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Review

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Endothelial cells-directed angiogenesis in colorectal cancer: Interleukin as the mediator and pharmacological target

Running head*: Endothelial cells-derived interleukins and tumor angiogenesis*

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List of abbreviations:

AMPK: adenosine monophosphate-activated protein

kinase CAFs: cancer-associated fibroblasts

COX-2: cyclooxygenase-2

CRC: colorectal cancer

CYTL-1: cytokine-like 1

ECs: endothelial cells

FGF-2: fibroblast growth factor-2

HIMEC: human intestinal microvascular endothelial cells

HUVECs: human umbilical vein endothelial cells

IFN: interferon

IHC: immunohistochemistry

IL: interleukin

mCRC: metastatic colorectal cancer

NF-κB: nuclear factor Kappa B

NO: nitric oxide

TGF: transforming growth factor

TME: tumour microenvironment

VEGF: vascular endothelial growth factor

VEGFR: vascular endothelial growth factor receptor

Highlights

- Vascular endothelial cells (ECs) function not only as the target of proangiogenic factors, but also as the cellular source of proangiogenic factors.
- This review provides an updated summary of available information on proangiogenic interleukins released by microvascular ECs as potential drivers of the tumor angiogenesis process.
- In addition, their potential as a novel candidate for antiangiogenic target for the treatment of CRC patients is discussed.

Abstract

Enhanced angiogenesis is a cancer hallmark and critical for colorectal cancer (CRC) invasion and metastasis. Upon exposure to proangiogenic factors, therefore, targeting tumor-associated proangiogenic factors/receptors hold great promise as a therapeutic modality to treat CRC, particularly metastatic CRC. Accumulating evidence from numerous studies suggests that tumor endothelial cells (ECs) are not only the target of proangiogenic factors, but also function as the cellular source of proangiogenic factors. Studies showed that ECs can produce different proangiogenic factors to participate in the regulation of angiogenesis process, in which ECs-derived interleukins (ILs) show a potential stimulatory effect on angiogenesis via either an direct action on their receptors expressed on progenitor of ECs or an indirect way through enhanced production of other proangiogenic factors. Although a great deal of attention is given to the effects of tumor-derived and immune cell-derived ILs, few studies describe the potential effects of vascular ECs-derived ILs on the tumor angiogenesis process. This review provides an updated summary of available information on proangiogenic ILs, such as IL-1, IL-6, IL-8, IL-17, IL-22, IL-33, IL-34, and IL-37, released by microvascular ECs as potential drivers of the tumor angiogenesis process and discusses their potential as a novel candidate for antiangiogenic target for the treatment of CRC patients.

Key words: Interleukin; Colorectal cancer; Endothelial cell; Angiogenesis

1. Introduction

Colorectal cancer (CRC) is a leading human cancer worldwide with high mortality, which will account for around 1.5 million newly diagnosed cases and half million death according to cancer statistics, 2022 [1]. Clinical data revealed that recurrence and metastasis are the main death reasons in patients with CRC [2]. For those patients, adjuvant therapies, such as chemotherapy and immunotherapy, are two principal adjuvant therapies. However, the sensitivity to chemotherapy and immunotherapy varies and drug resistance is frequantely observed overtime in matastatic CRC (mCRC) patients. Hence considerable work has been done in the serach of novel effective therapies for the management of recurring and mCRC.

It has been widely acknowledged that cytokines, such as vascular endothelial growth factor (VEGF) family and interleukin (IL)-1, IL-6 and IL-8, produced in the tumor microenvironment (TME), were involved in the progression, invasion and metastasis in CRC via multiple mechanisms (refer to Fig. 1), including the activation of many factors e.g., nitric oxide (NO) synthesis, cancer-associated fibroblasts (CAFs) and nuclear factor Kappa B (NF-κB) in the TME [3-10]. In relevant mechanisms, the stimulatory effect on the tumor angiogenesis process has been particularly emphasized. Evidence showed that proangiogenic cytokines could directly stimulate the proliferation and function of vascular endothelial cells (ECs), which enhanced the formation of new microvascular vessels by binding and activating their receptors on microvascular ECs [8, 9, 11-18]. Because angiogenesis process dynamic in the TME depends upon the balance between proangiogenic and antiangiogenic signals in CRC [19], great efforts have been made toward the design of novel precise targeted therapy using pharmacological inhibitors [20, 21]. Indeed, bioagents targeting proangiogenic factors/ receptors, such as VEGF or VEGF receptor family members, have been validated and shown to improve clinical outcome in patients with mCRC [22].

