-107	Inhibit	HIF	Inhibit angiogenesis
miR-622, miR-590-5p, miR-520a, miR-126, miR-27b, miR-150-5p, miR-1249	Inhibit	VEGF	
miR-218	Inhibit	Connective tissue growth factor	
miR-125a-3p, miR-143	Inhibit	PI3K/AKT	
miR-7, miR-375	Inhibit	EGFR	
miR-181a-5p	Inhibit	MMP-14	
miR-181a	Activate	SRC (increased VEGF secretion)	Promote angiogenesis
miR-1229	Inhibit	HIPK2 (inhibits VEGF angiogenic gene)	
miR-194	Inhibit	Platelet-reactive protein 1 (TSP-1 inhibits VEGF)	
miR-25-3p	Inhibit	KLF2/KLF4 (inhibit promoter activity of VEGFR2)	

Abbreviations: HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor.

survival and health because of its antitumor capability, and it can alleviate tissue damage by reducing the level of oxygen free radicals. A significant abundance variation of intestinal flora was found in patients with CRC compared with healthy people.[193] The abundance of intestinal flora is affected by hypoxia in the microenvironment.[194] Alterations in specific flora abundance might accelerate the formation and development of CRC. In addition, gut microbiota is involved in modulating immunity, transforming metabolome, and modifying the therapeutic effect.[154,195] Disturbance of the category and quantity of intestinal flora activates the NF-κB pathway by stimulating intestinal epithelial cells that can trigger an inflammation stage.[193] Furthermore, chronic inflammation is the key element in inducing CRC formation. Several pro-tumorigenic and anti-tumorigenic bacterial species and their respective products of metabolism disturb major signaling pathways such as Wnt, PI3K-Akt, MAPK, TGF-β, EGFR, mTOR, and p53.[196] Intestinal microflora also participates in the formation of the TME by mediating angiogenesis.[197] In general, bacterial toxins are related to pro-inflammatory processes, activation of angiogenesis, and cellular proliferation pathways.[198] Notably, among multitudinous intestinal microflora metabolites, bile acid can promote CRC progression through multiple mechanisms, including inhibiting apoptosis and enhancing cancer cell proliferation, invasion, and angiogenesis.[199] Some scholars have proposed the application of drugs for intestinal flora in combination with chemotherapy and immunotherapy to improve treatment response and tolerance.[198]

4 | TREATMENT STRATEGY

In recent decades, with the research progress on cancer etiology, treatment methods for CRC have been constantly updated and improved. Besides surgery, which is the most common treatment method, other approaches such as chemotherapy, targeted therapy, immunotherapy, and radiotherapy are used to improve therapeutic effectiveness and prognosis and extend the survival period and quality of life of patients with metastatic CRC (mCRC). For patients with neoadjuvant chemotherapy indications, 5-fluorouracil (5-FU), 5-FU plus leucovorin (LV), single-agent capecitabine, reduced-dose capecitabine plus oxaliplatin (XELOX), or oxaliplatin plus 5-FU plus LV (FOLFOX) are considered optimal treatment schemes.[200] On the basis of the staging of patients with CRC, postoperative adjuvant chemotherapy, including 5-FU plus LV, capecitabine, mFOLFOX6, or XELOX, might be selected. Among these plans, combination with oxaliplatin has the best treatment effect and the greatest benefit for patients.[201–203] FOLFIRI (doublet cytotoxic combinations of fluorouracil, leucovorin, and irinotecan) and FOLFOX are the two first-line treatment prescriptions for patients with mCRC, and they are presently recommended by European Society for Medical Oncology (ESMO) guidelines and the Pan-Asia adaptation of the guidelines.[2,204]

Clinical evidence has shown that combination with targeted therapy and chemotherapy significantly improves progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone in patients with mCRC.[200] Among various aspects, angiogenesis has been validated to be a key element in the pathogenesis of malignancy, and it has provided biological insights and subsequent therapeutic options.[10] Regarding its central status in tumor angiogenesis, VEGFs and their receptors are the major targets in anti-angiogenesis treatment.[205] Tumors highly dependent on VEGF-induced angiogenesis, such as CRC, renal cell carcinoma, and neuroendocrine tumors, might have a relatively satisfactory response to anti-VEGF drugs.[206] In addition, targeted drugs are recommended as first-line treatment drugs for most patients, unless contraindications exist.[30]

