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REVIEW

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NF-κB pathway and angiogenesis: insights into colorectal cancer development and therapeutic targets

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Abstract

Colorectal cancer (CRC) is currently ranked as the third most common type of cancer, contributing significantly to mortality and morbidity worldwide. Epigenetic and genetic changes occurred during CRC progression resulted in the cell proliferation, cancer progression, angiogenesis, and invasion. Angiogenesis is one of the crucial steps during cancer progression required for the delivery of essential nutrients to cancer cells and removes metabolic waste. During angiogenesis, different molecules are secreted from tumoral cells to trigger vascular formation including epidermal growth factor and the vascular endothelial growth factor (VEGF). The production and regulation of the secretion of these molecules are modulated by different subcellular pathways such as NF-κB. NF-κB is involved in regulation of different homeostatic pathways including apoptosis, cell proliferation, inflammation, differentiation, tumor migration, and angiogenesis. Investigation of different aspects of this pathway and its role in angiogenesis could provide a comprehensive overview about the underlying mechanisms and could be used for development of further therapeutic targets. In this review of literature, we comprehensively reviewed the current understanding and potential of NF-κB-related angiogenesis in CRC. Moreover, we explored the treatments that are based on the NF-κB pathway.

Keywords Angiogenesis, Colorectal cancer, Neovascularization, NF-κB, VEGF

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Introduction

The latest report released by the Global Cancer Observatory in 2022 states that colorectal cancer (CRC) ranks as the third most widespread type of cancer worldwide and has a significant impact on the overall number of deaths caused by cancer [1]. The most significant morphological prognostic factors are still the grade of the tumor, lymph node status and extent, and invasion of lymphatic and venous system [2]. Metastasis development is a significant worry for both patients and clinicians due to its potential fatality and homeostasis disruption (Fig. 1) [3, 4]. Moreover, metastasis and unrestricted invasive growth of malignancies depend on angiogenesis, which is suggested that tumors infrequently metastasize without the presence of angiogenesis [5]. The fundamental factors essential for the progression of metastatic CRC are the routes activated by the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) [6]. Angiogenesis, an intricate phenomenon marked by the development of fresh blood vessels from precursor endothelial cells, is involved in cancer development and is recognized as one of the principal features of this disease. Considering the nutritional demands of malignant tumor cells, encompassing essential elements such as oxygen and growth factors, it becomes imperative for them to be surrounded by a suitable blood supply to facilitate their expansion. The generation of tumor vasculature significantly contributes to the proliferation and dissemination of tumors. It has been postulated that the initiation of tumor development is strongly connected to the occurrence of tumor angiogenesis [7]. Receptors and ligands that are in tight regulation, mediate this process [8, 9]. In addition, a diversity of substances that stimulate the growth of blood vessels, such as endothelial growth factor (EGF), fibroblast growth factor (FGF), VEGF, transforming growth factor (TGF), platelet-derived growth factor (PDGF), thrombospondin-1 (TSP-1) and, involve in controlling this biological process [10–15]. It has been shown that numerous pro-angiogenic molecules, such as matrix metalloproteinase-9 (MMP-9), interleukin-8 (IL-8), and VEGF, are downregulated in tumor cells. Additionally, inhibition of NF-κB in these cells blocks their ability to develop angiogenesis [16]. Besides, studies have demonstrated that NF-κB is an essential factor in the viability of blood vessel endothelial cells when subjected to TNF, a type of cytokine frequently found in inflammation linked to cancer [17].

NF-κB, a specific protein known as "kappa-light-chain-enhancer" of activated B cells, is essential for the proper functioning of the immune system [18, 19]. It acts as a transcription factor, mediating communication between the cell's cytoplasm and nucleus, and controlling the expression of genes related to cytokine receptors, cytokines, and adhesive molecules involved in the inflammatory immune response [20, 21]. It plays a crucial function in numerous cellular processes in eukaryotes, comprising angiogenesis, inflammation, cell proliferation, and transformation [22, 23]. When the NF-κB is turned on, it moves to the nucleus and interacts with a specific DNA pattern, aiding in the activation of transcription [24]. Moreover, the elevated activity of NF-κB may contribute to the promotion of angiogenesis [25]. Recent research has additionally demonstrated that reducing NF-κB expression can result in reduced proliferation of synovial cells with a fibroblast-like appearance, induced cell death, and inhibited angiogenesis [26, 27]. With the improvement of therapeutic methods including immunotherapy, chemotherapy, radiotherapy, targeted therapy, and surgical resection, the patient's 5-year survival with CRC has been improved considerably [28–30], although disease relapse and metastasis are still challenging for CRC treatment [31]. Thus, uncovering the molecular pathways of CRC to identify novel targets and subsequently develop novel treatments is urgent.

In this paper, we aim to dissect the complex interplay between NF-κB signaling and angiogenesis in CRC, shedding light on potential therapeutic avenues for improved patient outcomes.