Phenotypic studies demonstrated multiple cellular sources for proangiogenic factors, many types of cells including immune cells, tumor cells and surrounding stromal cells produced proangiogenic factors within the TME [3, 8, 14-16], Recently, emerging evidence supports the involvement of microvascular ECs as a potential cellular source of proangiogenic factors, that participate in the regulation of the angiogenesis process [16, 23, 24]. For example, we and others have previously identified the expression of several proangiogenic ILs e.g., IL-8, IL-17A and IL-33 and their receptors in the tumor-associated microvascular ECs, and their relationships with clinicopathological features in patients with CRC [3, 25-30]. Although a great deal of attention was paid to the effects of tumor-derived and immune cell-derived proangiogenic cytokines [31-33], few studies described the potential effects of microvascular ECs-derived proangiogenic cytokines on the tumor angiogenesis process.

Since previous reviews of this research area have provided the background and highlighted the importance of several ILs e.g., IL-1, IL-6, IL-8, IL-37 and IL-38 released by immune cells or tumor cells contributing to EC pathological activation [31-34], therefore, this review will focus on the potential proangiogenic role of microvascular ECs-derived ILs and discusses their potential as a precise antiangiogenic therapeutic target for the treatment of CRC patients.

2. The importance of ECs in the regulation of tumor angiogenesis

The angiogenesis process is a critical event for the progression and metastasis of human cancers because blood vessels deliver oxygen and nutrients into the TME and support the growth, invasion, and metastasis of cancers when the growth of tumors exceed a certain size. New blood vessel formation from the precursors of vascular ECs is a complex and dynamic process [35], in which angiogenesis is the outgrowth and proliferation of capillaries from pre-existing blood vessels based on the balance between proangiogenic and antiangiogenic signals [1, 6-8]. For CRC development and progression, a significant angiogenic switch dynamic has been demonstrated throughout the colorectal adenoma-carcinoma sequence [36-38], which occurs at the early stage from the normal stage to the precancerous adenomatous stage and persisted to the CRC stage [39].

Microvascular ECs play a significant role in the tumor angiogenesis process. Many studies emphasized the importance of vascular ECs within the TME in CRC invasion and metastasis, and revealed that microvascular ECs were involved in epithelial proliferation, angiogenesis, stem cell maintenance, and stromal remodeling [40]. Phenotypic and functional studies of angiogenesis regulation demonstrated that microvascular ECs were both a target and a potential cellular source of proangiogenic cytokines in the CRC TME [3, 27]. For example, ligands of the VEGF family are well-known key regulators of tumor angiogenesis and are expressed by microvascular ECs and tumor cells in the CRC [41-43]. The proangiogenic effect of the VEGF family occurs via binding to VEGF receptors (VEGF-R1, VEGF-R2 and VEGF-R3) expressed on microvascular ECs in an autocrine manner [44, 45]. Phonotypic analyses confirmed that many proangiogenic factors were produced from a mixed cellular source that included tumor cells, infiltrating immune cells, surrounding stromal cells and microvascular ECs in the CRC TME [3, 27, 43, 46]. Compared to the intensive studies performed on the effects of tumor-derived proangiogenic factors on angiogenesis, few study was examined the effects of

microvascular ECs-derived proangiogenic factors on tumor angiogenesis. Bioagents that target VEGF/VEGFR signaling are widely used and show improved therapeutic efficacy in the treatment of mCRC [22, 47]. Therefore, examination of ECs-derived novel angiogenic factors in patients with CRC may provide new insights and help design future bioagents for targeting tumor angiogenesis [48].

