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Review Article

Nuclear factor-kappaB in inflammatory bowel disease and colorectal cancer

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Abstract: Mucosal immune system in gut plays a protective role in maintaining a balance between pro-inflammatory and anti-inflammatory mediators. This immunological balance is severely impaired in idiopathic inflammatory disease (IBD). Inflamed colonic mucosa demonstrates abnormalities in the molecular pathways before any histological evidence of dysplasia or cancer. In IBD, inflamed gut mucosa is characterized by a high level of pro-inflammatory cytokines like TNF-α, IL-6, and IFN-γ secreted by effector cells, which subsequently causes mucosal damage. There are several lines of evidence indicating that nuclear factor-kappaB (NF-κB) is a key regulator in this response. Activated NF-κB acts as a mediator in colorectal cancer (CRC) by inducing cellular proliferation, enhancing migration and up-regulating of anti-apoptotic proteins. Several genes have been found linked to IBD-associated cancers. Genome-wide association studies have also identified several associated genes. Alternatively it is assumed that chronic inflammation is the main cause of CRC which is supported by the fact that, colon cancer risk increases with duration over 10 years of IBD. These findings emphasize the importance of NF-κB inhibitor as a therapeutic target in CRC. This review focuses on the diverse roles of NF-κB in IBD related carcinogenesis and specific subunits of NF-κB family, providing insights to develop new therapeutic strategy in treatment of IBD as well as prevent subsequent development of CRC.

Keywords: NF-κB, IBD, CRC, therapy

Introduction

Colorectal cancer (CRC) is one of the most common cancers and the second leading cause of cancer death in the developed countries. Inflammatory bowel disease (IBD), both ulcerative colitis (UC) and Crohn's disease (CD) are risk factors of colorectal cancer. Several genes have been found linked to IBD-associated cancers [1-4]. Genome-wide association studies have also been carried out to identify associated genes [5, 6]. The other major risk factors include familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Both FAP and HNPCC have a well-defined genetic etiology, whereas IBD associated risk of colon cancer has been considered related to chronic inflammation. There are several studies showing a connection between inflammation and colon carcinogenesis [7, 8]. Regardless of underlying causes both IBD related colon cancer and sporadic CRC are characterized by a dysplasia-to-cancer sequence. There are various signaling pathways involved in colonic inflammation, and nuclear factor-kappa B (NF-κB) signaling pathway plays a central role among them. NF-κB transcription factors are implicated in the inflammation, development, growth and apoptosis [9-11]. This review will focus on the role of NF-κB in carcinogenesis of inflammation-associated CRC as well as NF-κB targeting therapeutic strategies that might aid in the treatment of CRC.

NF-κB family and signaling pathway

Nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB) is a protein complex [12] can either induce or repress gene expression by binding to specific DNA sequences in the promoters of target genes. These sequences are termed κb elements. The members of the transcription proteins are classified based on C-terminal structures. Class 1 includes p105 and p100. They undergo proteasomal processing before it is transferred to the nucleus. Class