The role of NF-κB in cancer: development, progression, and metastasis

NF-kB is a multifunctional transcription factor that governs the expression of several genes involved in cellular proliferation and cell survival in a broad spectrum of tumors in the primary signaling pathway. The active transcription factor NF-κB comprises a dimer made up of two subunits, p50 and p65 (also known as RelA) (Fig. 2) [21, 32]. When cells are not stimulated, the heterodimer is fully enclosed in the cytoplasm due to its binding with p65 inhibitor of kappa B-α (IKBα) [33]. A diverse range of mechanisms elucidated the dependence of malignant cells on the activated form of NF-κB, including viral and fusion proteins, mutations in IκB, heightened activity of IKK, excessive expression of receptors and ligands, in addition to mutations in NF-κB [34]. Upon activation, IKBα undergoes phosphorylation by the IKB kinase (IKK) and is subsequently targeted for degradation through the proteasome pathway. This process leads to the release of NF-κB, allowing it to move into the nucleus, where it initiates the transcription of specific genes that modulate cellular migration, inflammation, and proliferation. In comparison to normal cells, cancer cells exhibit irregular and persistent NF-kB activation,

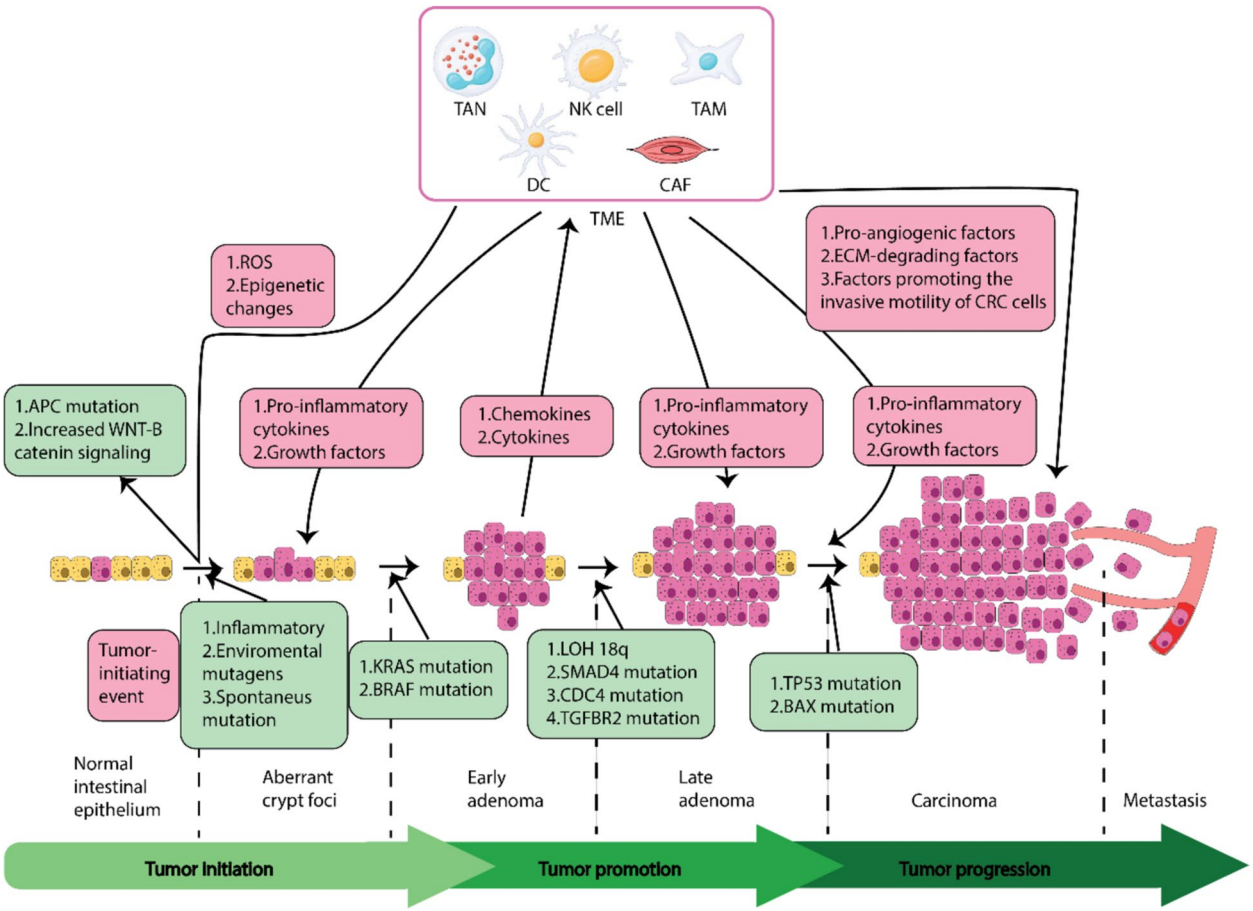

Fig. 1 The processes that lead to the development and growth of CRC involve multiple stages, starting with the initiation of a tumor through the transformation of healthy intestinal cells (IECs). This can occur due to various factors, such as mutations that occur spontaneously or exposure to harmful substances in the environment. Inflammation can also trigger changes in the genetic makeup (epigenetic changes) of intestinal cells, leading to tumorigenesis. The uncontrolled growth and division of these "initiated" cells, triggered by genetic mutations that promote hyperproliferation, such as of APC or other genes involved in the WNT pathway, along with additional mutations in genes like KRAS, TP53, or TGFBR2, and cancer-promoting factors in the tumor's surroundings, ultimately results in the development of malignant tumors, a process referred to as tumor promotion. Further alterations and modifications to the tumor microenvironment (TME) result