3. Proangiogenic ILs released by tumor-associated microvascular ECs within the CRC TME

3.1 IL-1

IL-1 family consists of two main cytokines IL-1α and IL-1β, both of them are the potent factors in the stimulation of vascular ECs and support of tumor angiogenesis [18, 49]. The role of tumor and immune cell-derived IL-1α and IL-1β as modulators of tumor angiogenesis has been well reviewed [13, 50-52]. In non-tumor diseases, studies showed that IL-1α activated and secreted from damaged ECs is associated with the process of local inflammation [53]. Thacker et al. [54] reported that IL-1β could significantly improve the functional capacity of lupus endothelial progenitor cells and myeloid circulating angiogenic cells. Lee et al. [55] further reported that IL-1β could enhance endothelial mesenchymal transformation in corneal ECs, which was mediated by fibroblast growth factor-2 (FGF-2) via an activation of the transcription factor NF-κB [56]. In CRC, studies have found that IL-1β is highly expressed in tumor ECs within the CRC TME [57]. In addition, studies have identified the expression of IL-1 receptor type 1 in vascular ECs [58, 59]. Therefore, ECs-derived IL-1β may exhibit an direct effect on ECs. However, the exact proangiogenic effects and mechanisms of ECs-derived IL-1α and IL-1β remain to be studied as compared with the well-studied tumor-derived IL-1 cytokines.

3.2 IL-6

IL-6 is an multifunction inflammatory cytokine produced by immune cells, tumor cells and stromal cells in the TME [60]. Extensive evidence has shown that IL-6/IL-6 receptor axis is closely associated with CRC initiation, invasion, and metastasis [61, 62]. Previous studies revealed that IL-6 gene was highly expressed in human umbilical vein ECs (HUVECs) under the stimulation of IL-1α or TNF-α and enhanced the proliferation of ECs [63]. Chen et al. [64] also revealed that the pretreatment with IL-4 could significantly enhance the production of IL-6 from TNF-α, IL-1 beta- or LPS-stimulated HUVEC. Li et al. [65] showed that histamine could stimulate the production of IL-6 from cultured human coronary artery ECs, which was enhanced by the co-treatment of endotoxin and TNF-α. A study by Nilsen et al. [66] reported that IL-6 can be secreted from cultured HUVECs and human intestinal microvascular ECs (HIMEC) under the stimulation of recombinant human IL-1β or TNF-α. Above data strongly indicated that microvascular ECs are the additional IL-6 cellular source and contribute to the formation of cytokine network in the intestine. Interestingly, several studies have demonstrated that IL-1β, TNF-α and histamine were significantly increased along the colorectal adenoma-carcinoma sequence [16, 57, 67, 68], suggesting a modulatory effect of these factors in modulating IL-6 secretion from microvascular ECs within the TME.

The proangiogenic effect of IL-6 has been intensively studied [61]. Huang et al. [69] showed that IL-6 stimulates VEGF-C expression in lymphatic ECs via the activation of Src-FAK-STAT3 signaling pathway, which is strongly suppressed by the Src-FAK signaling blockade. Other results also suggested that the stimulatory effect of IL-6 on tumor angiogenesis is through a VEGF-dependent pathway [70, 71].

3.3 IL-8

IL-8 is a potential chemokine/cytokine involving in multiple pathological changes including immune cell track and recruitment, stroma remodeling, angiogenesis, tumor progression and

metastasis in human cancers [72-79]. IL-8 is one of most studied proangiogenic factors in stimulating ECs [34]. Hu et al. [80] showed a proangiogenic effect of IL-8 in rats. In vitro studies, the administration of recombinant human IL-1β or TNF-α with cultured HUVECs and HIMEC could enhance the production of IL-8 from these cells [66]. Further studies have demonstrated that IL-8 could directly stimulate vascular EC survival, proliferation, and migration [72, 81-83], neutralizing antibodies to IL-8 receptors diminished IL-8-induced angiogenesis [81], indicating that IL-8-induced angiogenesis is mediated by its functional receptors expressed in ECs [72, 81, 84]. In addition, studies revealed that IL-8 produced from ECs participates in the stimulation of EC proliferation, migration and angiogenesis in a autocrine manner [73, 82]. Ju et al. [82] further showed that autocrine IL-8-induced EC migration was via the activation of Src phosphorylation, Rac1 activity and PAK1 phosphorylation pathways in a time-dependent manner. Petreaca et al. [85] reported that IL-8 could activate VEGF receptor signal and increase endothelial permeability and angiogenesis. In which, activation of Src kinases is required during IL-8-induced permeability. An inhibitor of Src kinases significantly blocked IL-8-induced VEGFR2 phosphorylation, receptor complex formation, and endothelial permeability [85]. We have previously shown that IL-8 and its functional receptors IL-8A and IL-8B were highly expressed in vascular ECs throughout human colorectal adenoma-carcinoma sequence. Considering the importance of angiogenic switch along the colorectal adenoma-carcinoma sequence, targeting ECs-derived IL-8 signal may be one of additional antiangiogenic options.