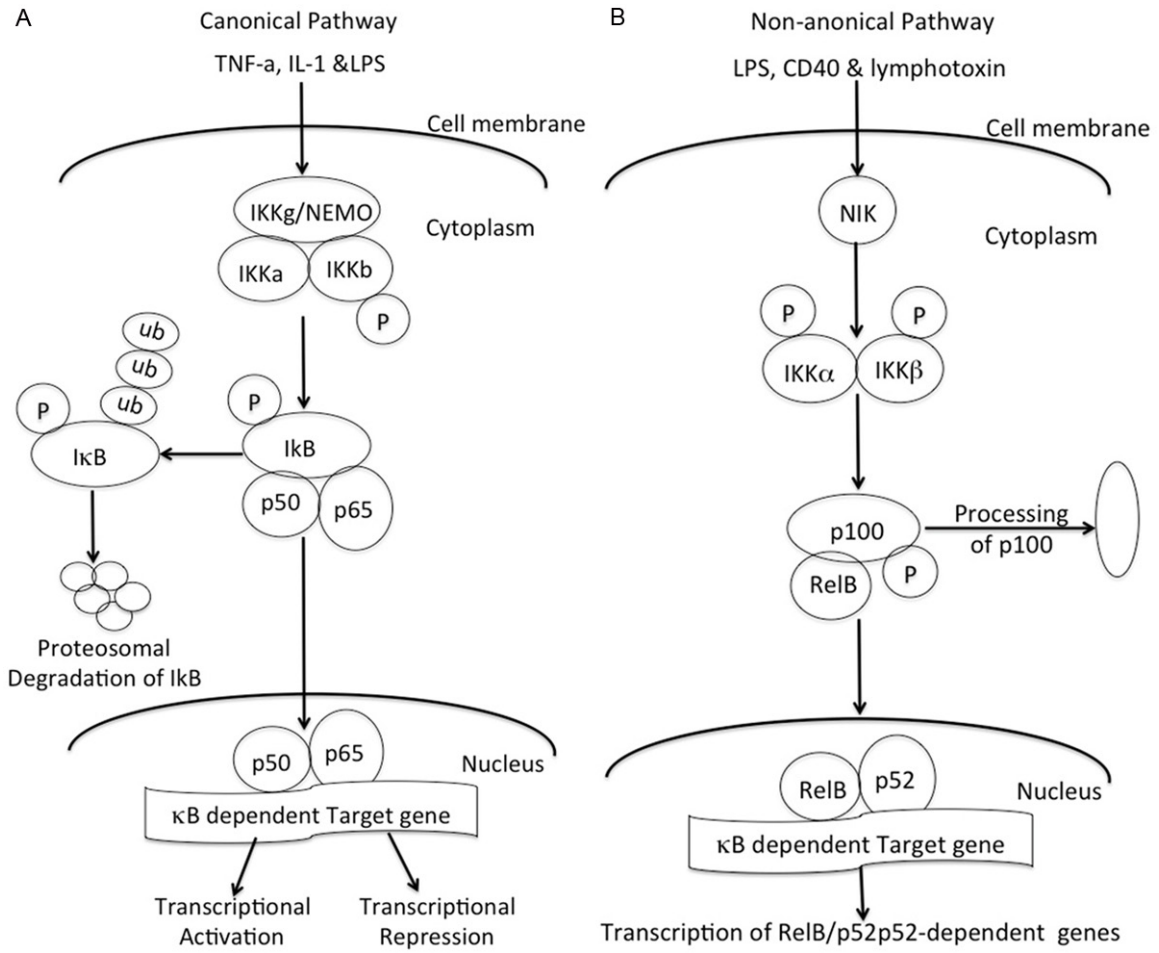

Figure 1. NF-κB Signaling Pathway. Canonical and non-canonical pathways of NF-κB activation: A. Canonical pathway induced by pro-inflammatory stimuli, such as TNF-α, IL-1 which lead to phosphorylation of the IKK complex (IKKbeta, IKKalpha and IKKgamma/NEMO), phosphorylation and degradation of IkappaBalpha which allows RelA/p50 NF-kappaB complexes to enter the nucleus and induce or repress the activation of a multitude of genes. B. Non-canonical pathway induced by specific stimuli (CD40, lymphotoxin, LPS). This leads to the induction of the NF-κB inducing kinase (NIK), which then activates IKKalpha homodimers leading to the phosphorylation of p100 and its proteolytic cleavage to p52 by ubiquitin-dependent processing by proteasome. The active RelB/p52 heterodimer then enters the nucleus and mediates gene transcription.