in the ability for these tumors to eventually spread to other body parts. The epithelial tissue of the tumor consistently communicates with cells in the TME using cytokines, chemokines, and growth factors. The initiation of tumor creation is heavily influenced by the existence of inflammation, which leads to the production of reactive oxygen species (ROS) and epigenetic changes. Furthermore, the provision of growth factors and pro-inflammatory cytokines also contribute to the advancement of cancer. Moreover, tumors could induce a pro-inflammatory environment by releasing cytokines and chemokines, resulting in a continuous cycle that aids in tumor progression. Several different kinds of cells play a role in this process, including cancer-linked fibroblasts, cells from CRC, dendritic cells, the extracellular matrix, loss of heterozygosity, natural killer cells, macrophages linked to tumors, and neutrophils associated with tumors

which significantly involves various cancer-developmental signaling cascades [35, 36]. Furthermore, NF-κB is implicated in a mutual association with different tumor suppressive agents. The components that restrain activity, in diverse manners, disrupt the functioning of NF-κB at a microscopic level. NF-κB, by engaging with co-partners p300 and CREB-binding protein (CBP) and elevating the amounts of murine double minute-2 (MDM2) protein, obstructs the adequate functioning of the cancer-inhibiting protein p53 [37–39]. The ongoing stimulation of NF-κB in instances of gastrointestinal, hepatocellular, cutaneous, cerebral, prostatic, pulmonary, and hematopoietic malignancies has been observed [40].

The regulatory factor NF-κB gave an essential part in managing the expression of various genes that are involved in both the early and advanced stages of aggressive tumor growth. These genes, such as cyclinD1, COX-2, Bcl2, VEGF, FLIP, ICAM-1, cIAP1, TRAF2, and MMP-9, are essential for enabling invasion and angiogenesis [41, 42].

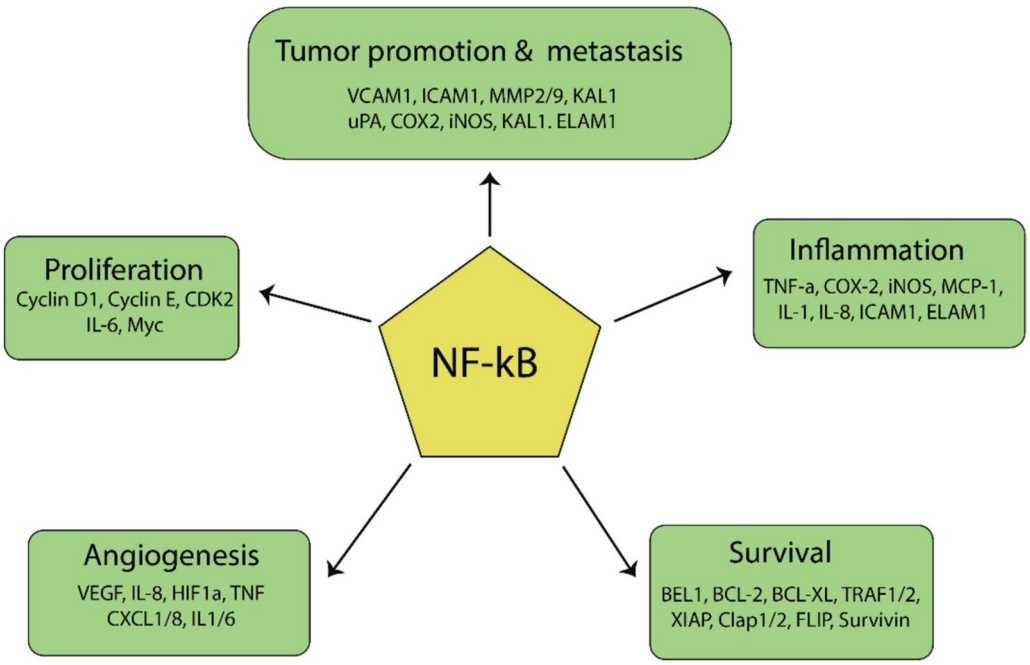

Fig. 2 Activation of NF-κB has a substantial influence on CRC. It triggers the expression of multiple genes involved in various processes, including cell proliferation, survival, angiogenesis, inflammation, and the progression of tumors and metastases