3.4 IL-17A

IL-17A is a main proinflammatory cytokine derived from TH17 cells, and it is associated with the growth, progression and metastasis of human cancers [86-88]. Increased IL-17A in serum and tumor tissues was reported in many types of human cancers [86, 89-91]. Studies showed that one of the possible mechanisms of IL-17A promotion of tumor progression is via its

regulatory effect on angiogenesis [4, 5, 19, 92]. Published data suggest that IL-17A is a potent proangiogenic factor, and it directly affects the angiogenesis of CRC via binding to its receptors expressed in vascular ECs and stimulating these cells to produce VEGF, which plays an important role in regulating angiogenesis [92]. Numasaki et al. [93] showed a higher microvascular vessel density in rat models for fibrosarcoma and colon adenocarcinoma transduced with IL-17A, in which IL-17A did not directly stimulate the growth of ECs, but it induced migration and cord formation of microvascular ECs [93]. Takahashi et al. [94] revealed that IL-17 along did not show the ability to stimulate the growth of human dermal microvascular ECs. However, IL-17 combined with proangiogenic factors, such as basic fibroblast growth factor, hepatocyte growth factor and VEGF, resulted in significant growth of human vascular ECs *in vitro* [94]. Inozume et al. [95] showed that IL-17 induced IL-8 release from human renal cancer cells, which is a strong proangiogenic cytokine [96]. Therefore, this evidence indicates that the proangiogenic effect of IL-17A occurs via an enhanced stimulatory capability on other proangiogenic factors and induces the growth of vascular ECs. Notably, we have previously observed that IL-17A is expressed in tumor-associated vascular ECs in colorectal adenomas/CRCs in addition to its expression in tumor cell and immune cells [26], which suggests a mixture of cellular sources for IL-17A. Liu et al. [97] reported that IL-17RA was expressed in microvascular ECs in patents with CRC. This evidence strongly suggests that microvascular ECs-derived IL-17A participates in the regulation of enhanced angiogenesis in CRC.

IL-17F, another main cytokine released from TH17 cells, can exert an antitumor effect in colon tumorigenesis via inhibiting tumor angiogenesis [98]. It is valuable to state variable effects of IL-17F on angiogenesis in different cancers [99]. Conflicting results have been reported and further research is needed.

3.5 IL-22

IL-22 production primarily from TH22 cells was also implicated in the regulation of tumor angiogenesis [19, 48]. Previous studies indicated that the production of IL-22 from activated TH22 cells was stimulated by a set of cytokines, including IL-1β, IL-6, IL-21 and IL-23 [100, 101]. Our studies showed that all of these upstream stimulators for IL-22 production were increased in patients with CRC [7, 57]. Doulabi et al. [102] found that the number of TH22-positive T cells in tumor tissues was markedly increased in patients with colon cancer, and Khare et al. [103] demonstrated that IL-22 receptor was intensively expressed in CRC mucosa and associated with the development of colorectal carcinogenesis. They also found that the expression of IL-22 receptor in CRC mucosa was accompanied with the activation of STAT3 signaling, which is a oncogenic transcriptional factor [103]. IL-22 expression in microvascular ECs within the TME has not been evaluated. However, Shang et al. reported that the IL-22 receptor was expressed in vascular ECs and recombinant human IL-22 (rhIL-22) and IL-22 from endometrial stromal cells of adenomyosis significantly increased the expression of IL-22R1 and IL-10R2 on human vein endothelial cells, and led to increased viability [104]. Stimulation with rhIL-22 or endometrial stromal cells promoted angiogenesis, treatment with an anti-human IL-22 neutralizing antibody blocked these effects [104]. IL-22 also promoted the production of angiogenic cytokines, such as IL-6, IL-8, and VEGF, from other types of cells. On the contrary, the neutralizing antibody for IL-22 reversed these effects [105, 106]. Because these cytokines played an important role in the CRC angiogenesis process [18], these findings suggest a possible regulatory effect of IL-22 on tumor angiogenesis via the functional regulation of vascular ECs.