4.1 | Targeting agents

Inhibition of angiogenesis by blocking VEGF is a major focus of targeted cancer therapy. The important functions of pro-angiogenesis molecules, which have strong relations with tumor growth, invasion, and metastasis, make them ideal targets in suppressing tumors including CRC.[32] VEGF is one of the most decisive factors that promote angiogenesis. Several different strategies have been applied to block VEGF, such as neutralizing anti-VEGF monoclonal antibodies, monoclonal antibodies that block VEGFRs, and small-molecule tyrosine kinase inhibitors (TKIs) that block VEGFR activation and downstream signaling Figure 1.[207]

Anti-VEGF: Bevacizumab is an IgG1 humanized monoclonal antibody (MoAB) against VEGF-A. Initially, it was recommended as a first-line treatment because it showed good results in phases I and II clinical trials. Bevacizumab plus chemotherapy, compared with chemotherapy alone, showed advantages for PFS (10.6 months vs. 6.2 months, $p < 0.001$) and OS (20.3 months vs. 15.6 months, $p < 0.001$).[208] Nevertheless, bevacizumab combined with standard first-line treatment did not show the expected advantages of treatment with ras mutation in a phase III clinical trial.[209] As a second-line treatment, bevacizumab plus FOLFOX had a better outcome than FOLFOX alone: 7.3 months versus 4.7 months ($p < 0.001$) in PFS and 12.9 months versus 10.8 months ($p = 0.0011$) in OS.[210] Therefore, it was recommended that bevacizumab be combined with a chemotherapy regimen. In addition, other researchers have proposed that bevacizumab can eliminate RAS mutant clones to convert RAS gene mutant, which is more dependent on angiogenesis compared with wild-type (WT) RAS genes.[211]

Aflibecept: Aflibecept is a fusion protein targeting VEGF-A, VEGF-B, and PlGF. It might exhibit a more comprehensive inhibition effect on angiogenesis because of its multiple targets compared with bevacizumab or ramucirumab.[30] VELOUR results[212] revealed that the OS median survival was 13.50 months in the FOLFIRI/aflibercept group versus 12.06 months in the control group. Moreover, FOLFIRI/aflibercept showed a remarkable improvement in the median PFS of 6.90 months versus 4.67 in the placebo ($p < 0.0001$). The response rate (RR) was 19.8% in the aflibercept group but 11.1% in the placebo group ($p < 0.0001$).[213] Strongly supported by existing research results, aflibercept combined with FOLFIRI can be an option for patients with DR or progression after oxaliplatin-containing treatment. Meanwhile, ESMO guidelines explicitly recommend

aflibercept as an alternative second-line treatment agent for RAS WT and RAS mutant patients.[30]

Anti-VEGF receptors: Ramucirumab is a humanized monoclonal antibody targeting the extracellular domain of VEGF receptor 2 (VEGFR2). It received US Food and Drug Administration (FDA) approval in 2015 for the second-line treatment of mCRC[214] combined with FOLFIRI, based on the results of the RAISE trial. Ramucirumab is a newcomer among the antiangiogenic agents that can improve overall survival with a safe and manageable toxicity profile.[215] Fruquintinib (HMPL-013), a long-term small-molecule, which can selectively inhibit VEGFR (VEGFR1, VEGFR2, and VEGFR3), has demonstrated several advantages, such as low off-target toxicity, good drug tolerance, and a remarkable effect in clinical studies. Thus, it is recommended as a third-line agent for the treatment of patients with CRC via other targeted therapy drugs.[216]

Numerous small-molecule TKIs exist.[217] Regorafenib is a multi-targeting kinase inhibitor (TKI) approved for the treatment of patients with mCRC as a third-line treatment for advanced CRC in comparison with standard chemotherapy.[218] This agent was originally developed as a RAF1 inhibitor. The dual blockade of VEGFRs and TIE2 can lead to accessional anti-angiogenesis effects and the distinctive regulation of vessel stability. In addition, it is a TKI of the VEGF signaling pathways,[219] enabling its continuous antiangiogenic effect even in tumors resistant to VEGF inhibitors. Moreover, regorafenib has the important effect of enhancing anti-tumor immunity via macrophage modulation.[220] Therefore, preliminary evidence suggested that this multi-kinase inhibitor might be an optimal combination partner for immune checkpoint inhibitors (ICIs).[221]