The control of cell growth and viability is influenced by this signaling mechanism, which remains consistently stimulated, resulting in the continual activation of genes related to cell proliferation, including cyclin D1, cyclin E, Myc, cyclin-dependent kinase (CDK)-2, and IL-6. As the improper regulation of NF-κB is frequently observed in cancerous cells, blocking this pathway could potentially limit cell proliferation [43]. The TME is involved in the development and progression of cancer cells, particularly in the case of CRC. TNFα and IL-6 have a central role in facilitating the interplay between cancer and inflammatory processes within the TME [44–46]. The high expression of TNF-α and IL-6 facilitates invasion, angiogenesis, metastasis, and therapeutic resistance [47]. Pro-inflammatory cytokines including IL-6 and TNF-α have mutual relationship with NF-κB; They could activate NF-κB while NF-κB induces the expression of them [48–51]. For instance, TNF-α activates NF-κB through induction of phosphorylation of IKB and further degradation of this protein allowing NF-κB to translocate to the nucleus and initiate transcription of target genes [52, 53]. IL-6 activates STAT-3 to promote the activation of NF-κB [49]. On the other hand, sustained production of TNF-α and IL-6 depend on the activation of NF-κB as during inflammatory processes NF-κB induced the expression of TNF-α [48, 50, 51]. The initiation of NF-κB can additionally trigger Stat3 activation, leading to amplified connections between cancerous cells and the TME [54]. The ability for tumors to continue growing is mainly dependent on how malignant cells interact with the TME [55].

CRC metastasis is a multifaceted process, including extracellular matrix degradation, decreased cell adhesion, the development of the cell's migratory ability, angiogenesis and alterations in the TME [56–58]. Additionally, multiple functional proteins, such as TPx, matrix metalloproteinases (MMPs), and VEGF regulate this process [59–61]. These proteins alter the function of many internal communication pathways within the cell, including the NF-κB pathway, thereby affecting the metastasis and invasion potential of CRC [62]. Ryan and colleagues successfully showed that inhibiting NF-κB significantly impedes the dissemination of CT-26 colon cancer cells in a mouse model of peritoneal metastasis, thus further validating these findings [63].

NF-κB can activate multiple transcription factors that promote the process of epithelial–mesenchymal transition (EMT) and the consequent spread of different types of cancer, such as ZEB2, snail, and twist [64–66]. Moreover, the mechanism of PI3K, AKT, and IKKα has been pinpointed as a key factor in regulating the function of NF-κB and β-catenin in human CRC cells, resulting in important influence on the expression of genes associated with the spread and growth of cancer cells [67].

Angiogenesis in colorectal cancer

Angiogenesis is a highly intricate process involving a delicate balance of stimulating and inhibitory factors responsible for the formation of new blood vessels. This plays a vital role in the progression of CRC and other types of cancer [68, 69]. Growth agents including epidermal growth factors (EGFs) and VEGF, TGF-β, TGF-α, FGF-2, PDGF, angiopoietins, membrane-bound agents (ephrins, integrins, MMPs, cadherins, EphB4, and hypoxia-inducible factor-1 (HIF-1) are the main molecules involved in angiogenesis [70, 71]. A dysregulation between anti- and pro-angiogenic factors, triggered by tumor cell mutations or hypoxia, activates the angiogenic switch and endothelial cell proliferation [72, 73]. Rapid tumor growth can induce hypoxia (oxygen deprivation), prompting HIF-1 activation and the release of pro-angiogenic signals for cell survival [73]. In CRC, the VEGF and EGFR pathways stand out as particularly important regulators of angiogenesis [74]. While numerous factors might have effect on VEGF pathway, hypoxia is the primary driver of its regulation in angiogenesis. This occurs through the activation of HIF-1 and HIF-2, both triggered by hypoxic conditions [75]. The process of angiogenesis initiation in CRC happens at an early stage, brought about by the lack of oxygen and nutrients. HIF-1, a protein complex made up of HIF-1α and β subunits, plays a crucial role in regulating gene expression during this response. When oxygen is limited, HIF-1α becomes more stable and partners with HIF-1β to form a functional complex. This intricate structure then binds to hypoxia response elements (HREs) and initiates the transcription of various genes that are stimulated by decreased levels of oxygen [68]. HIF-1α overexpression is observed in CRC and is an independent prognostic marker, correlating with elevated expression of cyclooxygenase-2 (COX-2) and VEGF-A, the latter linked to prostaglandin E2 (PGE2) production and increased vessel formation. Consequently, PGE2 has also been proposed as a prognostic marker in CRC [76]. VEGF, particularly VEGF-A, is the key driver of angiogenesis in CRC [77, 78]. It binds to tyrosine kinase receptors (VEGFRs), primarily VEGFR-2 on endothelial cells, migration, triggering proliferation, sprouting, and tube formation. VEGF also inhibits endothelial cell apoptosis, activates extracellular matrix (ECM) degradation enzymes, and regulates vascular permeability [79, 80]. Moreover, VEGF signaling is central to CRC biology, promoting cell proliferation through protein kinase C and MAP kinase pathways and enhancing the EGFR pathway [69, 74]. VEGFR overexpression is observed in CRC, and this overexpression, along with increased PlGF expression, correlates with poor prognosis and metastasis [81].

Angiopoietin-1 and 2 are additional factors that contribute to angiogenesis. Both of these proteins promote angiogenesis and increase endothelial cell migration for formation of new vessels, with higher Angiopoietin-2 levels linked to poorer outcomes in CRC {Fagiani, 2013 #552}[82]. Conversely, lower Angiopoietin-2 levels predict a better response to bevacizumab therapy, a VEGF inhibitor, in metastatic CRC patients [83, 84]. Understanding these diverse pro-angiogenic pathways across different cancers opens avenues for targeted therapeutic interventions. Anti-angiogenic drugs like bevacizumab, which blocks VEGF activity, have shown promise in CRC and other malignancies, highlighting the potential of harnessing these biological mechanisms for improved cancer treatment [85].