3.6 IL-33

IL-33 belongs to the IL-1 family, and the involvement of IL-33 and its functional receptor ST2 in the pathogenesis of the tumor angiogenesis process has been widely studied [3, 107-109]. Numerous studies reported that IL-33 promoted tumor progression and metastasis via the

remodeling of the TME and enhanced angiogenesis [107-109]. Choi et al. [107] demonstrated that IL-33 significantly increased the proliferation, migration, and morphologic differentiation of human ECs via ST2/TRAF6-mediated endothelial nitric oxide production in vivo. IL-33 increased endothelial permeability by reducing vascular endothelial-cadherin-facilitated cell-cell junctions in vitro [107]. Notably, knockdown of functional receptor ST2 blocked these effects of IL-33 [107]. Recently, Li et al. [110] revealed that IL-33 stimulated the proliferation and growth of CRC cells isolated *in vitro* is via an enhanced release of cyclooxygenase-2 (COX-2), which is a strong proangiogenic factor and deeply involved in the modulation of tumor angiogenesis [111]. Studies revealed that IL-33 could enhance the production of other proangiogenic factors, such as IL-8, from human umbilical vein ECs via the activation of JNK/c-Jun/AP-1 signaling pathway [112]. Moreover, IL-33 and its functional receptor ST2 significantly enhanced production of the NF-κB-dependent proangiogenic cytokines IL-6 and IL-8 from other types of cells e.g., fibroblasts [113], which are the main stromal cellular type and progressively increased in the tumor stroma [114]. Therefore, IL-33 is a potent proangiogenic factor and ST2 is the main functional receptor mediating the proangiogenic effect of IL-33 [108, 109].

IL-33 and its receptor ST2 form a network that plays critical roles in the activation of ECs in mice [115]. Phenotypic analysis of IL-33/ST2 in the TME revealed increased expression of IL-33 and its receptor ST2 in the tumor cells, stromal cells and microvascular ECs [27-29, 116]. Our study showed that both IL-33 and ST2 were highly expressed in microvascular vessels and co-expressed with CD34 positive vascular ECs [27, 28], which suggests an possible IL-33/ST2 autocrine action pathway in the adenoma/CRC TME that may be involved in the regulation of the tumor angiogenesis process.

However, there are also studies to report antiangiogenic function of IL-33 in eye [117]. This indicates that the effect of IL-33 on angiogenesis might be organic difference.

3.7 IL-34

IL-34, a cytokine produced by a wide range of cells including vascular endothelial cells, has been reported to be a proangiogenic cytokine under both physiological and pathological conditions [118, 119]. In the colon cancer tissues, increased expression of IL-34 was observed in tumor cells and lamina propria mononuclear cells [120]. From the published immunohistochemistry pictures, IL-34 immunoreactivity was also found in microvascular vessels near the colon cancer tumor mass [120]. Furthermore, data showed that the proangiogenic effect of IL-34 could directly activate several kinases e.g., PI3K, FAK, and ERK1/2, which importantly contribute to cell differentiation of ECs and indirectly via the enhanced production of other proangiogenic factors e.g., VEGR, monocyte chemoattractant protein-1, and IL-8 and activated macrophages [118, 120-125]. Further studies need to clarify the exact effects and mechanisms of ECs-derived IL-34 on the modulation of tumor angiogenesis in the CRC.

3.8 IL-37

IL-37 is a newly identified cytokine of the IL-1-like family. In contrast to the proinflammatory function of other IL-1 family members, IL-37 may have anti-inflammatory activity via inhibition of the production of proinflammatory cytokines and chemokines [34]. Although the role of IL-37 as a protumor or antitumor factor is controversial [126-128], however, its proangiogenic effect was recently reported [129]. Most of the interleukins belong to the IL1-like family acting on ECs in an autocrine or a paracrine manner [34], and the target receptor for IL-37 is IL-18R [34], which was highly expressed in vascular ECs [130]. Yang et al. [129] recently reported that IL-37 was highly expressed and secreted by vascular ECs, and the expression of IL-37 was upregulated under hypoxic conditions. IL-37 significantly promoted the proliferation, survival, migration of ECs, the formation of capillary, and vessel sprouting