2 includes RelA, RelB, and c-Rel. These factors contain a transcription activation domain, which provides them transcriptional ability. In unstimulated cells, the majority of NF-κB dimers are inactivated and remains in the cytoplasm by association with small inhibitory molecules called IκB proteins. This association results in inactivation of NF-κB [13, 14]. IκBs bind to NF-κB dimmers and block their nuclear localization, thereby causing their cytoplasmic retention. The members of IκB family are IκBα, IκBβ IκBγ, IκBε, Bcl-3, p100, and p105. Upon stimulation IκB proteins undergo IκB kinase-dependent (IKK-dependent) phosphorylation, polyubiquitination and subsequent proteasomal degradation of IκB proteins elements. Thus released transcription proteins are free to translocate to the nucleus and to bind therein to the κB elements in the promoters and enhancers of target genes. NF-κB subsequently controls the expression of genes that are key regulators of growth, differentiation, survival, apoptosis, tumorigenesis, embryonic development, metastasis and immune and inflammatory responses.

Two different Intracellular pathways are involved in activation of NF-κB, the classic and the alternative signaling pathways (**Figure 1**). The classical or canonical pathway requires activation of the ReLA/p50 dimer. Upon stimulation by cytokines, growth factors, viral or bacterial

proteins, or oxidative stress this pathway is activated by many receptor types, including tumor necrosis factor receptors (TNFRs), toll-like receptors (TLR), and interleukin 1β (IL-1β), then relay cytoplasmic signals to activate the p50/p65 heterodimer, resulting in expression of genes encoding regulators of innate and adaptive immune responses, pro-survival signals, and development genes [15-17]. The classic pathway relies on IKKβ, IKKγ, and IκB proteins for activation. When stimulated by their appropriate receptors IκB proteins are phosphorylated on specific serine residues by IKKα/IKKβ complex leading to ubiquitin-dependent IκB degradation by proteasome [18]. Free RelA/p50 dimers are ready to translocate to nucleus and to bind therein to the κB elements. This pathway plays an important role in innate immunity and inflammation [19].

The alternative or non-canonical pathway is triggered by certain members of the TNF cytokine family receptors including CD40, lymphotoin β (LTβR) and B-cell activating factors (BAFF), as well as human T-call leukemia virus (HTLV) and epstain-Barr virus (EBV), and results in selective activation of RelB/p52 heterodimers. This pathway causes activation of IKKα by the NF-κB-inducing kinase (NIK), followed by phosphorylation of the NF-κB p100 subunit by IKKα, resulting in proteasome-dependent processing of p100 to p52, triggering activation of RelB/p52 heterodimers that allows the nuclear translocation of this heterodimers and their binding to DNA to inducing the expression of NF-κB target genes. This pathway is important in the control of development and function of secondary lymphoid organs and B-cell maturation and survival [20-22]. Activation of NF-κB by both pathways regulates cell survival, death and has been now implicated in carcinogenesis [23-26].

Chronic inflammation and cancer, the role of NF-κB

Acute inflammation is a protective response to tissue damage and to maintain tissue homeostasis. On the other hand, chronic inflammation can trigger carcinogenic events and eventually leading to transformation of normal cells into malignant cells [27, 28]. An estimation in epidemiological studies found that over 20% of all human cancer is associated with chronic inflammation [29]. Studies on gastrointestinal and hepatobilliary cancer found that chronic inflammation acts as a tumorigenic factor. The interrelationship of chronic inflammation and tumorigenesis in gastrointestinal tissue is not yet clear, but one possibility is that the intestinal epithelial cells are physiologically exposed to various dietary environments that contain pro-inflammatory microorganisms. A recent study revealed that chronic inflammation promoted colorectal cancer by altering the composition of gut microbiota [30]. The microenvironment that contributes to tumor development is comprised of various cell types, including the infiltrating inflammatory cells, as well as a host of soluble mediators such as cytokines, chemokines, growth factors and various other proteases. These factors then act on epithelial cells to trigger multiple intracellular signaling pathways which finally activate transcription factors. Under persistent inflammatory state they act in tumorigenesis by expression of multiple genes. The most known transcription factor in this process is NF-κB [31]. Originally NF-κB transcription protein is associated exclusively with immunity and inflammation, and it is also proven that such a transcription factor also has essential role in epithelial tissues, as coordinating antibacterial immunity and maintaining barrier function in the gastrointestinal system [32, 33]. Deregulation of normal NF-κB activity, such as expression of an abnormal form of the protein, or interference with transcriptional activity from the normal gene, has been shown to be involved in the development of leukemia, lymphomas, and solid tumors [34]. Activation of apoptosis-resistant genes by NF-κB family members also influences tumor development; this is one of the mechanisms to develop resistance to radiotherapy and chemotherapy [35]. Although the exact mechanism of inflammation initiating neoplasm is still not completely understood, the NF-κB could well be an important player in this process since it is activated in chronic inflammation. Verchow who hypothesized that malignant neoplasm arises at regions of chronic inflammation, reasoned that various "irritants" caused tissue injury, inflammation, and increased cell proliferation [36, 37]. Deregulation of such homeostasis predisposes to IBD and CRC [38]. NF-κB, by orchestrating inflammatory responses, cell survival and growth, exerts a fundamental role in the interplay between cancer and inflammation [39].

