The Role of Angiogenesis in Colorectal Polyps and Cancer: a Review

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ABSTRACT
Colorectal cancer remains a leading cause of morbidity and mortality worldwide. Most colorectal cancers begin as a growth of tissue called a polyp, some types of which can change into cancer over the course of several years. Angiogenesis, the formation of new blood vessels, is known to play a key role in the initiation, growth and progression of polyp and colorectal cancer. In this review, we discuss the mechanisms involved in colorectal cancer and polyp angiogenesis.

Keywords: Colorectal Neoplasms, Polyps, Angiogenesis.
INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, accounting for approximately half a million deaths each year (1-3). The major risk factors for CRC include genetic predisposition and environmental factors, including smoking, physical inactivity, obesity and consumption of processed meat and alcohol (4). These factors cause genetic and epigenetic changes, followed by transformation of normal colonic mucosa into invasive carcinoma (5). Colorectal polyps result from abnormal cell proliferation in the colorectal mucosa. According to histological and morphological features, colorectal polyps are divided into neoplastic (adenoma and carcinoma) and non-neoplastic (hyperplastic, hamartomatous and inflammatory) types (6). Neoplastic polyps, also known as adenomatous polyps, are sub-classified by their histology appearance as tubular, villous and tubulo-villous adenomas (7). Studies have demonstrated that villous adenomas account for approximately 5-10% of neoplastic polyps, most of which are suspected to have dysplasia. Approximately 10-15% of neoplastic polyps show both morphological futures of villous and tubular types (7). Adenomatous polyps are not typically transformed to malignant cells, but characterization of the CRC features show that adenomatous polyps originate from the adenomatous polyps and adenoma–carcinoma sequence (3). In addition, some hyperplastic polyps demonstrated to have the potency of CRC initiation (8).

Common abnormalities associated with CRC include microsatellite instability (MSI), chromosomal instability (CIN) and the CpG island methylator phenotype (9, 10). MSI is a condition of genetic hypermutability resulting from impaired DNA mismatch repair system, accounting for approximately 15-20% of all CRC cases diagnosed (11). Importantly, 3-5% of hereditary nonpolyposis CRC (HNPCC, a genetic disease of autosomal dominant inheritance) incidents result from a germ line mutation in the DNA mismatch repair genes, including MSH2, MLH1, PMS2, MLH3, MSH3, PMS1 and Exo1. Meanwhile, 15% of sporadic MSI tumors have been reported to undergo hyper-methylation in the promoter region of MLH1 (11). CIN, the most common cause of genomic instability in CRC, is characterized by gain or loss of whole chromosomes or chromosomal regions harboring genes, leading to activation of oncogenes (such as K-ras, cSrc and c-myc) and inactivation of tumor suppressor genes (such as adenomatous polyposis coli, P33 and hetrozigosity for the long arm of chromosome 18) (12-14). The CpG island methylator phenotype is another cause of tumorigenesis characterized by the hypermethylation of CpG islands located at promoter regions, resulting in missregulated activity of the tumor suppressors or oncogenes (11, 15). Cancer cells secrete growth factors capable of promoting the formation of new blood vessels (angiogenesis), which is involved in tumorigenesis and cancer cell growth. The two mechanisms for the formation of new blood vessel can be categorized into vasculoogenesis (the formation of first primitive vascular plexus de novo) and angiogenesis (the formation of new vessels from preexisting vessels) (16, 17). Angiogenesis is an essential process in cancer progression, in which vascular endothelial growth factors (VEGFs) play a critical role (9). There is increasing evidence showing that cancer cells are major sources of VEGF (18). In this review, we discuss the mechanisms involved in CRC and polyp angiogenesis, angiogenesis regulation and therapeutic methods for angiogenesis inhibition.