Influenced by NF-κB, the progression of CRC and the formation of new blood vessels (angiogenesis) are significantly accelerated due to the promotion of pro-angiogenic factors, such as VEGF [86]. NF-κB normally remains inactive in the cytoplasm, bound by inhibitory proteins (IκBs). However, upon activation by various stimuli, IκBs are degraded, enabling NF-κB to move to the nucleus and modify the expression of genes involved in various cellular processes [87]. The NF-κB pathway alters the rate of expression of several crucial genes associated with tumor angiogenesis like MMP-2, PDGF-BB, and MMP-9 and also amplifies the pro-angiogenic effects of other signaling pathways (e.g., Wnt/β-catenin) through interactions, further promoting tumor vascularization [88]. Therefore, understanding the intricate relationship between NF-κB and angiogenesis in CRC development is crucial. Targeting this pathway could offer novel therapeutic strategies to impede tumor growth and progression by restricting angiogenesis and availability of nutrients.

NF-κB-related angiogenesis in CRC development

NF-κB-mediated angiogenesis is significantly involved in promoting tumor growth and development. Recent studies have highlighted the consistent activation of the NF-κB in CRCs and also other diverse cancer types, including leukemias, lymphomas, melanomas, breast cancers, and pancreatic malignancies [89]. These studies suggest an association between activated NF-κB and detrimental features of tumor cells, comprising, boosted resistance to apoptosis, enhanced cell proliferation and metastatic potential [90].

NF-κB pathway holds a critical position in CRC progression by regulating various cellular processes [91]. NF-κB induces the expression of anti-apoptotic proteins, comprising Bcl-2-associated athanogene-1 (BAG-1), B-cell lymphoma 2 (Bcl-2), and B-cell lymphoma-extra-large (Bcl-xL), thereby promoting cell survival and inhibiting apoptosis [91]. Additionally, promoted NF-κB activity in CRC enhances the expression level of

pro-inflammatory cytokines (IL-6, TNFα, IL-1β), angiogenic agents (IL-8, HIF-1α, VEGF), and metastatic genes (cytoskeletal genes, chemokines, MMPs [92]. Furthermore, abnormal activation of upstream regulators, specifically protein arginine methyltransferase 5 (PRMT5), has been proven have an important part in the NF-κB-induced impact on proliferation, anchorage independence, and migratory capabilities of CRC cells [93, 94]. It was also shown that High B7-H3 expression, an immune checkpoint protein regulating CRC angiogenesis, related to increased VEGFA expression in CRC patients through the NF-κB signaling pathway. This finding supports the potential role of the B7-H3/NF-κB/VEGFA axis in CRC angiogenesis [95]. Constant activation of NF-κB in CRC demonstrated its significant part in angiogenesis, ultimately promoting tumor growth. NF-κB activation was inhibited by silencing IKKβ, a crucial component in the activation pathway, via small interfering RNA (siRNA). In vivo experiments demonstrated a palpable suppression of tumor growth and reduced vascularization in these knockdown cells [89]. Other studies utilizing microarrays and protein arrays already established a link between NF-κB activation and elevated expression of several angiogenic chemokines [96, 97].

A recent investigation has pinpointed crocin, a type of nutrient found in the Himalayan crocus plant, as a possible candidate for targeting the NF-κB pathway, providing a hopeful avenue for hindering the growth of new blood vessels and spread of cancer cells in CRC. Research has shown that the compound crocin can significantly reduce the production of VEGF and block the activation of NF-κB in human CRC cells stimulated by TNF-α. Additionally, crocin was found to strongly inhibit NF-κB activity in a dose-dependent manner, even in the absence of TNF-α. Altogether, the results imply that crocin could potentially suppress both angiogenesis and metastasis through its ability to regulate NF-κB and counteract the TNF-α/NF-κB/VEGF pathway [98].

Another significant developmental way that NF-κB interact with TME in CRC [99]. This complex interplay creates a pro-inflammatory and supportive environment for cancer cells. The heightened levels of NF-κB activity observed in cancerous cells lead to the liberation of inflammatory mediators, like IL-6 and TNF-α, within TME [100]. In relation to CRC, TNF-α and IL-6 are key players in mediating inflammation and promoting cancer progression within the TME [45, 46] and high levels of these cytokines in tumor tissues and serum correlate with poor patient prognosis [101]. The TME is influenced by these cytokines, causing various kinds of cells such as CAFs, immune cells, and non-cancerous cells to produce IL-6 and TNF-α. This process creates a cycle of positive reinforcement that strengthens NF-κB activation [54, 55, 102].These cytokines contribute to invasion, angiogenesis, metastasis, and therapeutic resistance in CRC [47, 55]. Additionally, mutations in other signaling pathways, like RAS-RAF and miRNA dysregulation, can enhance NF-κB activity [103]. Once the NF-κB pathway is activated in cancer cells, there is an increase in the expression of multiple genes that promote the creation of an environment that supports both inflammation and tumor growth. These genes produce molecules such as Bcl-xL and Bcl-2, which prevent cell death, as well as inflammatory substances like TNF-α and IL-6, and factors that promote the formation of blood vessels, such as VEGF and IL-8. Additionally, the expression of chemokines that contribute to inflammation is also amplified [1]. This further perpetuates the pro-inflammatory state and promotes tumor growth, invasion, and metastasis [92]. Understanding this intricate interplay between NF-κB and the TME holds immense potential for developing novel therapeutic strategies to target cancer progression.