Chronic inflammation and IBD

IBD is a chronic inflammatory process. Crohn's disease (CD) and ulcerative colitis are the two major forms of IBD. It has been found that the

involvement of damaged epithelia and activated immune cells in the inflamed mucosa plays an important role in their pathogenesis [40-42]. The main complication is colitis-associated cancer (CAC) after long standing IBD, usually over 5-10 years after onset [43]. For many years, It is presumed that chronic inflammation is the cause of CAC and the risk increases with advanced age, certain genetic features, smoking status, diet, the extent of physical activity, virus infection, environmental influences, intake of exogenous hormones alcohol ingestion [44, 45], longer duration of colitis, greater anatomic extent of colitis, the concomitant presence of other inflammatory manifestations. The site of inflammation is characterized by high levels of cytokines, growth factors and ROS, which regulates the subsequent accumulation of leucocytes, and stimulate endothelial cells and fibroblasts to divide and produce components for tissue remodeling. The microenvironment, rich of inflammatory cells and cytokines, damage DNA and alter cell survival and drive the carcinogenic process. There are several studies proved that cytokines released during inflammation may contribute to cancer development, and those acting via the activation of NF-κB [37, 46]. Colonic biopsies taken from patients with IBD demonstrate higher rates of mitosis as well as apoptosis, especially in areas of active, as opposed to quiescent inflammation [47]. However, increased epithelial cell turnover likely contributes to carcinogenesis, and insufficient to cause cancer.

Regardless of the underlying condition almost all CRCs (sporadic or colitis- associated colorectal cancer), develop from a dysplasia-to-cancer sequence and multiple genetic mutations must occur before a carcinoma develops. In sporadic colon cancer (CRC) the dysplastic precursor is the adenomatous polyp (adenoma). Intratumoral immune cells are recruited after the tumor is formed and so in this case chronic inflammation follows tumor development. In contrast, dysplasia in IBD-associated CRC can be polypoid or flat, localized, diffuse, or multifocal and once found, enhance the risk of neoplasia in entire colon. This biological behavior increases clinical cancer surveillance in IBD patient's more than normal population. This also raises the possibility of involvement of chronic inflammation and cytokines in the pathogenesis of CRC.

NF-κB in intestinal epithelial cells

Although activation of NF-κB has been shown in inflammatory cells and intestinal epithelial cells, normal functioning of NF-κB is essential for maintenance of epithelial cells homeostasis in the gut [48]. In gut epithelial cells, NF-κB regulates epithelial integrity and interaction between the mucosal immune system and the gut microflora. Alteration of normal function is found in chronic inflammation. Dysregulated cytokine production and related signaling activation by inflamed intestinal epithelial cells and myeloid cells have been implicated in the pathogenesis of IBD, and NF-κB has turned out to be one of the major regulatory components in this complicated phenomenon [49]. The amount of NF-κB activity is correlated with the severity of inflammation [50]. The increased level of NF-κB expression in mucosal macrophages is accompanied by an increased secretion of TNF-α, IL-1, and IL-6 [51].