from aortic rings, and this effect was extraordinarily strong and comparable to VEGF. In addition, IL-37 stimulated activation of survival signals, such as extracellular signal-regulated kinase and AKT, in ECs. In vivo, IL-37 potentially stimulated vascular vessel growth in implanted Matrigel plugs in a dose-dependent manner with comparable potency to basic fibroblast growth factor. Administration of IL-37 in mice with retinal vascular development resulted in enhanced neovascularization [129]. Ballak et al. [131] reported that IL-37 enhanced the function of ECs in old mice. Zhao et al. found that recombinant human IL-37 induced proangiogenic response in ECs occurred via transforming growth factor beta (TGF-β) in a mouse model of Matrigel plugs and oxygen-induced retinopathy via increased synthesis of NO and reduced levels of reactive oxygen species in ECs, which was accompanied by an increase in the phosphorylated adenosine monophosphate-activated protein kinase (AMPK) to AMPK ratio [132]. Notably, the expression of IL-37 in CRC tissues was lower than nontumor tissues, Zhu et al. [127] showed that CRC patients with low IL-37 levels were significantly associated with diminished disease-free survival and overall survival. These findings suggest that IL-37 plays a weak role in the regulation of angiogenesis in CRC. The regulatory effect of IL-37 in CRC angiogenesis has not been evaluated.

3.9 Other novel proangiogenic cytokines

Cytokine-like 1 (CYTL-1) is a novel proangiogenic factor produced by endothelial progenitor cells under hypoxic condition, which supports the formation of new vascular vessels in combination with VEGF-A that is produced locally by hypoxic cells [133]. CYTL-1 promotes the growth and metastasis of neuroblastoma cells [134]. Further investigation of the role of CYTL-1 within the CRC TME are needed in the future.

4. Potential significance of vascular ECs-derived ILs as a novel precise antiangiogenetic target for the treatment of CRC

The targeting proangiogenic factors or their receptors expressed in microvascular ECs using pharmacological inhibitors have now been an established second- or third-line treatment option for the management of mCRC and shown a promising therapeutic efficacy [47]. Clinical trials and studies showed that targeting tumor-associated angiogenic factor/receptor bioagents was an effective strategy in the management of mCRC [47, 135]. For example, antibodies targeting VEGF or VEGFR1 or VEGFR2, such as bevacizumab (a humanized anti-VEGF-A monoclonal antibody) and ramucirumab (anti-VEGFR-2 extracellular domain monoclonal antibody), significantly blocked the angiogenesis process and improved the clinical outcomes in patients with mCRC [45, 135]. The combination of antiangiogenic factor/receptor antibodies with other anticancer bioagents showed better efficacy in the management of mCRC compared to monotherapy with antiangiogenic bioagents [47]. However, not all the CRC patients respond to current antiangiogenic antibodies equally, and the development of resistance is frequently found [47]. One of the resistance mechanisms is that the tumor develops compensatory factors to restore angiogenesis pathways, and studies revealed that hypoxia-triggered upregulation of alternative proangiogenic factors were involved in this process [20]. If resistance occurs in patients with mCRC, second-line therapeutics with alternative antiangiogenic therapies, rather than anti-VEGF or VEGFR-targeted therapy continuation, must be considered [136]. Therefore, clinical considerations stimulated increasing interest from researchers to seek and develop novel bioagents that target novel proangiogenic cytokines in CRC.

We recently demonstrated that CRC mice dosed with anti-IL-17A antibodies showed significantly reduced tumor growth and progression [137]. Several monoclonal antibodies that target IL-17 signaling successfully passed phase III clinical trials for human diseases. These antibodies represent new options for potential CRC treatments. Therefore, it would be interesting to evaluate the therapeutic effect of these antibodies alone or combined with chemotherapy in treating relapsed CRC or mCRC [138]. Studies showed that ST2 was the

main functional receptor mediating the biological effects of IL-33 [139], and targeting ST2 signaling may inhibit tumor angiogenesis [107, 108, 140, 141]. Because microvascular ECs are a cellular source of proangiogenic cytokines and receptors, the ECs that line the luminal surface of microvascular vessels might be a promising therapeutic target of relevant human diseases [142]. Therefore, the discovery of specific drug delivery molecules or vehicles with pharmacological inhibitors that selectively block the proangiogenic cytokine/receptor signals expressed in microvascular ECs is particularly interesting and important. Recent studies identified several selective drug delivery approaches using monoclonal antibodies against surface markers of vascular ECs, particularly cell adhesion molecules or nanocarriers [142-144]. Using these approaches as drug delivery systems, future studies evaluating the therapeutic efficacy of proangiogenic cytokine or relevant receptor inhibitors that precisely target microvascular ECs-derived proangiogenic cytokines may provide novel clinical translational information for the intervention of tumor angiogenesis within the CRC TME.