However, prolonged VEGF blockade enhances tumor hypoxia, causes resistance to hypoxia-induced apoptosis, and increases VEGF expression, thereby promoting tumor aggressiveness.[222,223] Aside from VEGFR, EGFR is another commonly used target in treating the anti-angiogenesis of CRC.[224] The treatment strategy often has two directions: monoclonal antibodies that block EFGR and inhibitors targeting intracellular tyrosine kinase. As a chimeric IgG antibody, cetuximab leads to the internalization and degradation of EGFR after binding to its external domain.[225] However, immunity reactions might occur as cetuximab is a murine-human chimeric antibody. Panitumumab is the perfect solution to this issue; it is an antibody that is fully humanized and does not induce cytotoxicity mediated by antibody-dependent cells.[226] Cetuximab and panitumumab are approved as first-line treatment agents for CRC by the FDA. However, anti-EGFR drugs are not recommended for priority use in second- or third-line treatment of CRC because they do not show good statistics in PFS or OS.[227] Approximately 45% of colon cancer cells present RAS mutations.[228] In patients with mCRC, the proportions of KRAS, NRAS, and HRAS mutations are 40%–50%, 2%–9%, and 1%–2%, respectively.[229] The KRAS proto-oncogene encodes a GTPase protein (KRAS) that is crucial in copious molecular pathways including the EGFR pathway.[230] With high-frequency occurrence in CRC KRAS mutations, KRAS G12V is related to multiple aspects of tumor clinical pathology, such as invasion and poor prognosis. Moreover, it is linked to undesirable therapeutic effects of anti-EGFR agents. There are interactions between KRAS G12V and HIF-1α. Furthermore, KRAS G12V promotes the expression of HIF-1α, whereas overexpressed hypoxia or HIF-1α activates KRAS G12V. Only patients with WT RAS tumors receive a clinical benefit from anti-EGFR antibody therapy.[231] Hypoxia is related to anti-EGFR therapy resistance. Thus, adding HIF-1α inhibitor PX-478 to it might achieve a good therapeutic effect.[232] Moreover, KRAS mutations can represent the response to EGFR inhibitors as a negative predictive factor.[231] With the introduction of anti-EGFR in the treatment of RAS WT mCRC, the optimal sequencing between anti-VEGFs and anti-EGFRs in this population of patients has been a matter of intense debate. For example, data from Francesca showed that using anti-EGFRs in the first-line setting for the right CRC (RC) should be avoided when other therapeutic alternatives are available.[233] Meanwhile, for RAS WT metastatic CRC patients with left-side colon tumors, chemotherapy plus anti-EGFR agents are recommended as first-line treatment.[43]

Ingredients from traditional Chinese medicine, such as several phenolic compounds (e.g., flavones, phenolcarboxylic acids, and ellagitannins),[234] hyperforin,[235] Raddeanin A,[236] and matrine[237] suppress CRC by inhibiting angiogenesis and other mechanisms. However, the details are not clearly explained. These promising pharmaceutical ingredients have not been approved as standard treatment drugs, which might be used as an adjuvant treatment.

4.2 | Drug resistance

Drug resistance cannot be ignored in the treatment of CRC. Data from Bardelli et al. reported that DR occurs in approximately 80% of cases during treatment.[238] The mechanisms of DR are divided into the following three aspects: transformation in VEGF dependence, alternative pathways, and stromal cell interactions.[32] As described, anti-angiogenic therapies might cause hypoxia and increase HIF-1a expression, which are known as drivers of EMT. Moreover, HIF-1 has multiple functions to promote cancer cell survival in the hypoxic environment. Resistance to anti-angiogenesis agents involves several different but related mechanisms: recruiting various BMDCs, which differentiate into ECs, pericytes, and pro-angiogenic monocytes, such as TAM; enhancing and increasing pericyte coverage, which safeguards tumor blood vessels; and increasing invasiveness of tumor cells, thereby leading to vessel co-option.[28,239,240]

Compensatory pathways in angiogenesis are nonnegligible in DR. TGF-β, FGF 2, PDGF, Ang-2, and IL-1 are assumed to be highly relevant to anti-VEGF resistance in cancer.[241] Alternative angiogenic factors and their pathways are shown in Table 2. Others involve EGF, G-CSF, PlGF, HGF, stromal cell-derived factor-1, and IGF.[242] The table below shows that Ras/Raf/MEK/ERK and PI3K/Akt are the major downstream signaling pathways. Interestingly, these two pathways are also the dominant cascades of EGFR activation,[199] which indirectly validates the crosstalk between VEGF and EFGR. Other mechanisms might include EGF overexpression, EGFR alteration, RAS/RAF/PI3K gene mutations, ERBB2/MET/IGF-1R activation, metabolic remodeling, MSI, and autophagy.[243]