Search strategy

A literature search strategy was performed for all English literature published before 2018. The search was carried out using electronic databases including PubMed, Embase, Scopus and Web of Sciences. The following keywords were used in the search strategy: ‘colorectal cancer’, ‘epidemiology’, ‘incidence’, ‘mortality’, ‘risk factor’, ‘survival’, ‘Polyp’, and ‘VEGF-A’.

Angiogenesis

Angiogenesis is a complex process that facilitates the delivery of nutrients and oxygen to cells by formation of new blood vessels. This process plays an important role in cancer development by promoting tumor growth and metastasis (19). It involves proliferation of activated endothelial cells, migration of the endothelial cells to remote targets, assembly of endothelial cells into new capillary tubes, followed by the synthesis of a new basement
membrane and maturation of vessels with the formation of a vascular lumen (20). There is accumulating evidence suggesting that a variety of molecular pathways involved in angiogenesis may have therapeutic potentials.

**Angiogenesis factors**

Both vasculogenesis and angiogenesis are regulated by precise balance between the pro-angiogenic and anti-angiogenic factors (16). Angiogenic growth factors and cytokines include VEGF, fibroblast growth factor (FGF), tumor necrosis factor-alpha (TNF-α), TGF-β and angiopoietins (Angs) (21). In addition, several signaling pathways including VEGF, Notch/delta, Ephrins/Ephs, semaphorin/plexin/neuropilin, Slit-Robo hedgehog and Sprouty are involved in the initiation and progression of angiogenesis (22).

**VEGF**

VEGFs play an important role in the regulation of tumor angiogenesis. The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor (PGF), VEGF-E (Orf-VEGF) and *Trimeresurus flavoviridis* svVEGF (23).

Hypoxia is widely recognized as a key driving force for tumor angiogenesis via induction of VEGF and other direct-acting angiogenic factors. In addition, VEGF expression and secretion increase following activation of hypoxia-inducible factor 1-alpha (HIF-1 alpha), a subunit of a heterodimeric transcription factor HIF-1) in hypoxic conditions (24). The biological effects of VEGF are mediated by VEGF receptors (VEGFR), which are divided into three main subtypes: VEGFR-1, VEGFR-2 and VEGFR-3. These receptors may be membrane-bound or soluble depending on alternative splicing, and can bind to VEGF isoforms (24, 25).

VEGFR-1 binds to VEGF-B and PGF and exerts a positive regulatory effect on angiogenesis (26). VEGFR-2, which binds to VEGF-A, also has a pro-angiogenic function and enhances endothelial cell proliferation, migration and invasion. VEGF-C and VEGF-D bind to VEGFR-3, which mainly mediates lymphangiogenesis (19, 26).

**Role of Ang in Angiogenesis**

Tie-1 and Tie-2 tyrosine kinase receptors expressed specifically on vascular endothelial cells are essential for vascular maturation during developmental, physiological and pathological angiogenesis. Angs-1-4 have been identified as bona fide ligands for the Tie-2 receptor, while Tie-1 remains an orphan receptor capable of heterodimerization with Tie-2 and modulating Tie-2 signal transduction (27). Ang-1, Ang-2 and Ang-4 were demonstrated to play an important role in angiogenesis and metastasis in cancer. While Ang-1 is widely expressed in normal adult tissues, Ang-2 is expressed in a variety of human malignancies, including carcinomas of the colon, liver, stomach, lung and thyroid, as well as malignant gliomas (28-35). In addition to normal cells, Ang-1 is expressed in tumor cells and binds to Tie1 and Tie2 on the vascular endothelial cells (27). Ang-2 is expressed on endothelial cells and binds to the Tie-1 and Tie-2 receptors. Moreover, VEGF-A, platelet-derived growth factor, insulin like growth factor and other pro-angiogenic factors stimulate Ang/Tie signaling and lead it to angiogenesis (27, 36).