Epi/genetic alterations are crucial for the step-wise CRC development, accumulating over time and driving its progression [104]. Over half of genetic alterations observed in patients with CRC through cBioportal for Cancer Genomics involve the NF-κB signaling pathway, highlighting its significant role in the disease [91].

NF-κB serves a crucial function in regulating the immune system and impacting angiogenesis by governing critical genes in both the classical and alternative pathways. When triggered by different ligands, the canonical pathway prompts the movement of p65 and p50, which then has the potential to activate the expression of genes that play a role in angiogenesis [105]. The non-canonical pathway, responding to specific stimuli, such as ligands of LTβR, BAFFR, CD40, and RANK, involves p100 processing and might also impact angiogenesis by directly regulating relevant genes. MicroRNAs (miRNAs) play a complex role in CRC progression, impacting both oncogenesis and tumor suppression. Notably, the mutational landscape of CRC can influence its miRNA profile [106]. These specific miRNAs function by targeting the mRNA in order to control the production of proteins that have important function in the NF-κB pathway. Upon further investigation, it has been confirmed that multiple miRNAs have verified NF-κB binding sites within their promoters, indicating direct manipulation by NF-κB [107]. These miRNAs, often involved in modulating inflammatory responses, can exert either pro- or anti-inflammatory effects [108]. This complex interplay between genetics and epigenetics further emphasizes the intricate regulatory network governing NF-κB-related angiogenesis. Other genetic alterations, including mutations, deletions, and amplifications, affect different components of the NF-κB pathway in CRC patients. This includes not

only mutations within the NF-κB family members themselves, but also polymorphisms and alterations in other regulatory genes of the pathway [104].

For example, in a study, analysis of 348 colon cancer samples of CRC samples revealed significant genetic changes in multiple NF-κB family member genes, including RelA (2.5%), RelB (5%), Rel, NF-κB1, and NF-κB2. This suggests a potential role for these alterations in CRC progression. Different types of mutations were identified, including missense, deletion, insertion, and nonsense mutations, affecting various protein regions [109]. Moreover, apart from changes in the NF-κB family, numerous modifications in the genes involved in controlling the NF-κB signaling pathway have been observed in individuals with CRC. This underscores the significant impact of the pathway on the development of CRC. A recent research project investigated the NF-κB pathway in CRC by analyzing 84 key genes in paired tumor and peritumoral tissues compared to normal colon. As expected, most genes were upregulated in tumors, particularly those in the IL-1 signaling pathway (e.g., IL1A, IL1B, IRAK1, IRAK2, CHUK) [105]. The extensive presence of genetic alterations in the NF-κB pathway in CRC suggests promising avenues for developing novel therapeutic strategies to target this pathway and potentially treat the disease.

Treatments-based NF-κB signaling pathway in CRC

For resectable CRC, surgical excision remains the cornerstone therapy; inoperable cases require conventional approaches, including immunotherapy, radiotherapy, and chemotherapy. However, these modalities are encumbered by cytotoxicity and non-selectivity, engendering adverse effects [110, 111]. According to the advancement and confinement of the CRC, combining the mentioned treatments can be used. Even with such strategies, recurrent CRC and the subsequent evolution of multidrug resistance remain prevalent, affecting approximately 50% of the cases [112]. Despite considerable advancements in both the screening and treatment processes of CRC, the rate of deaths remains alarmingly high [113]. Therefore, it is important to create innovative treatments for CRC that specifically target resistant tumors. This section explores some of these emerging treatments that impact the NF-κB signaling pathway in CRC.

Macelignan

Recently, the use of natural products in cancer therapy has become a novel topic, given their numerous benefits, such as having multiple targets, established use, cost-effectiveness, and minimal toxicity [114]. Macelignan, derived from nutmeg, is garnering interest for its diverse biological functions, which include neuroprotection, antioxidation, and anti-inflammatory actions. However, the effects of macelignan on macrophage polarization within the TME have yet to be elucidated [115, 116].

Macrophages, integral components of the TME, can be divided in subgroups, M1 and M2 subtypes (classically and alternatively activated, respectively), in interaction with environmental signals [117]. M2 subtype macrophages contribute to increased tumor progression and development by enhancing invasion, migration, and proliferation and are associated with poor prognosis [118]. Research has shown that M2 macrophages contribute to the advancement of tumors through the production of specific substances, such as IL-1, IL-17, and IL-6, which facilitate the growth of tumors [119]. Within the TME, Tumor-associated macrophages (TAMs) are critical in promoting angiogenesis, metastasis and tumor growth. One study demonstrated that TAMs derived from malignant gastric cells were predominantly M2 subtype, implicating M2 macrophages in the metastasis of gastric cancer [120]. Che N et al. discovered that macelignan can disrupt the polarization of M2 macrophages by stimulating the ROS-dependent PI3K/AKT pathway, which effectively impedes the progression of CRC-induced liver cancer through the IL-1β/NF-κB signaling pathway.