The role of NF-κB in CRC is also established by mouse models [52, 53]. Intestinal epithelial cell- specific inhibition of NF-κB synthesis via conditional ablation of IKKγ or by conditional inactivation of both the IKKα and IKKβ subunits essential for NF-κB activation, results in the spontaneous development of severe chronic intestinal inflammation in mice. Deficiency of NF-κB causes colonic epithelial cells to enter apoptosis, impaired expression of antimicrobial peptides, and inhibits translocation of bacteria into the mucosa. NF-κB signaling maintains the host-microbiota homeostasis [48].

NF-κB and CRC, the role in carcinogenesis

Activation of NF-κB and tumorigenesis, a molecular link with chronic inflammation is recently established. Transformation of normal epithelial cells to malignant cells requires genetic aberrations such as nucleotide alterations and chromosomal translocation. Several lines of evidence revealed that inflammatory stimulation of epithelial cells triggers the aberrant expression of DNA mutator enzymes, which initiate or promote oncogenic pathways by enhancing susceptibility to mutagenesis. Nucleotide editing enzymes, including activation-induced cytidine deaminase (AID), induce genetic changes in human DNA sequences via their cytidine deaminase activity [54, 55]. NF-κB plays a major role in the regulation of AID expression. This enzyme's intrinsic mutagenic potential could be

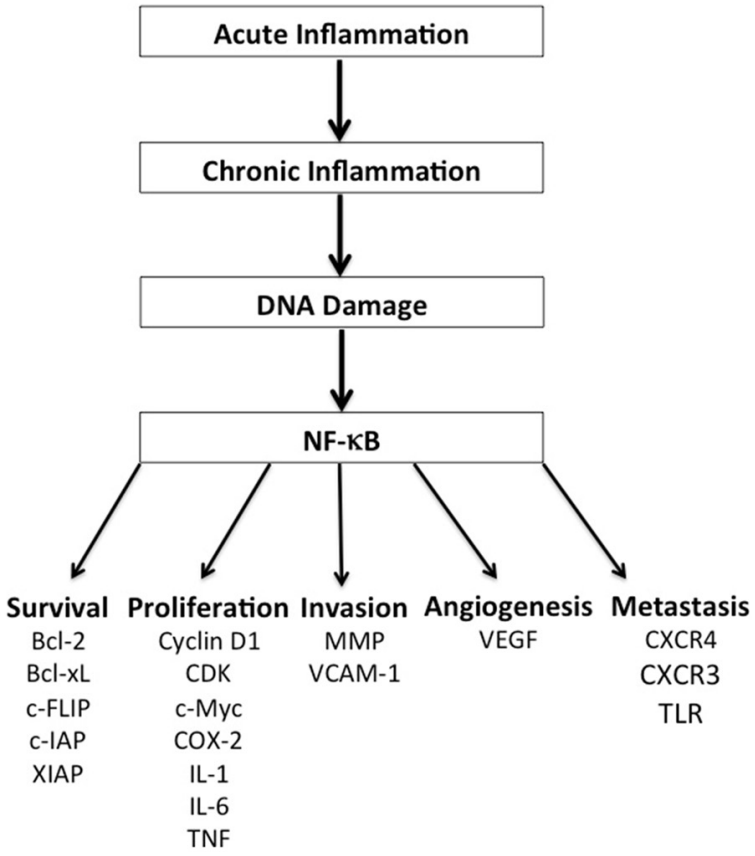

Figure 2. Inflammation and NF-κB. Inflammation and NF-κB activation: Roles of the NF-κB-mediated inflammatory pathway in cellular transformation and in cancer cell survival, proliferation, invasion, angiogenesis, and metastasis.

induced in response to pro-inflammatory cytokines as well as infectious agents that mediate the activation of NF-κB in epithelial cells. Continuous AID gene expression promotes the accumulation of genetic alterations in various genes with oncogenic potential, the definitive evidence for a causal link between AID and tumorigenesis. All the evidence proves that AID expression mediated by NF-κB activation in response to inflammation might be a mechanism for malignant transformation of gastrointestinal epithelial cells during process of carcinogenesis [56]. In normal cells NF-κB is transiently activated while in cancer cells it exhibits sustained activation [57, 58]. Subsequently to its persistent activation, NF-κB signaling pathway has been shown to regulate expression of many genes implicated in cell survival, proliferation, tumorigenesis, invasion, angiogenesis, and metastasis (**Figure 2**) and resistance to treatment. Sustained activation of NF-κB promotes growth of CRC as well as other cancers.