5. Conclusion and perspectives

Collectively, emerging information suggests that microvascular ECs can be both the target and producers of various proangiogenic ILs and their vital role in the regulation of tumor angiogenesis should not be ignored. We incorporated integrated analyses of current published data and summarized the potential direct- and indirect-action pathways of microvascular ECs-derived proangiogenic ILs in the regulation of tumor angiogenesis (refer to Fig. 2).

The identification of novel proangiogenic factors and relevant receptors expressed in microvascular ECs may provide novel insights for the understanding of proangiogenic regulatory mechanisms and design of novel precise antiangiogenetic therapies. From the perspectives of understanding the pathogenesis of tumor angiogenesis and developing novel

angiogenesis target strategies, studies further defining the action pathways and clarifying the relevant molecular mechanisms of ILs in EC-directed tumor angiogenesis process are needed.

Statements & Declarations

Author Contributions:

GC: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Draft manuscript. **HL:** Data curation; Formal analysis; Investigation; Visualization and review draft. **JBL:** writing-review and editing. All authors read and agreed to the submitted version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Figure legends

Figure 1 legend

The postulated multiple mechanisms of cytokine involved in the progression, invasion, and metastasis in CRC

Many cytokines, such as vascular endothelial growth factor (VEGF) family and interleukin (IL)-1, IL-6, and IL-8, within the in the tumor microenvironment (TME), were involved in the progression, invasion, and metastasis in CRC via multiple mechanisms, in which many factors e.g., nitric oxide (NO) synthesis, cancer-associated fibroblasts (CAFs) and nuclear factor Kappa B (NF-κB) were activated under the stimulation of cytokines.

Figure 2 legend

Schematic summary of the stimulatory effects of vascular ECs-derived proangiogenic interleukins (ILs) on CRC angiogenesis.

ECs-derived proangiogenic ILs have been hypothesized to stimulate tumor angiogenesis via either an direct action on their receptors expressed on the endothelial progenitor cells or an indirect way through enhanced production of other proangiogenic factors for example VEGF.