To conclude, macelignan, a compound derived from nutmeg, shows promise as a cancer treatment through its impact on macrophage polarization within the TME. It specifically acts on M2 macrophages, recognized for their role in tumor growth, by obstructing M2 polarization through the ROS-regulated PI3K/AKT pathway. This significantly hinders CRC metastasis through the IL-1β/NF-κB pathway, highlighting macelignan's effectiveness in interfering with crucial tumor progression processes.

Parthenolide

Parthenolide (PTL), derived from the Tanacetum parthenium, commonly known as feverfew, primarily inhibits the NF-κB signaling pathway. Treatment with PTL is linked to reduced angiogenesis, proliferation, migration, and invasion across various cancers, including lymphoma and breast cancer [121, 122]. Notably, in cell models of CRC, PTL impedes the effects of hypoxia, limits the rate of cell growth, and reduces invasiveness by interfering with the signaling of hypoxia-inducible factor 1 [123, 124]. Furthermore, it has been demonstrated that PTL effectively stops the functioning of NF-κB by preventing its breakdown and hindering its ability to bind to DNA [125].

Gehren and colleagues [126] demonstrate that the PTL's antitumor effect on CRC cells is not restricted to inhibiting the NF-κB pathway; it also appears dependent on the p53 mutation status. Consequently, PTL's

blockade of the NF-κB pathway not only decreases proliferation of cells, but also encourages apoptosis, diminishes the invasiveness activity of CRC cells, and restores organization by re-establishing E-cadherin-mediated cell-to-cell adherence. In summary, PTL a compound extracted from feverfew with sesquiterpene lactone structure, obstructs the NF-κB pathway, resulting in decreased cellular growth and invasion as well as increased programmed cell death in CRC. This inhibitory effect is modulated by the PT53 mutation status, underscoring PTL's complex role in CRC therapy through its impact on critical cancer-related pathways and modulating tumor cell dynamics.

Ginger

Natural deep eutectic solvents (NaDES) are recognized as eco-friendly solvents. They are widely employed due to their beneficial attributes, which include straightforward synthesis, affordability, minimal toxicity, eco-sustainability, biodegradability, non-flammability, and little to no volatility [127]. Additionally, ginger, scientifically known as Zingiber, possesses significant medicinal properties. Ginger has demonstrated a broad spectrum of pharmacological effects, notably in combating metabolic syndrome, cancer, inflammation, and bacterial infections [128]. It also acts as a potent antioxidant. The primary source of health benefits from ginger extract is due to its abundant amount of bioactive polyphenols, specifically shogaols and gingerols [129].

Research on the chemopreventive properties of ginger extract against CRC has garnered interest. The process can effectively hinder the rapid growth of cancerous cells and trigger programmed cell death in diverse types of abnormal cells in vitro [130]. Additional studies are required concerning the anticancer effects of ginger extract processed with a natural deep eutectic solvent (NaDES) on CRC cells resistant to chemotherapeutic drugs. The C-X-C chemokine receptor type 4 (CXCR4) is involved in regular cellular functions and is essential for regulating embryogenesis [131]. Contrastingly, increased expression of CXCR4 is observed in a variety of neoplasms, like CRC [131, 132]. Increased levels of CXCR4 have been linked to an unfavorable prognosis and the emergence of resistance to drugs in patients with CRC [132]. Specifically, the overexpression of CXCR4 in CRC cells resistant to oxaliplatin appears crucial for the emergence of resistance to oxaliplatin [131]. Moreover, the pathways of communication that are triggered by CXCR4 may greatly influence the potential for cells in CRC to become resistant to drugs [133].

Furthermore, a multitude of studies have shown that an increase in NF-κB signaling significantly enhances the ability of cancer cells to withstand the effects of chemotherapy. This connection between the activation of NF-κB and the emergence of drug-resistant tumors provides strong evidence of its significant impact on chemotherapy resistance [134]. Additionally, the activation of sNF-κB has the potential to increase the levels of CXCR4 through its binding to the CXCR4 promoter, resulting in heightened migration and spread of cancer cells [135]. A study by Lee and colleagues [136] revealed that the use of fermented NaDES-treated ginger extract has the capacity to increase the efficacy of oxaliplatin in treating CRC cells that have developed a resistance to it. This is achieved by suppressing the activity of CXCR4 and the NF-κB signaling pathway. In essence, incorporating NaDES-treated ginger extract into treatment plans has the potential to enhance the effectiveness of oxaliplatin against drug-resistant CRC by inhibiting the CXCR4 and NF-κB pathways. This makes the extract a promising supplement to traditional treatment methods. The polyphenolic components in the extract are likely to interfere with crucial mechanisms associated with chemoresistance, cell movement, and the persistence of cancer cells, thereby accentuating the value of including bioactive compounds sourced from foods within the cancer treatment paradigm.