**Clinical Data of VEGFs**

Binding of VEGF-A to VEGFR-2 and regulation of angiogenesis enhance endothelial cell proliferation, migration and survival. Elevated levels of VEGF-A have been detected in some cancers such as CRC and breast cancer (26). Some studies have shown that decreased expression of VEGFR-1 in tumors was correlated with decreased survival rate and high-stage disease in pancreatic cancer (39). The expression of VEGF along with VEGFR-1 and VEGFR-2 in tumor cells has been demonstrated. It has been recently reported that VEGF, VEGFR-1 and VEGFR-2 are significantly overexpressed in adenocarcinomas and serrated adenomas when compared with hyperplastic polyps (40, 41). VEGF-B enhances survival of endothelial and smooth muscle cells, and up-regulates the expression of pro-survival genes. Overexpression of VEGF-B in some cancers, such as ovarian, colorectal, renal and prostate cancer is thought to be correlated with disease stage and expression of VEGFR-1 (42, 43). VEGF-C expression is associated with advanced metastatic CRC, and VEGF-D plays a role in lymph angiogenesis and lymphatic metastasis. Both VEGF-C and VEGF-D bind to VEGFR-2 and VEGFR-3 (26). These
clinical data could be useful for finding a suitable anti-angiogenic therapy for CRC patients.

**Anti-angiogenic therapy**

In 1971, Folkman described the therapeutic implications of tumor angiogenesis and the concept of tumor angiogenesis. Based on their mechanism of action, there are four approaches for anti-angiogenic therapy, including blockage of the angiogenic factors or receptors such as VEGF and VEGFRs, direct inhibition of proliferation or survival of endothelial cells, prevention of extracellular matrix and basal membrane degradation, as well as inhibition of vascular cellular adhesion molecules, such as integrin αvβ3 (44). The most common therapies include blocking endogenous tumor VEGF expression, preventing VEGF binding and its signal transduction, and neutralizing VEGF in the microvascularization process. Targeting VEGF expression by Bevacizumab is a notable treatment approach for CRC (26,45,46). Bevacizumab is a recombinant human monoclonal antibody that directly targets synthesis of VEGF during tumor growth, decreasing angiogenic cell signaling and blood supply for tumors. The drug is usually used in combination with chemotherapeutic drugs for patients with metastatic CRC. Studies suggest that this therapeutic approach can improve patients’ survival rate by almost five months (26, 45).

Aflibercept is a recombinant fusion protein that binds to VEGFR-1, VEGFR-2 and PIGF in tumor xenograft models. This protein prevents angiogenesis and growth of new and established tumors and decreases vessel density, blood flow and risk of metastasis. Aflibercept also has negative effects on hypoxia-induced angiogenesis (47,48).

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NCT01120288, NCT01210222 and NCT01193868 are some preventing agents for other angiogenesis regulators such as HIF-1 alpha, Ang-1 and Ang-2, as well as the Notch signaling pathway (26). Aflibercept is also known as VEGF-Trap, and serves as VEGF decoy receptor that binds to circulating VEGFs and inhibits the activity of VEGF-A and VEGF-B. Same events can occur in the case of PGF, which inhibits the growth of new blood vessels.

Application of tyrosine kinase inhibitors (TKIs) is another approach to block angiogenesis. TK receptors including VEGFR, FGFR and platelet-derived growth factor receptor are thought to play a key role in angiogenesis and are involved in multiple signaling pathways. TKIs such as Imatinib, Sorafenib, Sunitinib, Pazopanib and Axitinib bind to the ATP binding site and inhibit the activation of more than one receptor, resulting in angiogenesis blockage (49).

**CONCLUSION**

Angiogenesis plays an important role in tumor growth, malignancy, migration and metastasis. Since most CRCs derive from adenomas, finding molecular mechanisms and effective factors in polyps and tumor angiogenesis provides a clear insight into the development of polyps and cancer cells and progression to malignancy.

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**CONFLICT OF INTEREST**

All contributing authors declare no conflict of interest.

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