Fig. 1

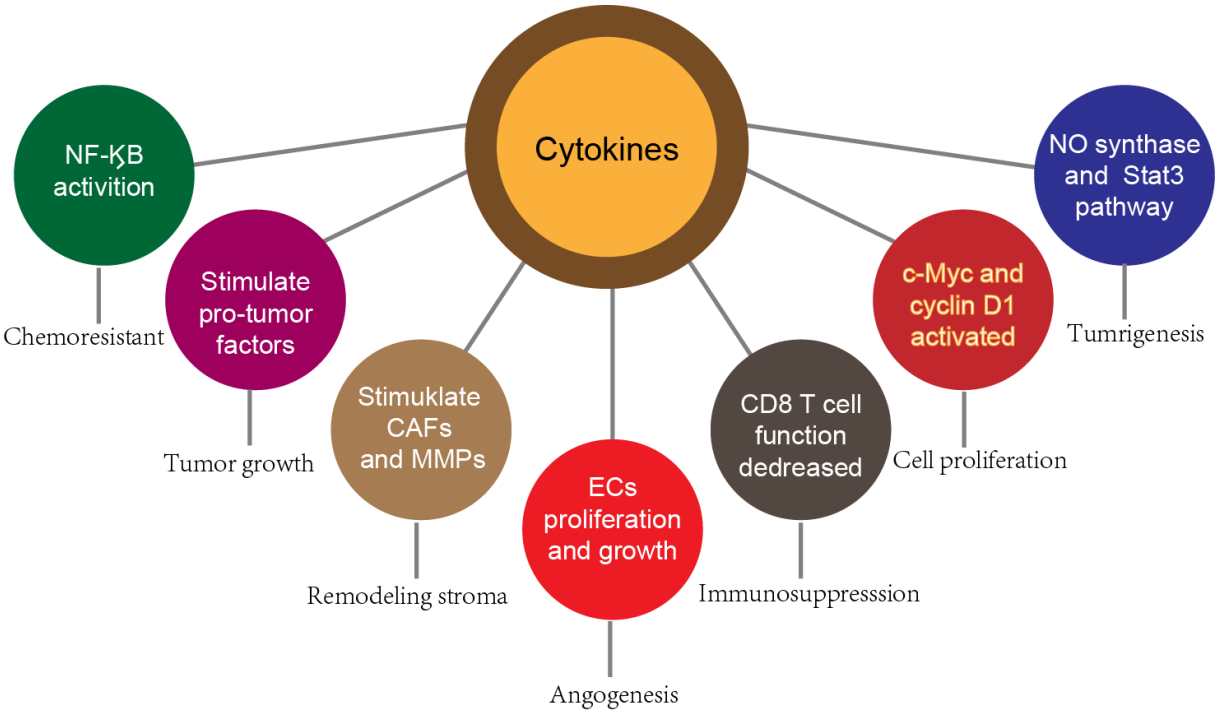
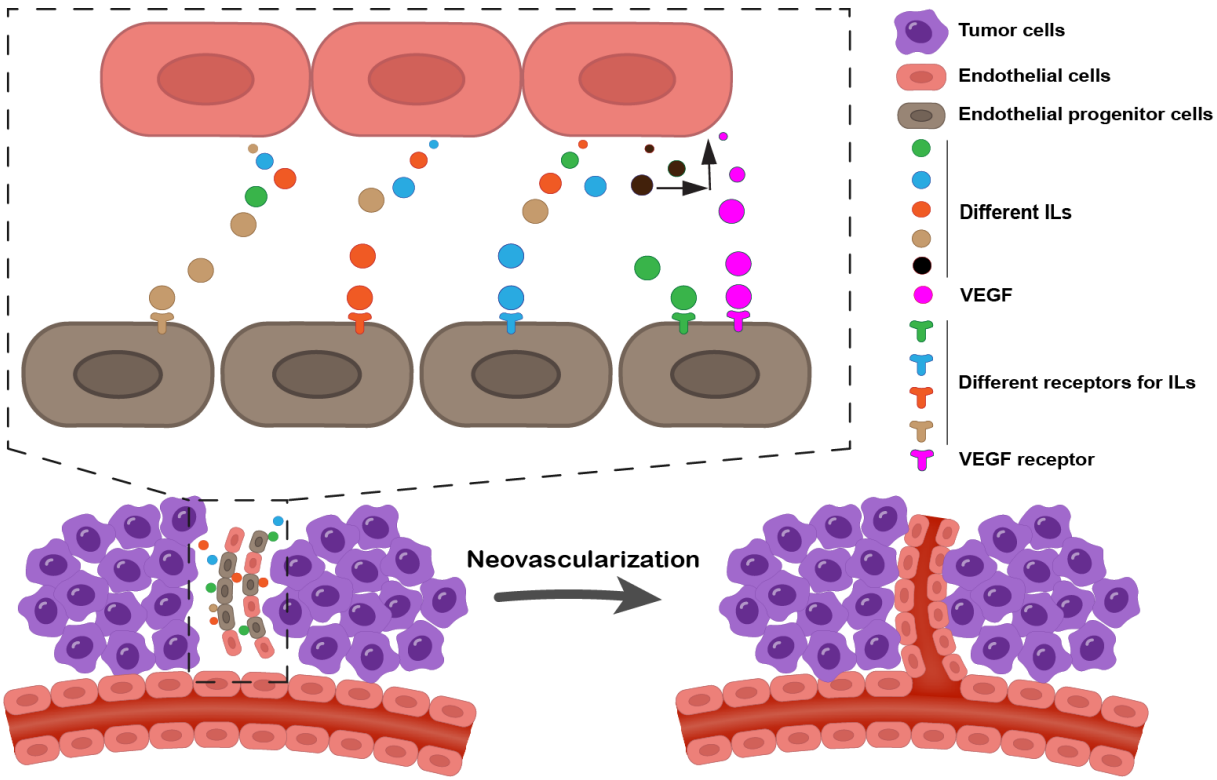

Cytokines
NF-ĸB activition
Chemoresistant
Stimulate pro-tumor factors
Tumor growth
Stimuklate CAFs and MMPs
Remodeling stroma
ECs proliferation and growth
Angogenesis
CD8 T cell function dedreased
Immunosuppresssion
c-Myc and cyclin D1 activated
Cell proliferation
NO synthase and Stat3 pathway
Tumrigenesis

Fig. 2


Tumor cells
Endothelial cells
Endothelial progenitor cells
Different ILs
VEGF
Different receptors for ILs
VEGF receptor
Neovascularization