Conclusion

In conclusion, this examination places primary emphasis on the role of NF-κB in the growth and spread of CRC, specifically in relation to the process of angiogenesis. Furthermore, the potential areas for intervention were specifically emphasized. The overall process is regulated by a complex balance of factors that either stimulate or inhibit angiogenesis. The complex interplay of molecules and pathways involved in angiogenesis including VEGF, EGF, and HIF-1α along with NF-κB underscores the potential for targeted therapeutic interventions, including the use of anti-angiogenic drugs like bevacizumab. However, further studies would be needed for better understanding of the role of these molecules, their interaction, and also their upstream regulators for better design of pharmacological molecules in the CRC field. Therapeutic strategies targeting the NF-κB pathway could be a promising therapeutic target for inhibition of angiogenesis and further reduction of tumor progression in the field of CRC treatment. Finally, further thorough investigations are required to comprehend better the angiogenetic role of NF-κB in CRC. Also, there is a rising desire for effective techniques to better translate the in vitro and animal study outcomes into the clinic (Table 1).

Table 1 NF-κB-related angiogenesis in colorectal cancer

Agent (year)	Sample study	Effect	References
Curcumin (2016)	Human tumor-derived colorectal adenocarcinoma cell lines	Curcumin and oxaliplatin decreased NF-κB pathway chemokine expression, enhancing CRC treatment efficacy	[137]
Ginsenoside (2017)	Human CRC cell lines	Ginsenoside *exerted antitumor effects in CRC by downregulating C/EBPβ/NF-κB signaling, inhibiting cell proliferation*	[138]
Resveratrol (2018)	Human colon cancer lines	Resveratrol modulated PD-L1 via NF-κB, enhancing tumor cell sensitivity to immunotherapy, and induces apoptosis	[139]
Morin (2019)	Human CRC cell lines	Morin impacted CRC cases by inhibiting tumor growth via NF-κB signaling suppression	[140]
Curcumin analog (2019)	Human colon cancer lines	Curcumin analog deactivated NF-κB, reducing cancer stem cell phenotype and increasing apoptosis in CRC	[141]
Green tea (2019)	Human CRC cell lines	Green tea enhanced CRC sensitivity to chemotherapy by hindering NF-κB/miR-155-5p pathway	[142]
Gilteritinib (2020)	Human CRC cell lines	Gilteritinib induced p53 up-regulated modulator of apoptosis-mediated apoptosis in CRC via NF-κB pathway, enhances chemosensitivity	[143]
Onion peel (2021)	Human colorectal adenocarcinoma cell line with epithelial morphology	Onion peel extract reduced CRC growth and progression by downregulating L1 cell adhesion molecule and NF-κB	[144]
Crocin (2022)	Human colon cancer lines	Crocin inhibited CRC angiogenesis and metastasis via VEGF downregulation and NF-κB pathway modulation	[145]
Liquidambar orientalis (2022)	Human CRC cell lines	*Liquidambar orientalis* extract promoted late apoptosis in CRC via NF-κB related pathway modulation	[146]
Ficus dubia (2022)	Human CRC cell lines	*Ficus dubia* latex inhibited CRC cell proliferation by downregulating NF-κB and related proteins	[147]
Fermented ginger (2022)	Human CRC cell lines	Fermented ginger extract enhanced oxaliplatin efficacy in CRC via NF-κB and CXCR4 suppression	[136]
Chang Qing formula (2022)	Male SD rats	Chang Qing formula ameliorated colitis-associated CRC by lowering IL-17A, NF-κB, impacting inflammation and angiogenesis	[148]
Baicalin (2022)	Human CRC cell lines	Baicalin targeted TLR4/NF-κB pathway, inhibits CRC cell growth, migration, and induces apoptosis	[149]
Calebin A (2023)	Human colon cancer lines	Calebin A reduced CRC viability, and proliferation, suppresses NF-κB, HIF-1α	[150]
Vitexin (2023)	Human colon cancer lines	Vitexin and aspirin combo inhibited CRC by targeting NFKB1 and COX-2, reducing proliferation	[151]
Libidibia ferrea (2023)	Male Balb/c mice	*Libidibia ferrea* increased CRC apoptosis significantly by downregulating NF-κB gene expression	[152]
Parthenolide (2023)	The human colorectal adenocarcinoma cell lines	*Parthenolide reduced CRC proliferative and invasive potential by inhibiting NF-κB signaling and p53 interaction*	[126]
Macelignan (2024)	Human CRC cell lines HCT116	*Macelignan suppressed CRC metastasis by inhibiting M2 polarization and IL-1β/NF-κB pathway activation*	[116]
Osmanthus fragrans (2024)	Human CRC cell lines	*Osmanthus fragrans* exhibited anti-CRC effects by modulating inflammatory pathways and inducing apoptosis via NF-κB	[153]
Broccoli grown with deep sea water mineral (DSWM) fertilizer (2024)	Mice	DSWM-broccoli inhibited colon cancer progression by regulating NF-κB, apoptosis, and cell cycle arrest	[154]

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Author contributions
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