TABLE 2 Alternative angiogenic factors and their pathways[241]

Ligands→	Ang-2	Bv8	bFGF	IL-1	PDGF	PlGF	TGF -β1
Receptors→ Pathways↓	Tie2	PROKR2	FGFR	IL-1RI, IL-1RAcP	PDGFR	VEGFR1, NRP1/2	TGF-βRII, TGF -βRI
Ras/Raf/MEK/ERK	▲	▲	▲				
PI3K/Akt	▲		▲		▲	▲	
JAK/STAT			▲				
PLCγ			▲		▲		
NF-κB				▲			
JNK				▲			
P38/MAPK				▲		▲	
Smad							▲

Note: ▲: regulating downstream pathways.
Abbreviation: VEGF, vascular endothelial growth factor.

Molecular and biochemical mechanisms are related to the phenotypic changes that support carcinogenesis, including apoptosis inhibition, reinforced tumor cell proliferation, increased invasiveness, cell adhesion perturbations, angiogenesis promotion, and immune surveillance inhibition.[231] Tumor immune escape implies that tumor cells escape from immune surveillance and inhibit the immune response of the host.[244] Tumor cells have developed several mechanisms to avoid detection by immune cells. Secretion of soluble immunosuppressive factors, such as TGF-β and IL-10, or downregulation of major histocompatibility complex (MHC 1) expression might all be related to immune escape.[245] IC modulation is another well-known mechanism by which tumor cells suppress the local immune response. IC receptors, including programmed death 1 (PD-1), cytotoxic T lymphocyte antigen 4 (CTLA-4), and CD279, contribute to inactivating and exhausting tumor-related T cells.[246]

ICIs represent a new time for cancer treatment. They selectively combine with immunosuppressive molecules on the surface of immunocytes (e.g., CTLA-4) or on tumor cells, such as PD-1 or their ligand (PD-L1), to block tumor cells' immune escape.[247,248] Ipilimumab, pembrolizumab, and nivolumab are three types of ICIs approved by the FDA in 2015 for CRC treatment in patients with mismatch repair defects or microsatellite instability.[221,249] Nivolumab and pembrolizumab are anti-PD1 drugs that competitively bind with PD-1, thereby blocking tumor immune evasion mediated by the combination of PD-1 and its ligands, PD-L1 or PD-L2. By contrast, ipilimumab inhibits the combination of CTLA-4 and a cluster of differentiation 80/86 (CD80/CD86), which attenuates T-cell activation. Nevertheless, the application of ICIs remains limited because of the lack of sensitive markers and inevitable DR.[154]

5 | DISCUSSION

To date, although anti-angiogenesis agents, with their highlighted advantages such as improving oxygen levels and drug delivery through vascular normalization, carry weight in the treatment of CRC, their therapeutic efficacy remains far from satisfactory. However, ensuring that every patient receiving treatment achieves satisfactory results in one unified plan is never an easy task. With the increase in knowledge about CRC, novel targets have been identified. Nevertheless, therapy resistance and unresponsiveness to immunotherapy remain major treatment obstacles. However, the treatment scheme selection based on biomarkers for patients with CRC remains limited because of the incomplete accuracy of conventional biomarkers in diagnosis, prediction, and prognosis. Thus, further studies are necessary to develop clinically applicable biomarkers. However, developing appropriate therapeutic programs to increase ICI activity and efficacy through the regulation of gut microbiota in patients with CRC is another clinical challenge. Artificial intelligence shows promise and will takes us into a new era to persistently improve molecular prediction algorithms from the sea of usable data. It might help us explore new methods to overcome the predicaments of the current antitumor strategy.

AUTHOR CONTRIBUTIONS

Zhenni Yang: Writing – original draft; writing – review and editing. **XuQian Zhang:** Writing – review and editing. **Xiaozhe Bai:** Writing – review and editing. **Xiaonan Xi:** Supervision. **Wentian Liu:** Supervision. **Weilong Zhong:** Formal analysis; project administration; supervision.

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The authors declare that they have no competing interests.

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ORCID

Zhenni Yang https://orcid.org/0009-0000-0605-6521
Xuqian Zhang https://orcid.org/0000-0003-1388-993X
Weilong Zhong https://orcid.org/0000-0002-7139-169X

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