NF-κB is engaged in tumorigenesis by upregulating the anti-apoptotic pathway and potentiates tumor cell survival. Anti-apoptosis plays a vital role in the maintenance of cancer cells. Canonical pathways of NF-κB are known to activate the transcription of a group of anti-apoptotic proteins, which can be divided into two groups. The first group mainly includes inhibitors of apoptosis proteins (IAP) Ciap1, Ciap2, XIAP and CFLIP [59]. The second group mainly includes Bcl-2 family members, including Bcl-2 and BclxL [60]. In addition to transcription, inhibition of NF-κB activity elevates JNK activity and induces apoptosis, suggesting that NF-κB inhibits apoptosis via inhibition of JNK activity [61].

Recent studies showed that the pro-survival function of NF-κB is related to its expression of target genes of the phosphoionositide 3-kinase (PI3K/Akt cascade), one of the key elements in promoting cell proliferation and cell growth. The other cell cycle regulatory pathways that are regulated by NF-κB mediated transcription are Cyclin-D1, c-myc, CDK, IL-1, IL-6, and TNF. As a transcriptional factor, NF-κB binds to their promoters and thereby controls cell growth and proliferation [62, 63]. Activation of NF-κB also controls cell proliferation by activating genes of growth factors, granulocyte-colony stimulating factor (G-CSF), and bone morphogenic protein [64, 65]. Colon cancer growth inhibition via inhibition of NF-κB inhibition has been proven [66]. Studies on some other cancers like lung and breast cancers have been shown the similar results [67].

Formation of new blood vessels is essential for tumor progression, and has been shown to be dependent on growth factors (e.g. TNF, VEGF) and chemokines (e.g. monocyte chemoattactant protein-1, IL-8) [68, 69]. VEGF is regulated by hypoxia-inducible factor and by NF-κB [70]. Other factors known as angiogenic factors are also chemokines that are mainly regulated by

NF-κB, and inhibition of NF-κB in CRC suppresses these chemokines secretion from tumor cells. Additionally, by mediating the production of cyclooxygenase 2 (COX-2), vascular cell adhesion molecule (VCAM) and matrix metalloproteinases (MMPs) it also enhances angiogenesis and invasiveness [71-73]. It has been shown that angiogenesis-promoting COX-2 is induced by NF-κB in inflammation and is found to increase in colorectal cancer in more aggressive forms [74]. Some studies have shown that, gelatinases (MMP-2 and MMP-9) and CXCR4 expression is regulated by NF-κB activation and are the prognostic factors in many solid tumors. They play a role in the degradation of the extracellular matrix and basement membrane and thereby tumor invasion.

For a successful metastasis, the surrounding environment must be suitable for tumor cells to grow. Recent studies have shown that tumor cells activate the macrophages through TLRs and that activated macrophages promote metastasis [75]. TLR is one of the factors that activate NF-κB, and thereby promotes metastasis. Metastasis of tumors is also an important factor that influences the prognosis of patient. In many tumors, including CRCs, NF-κB activation has been reported to promote metastasis of cancer cells [76, 77]. Study of experimental murine colon cancer metastasis model revealed that lipopolysaccharide (LPS)-induced metastatic growth response depends on both TNF-α production by host hematopoetic cells and NF-κB activation in tumor cells. NF-κB inhibition in both colon and breast cancer cells converts the LPS-induced growth response to LPS-induced tumor regression [78]. This study proved a clear role of NF-κB in tumor invasion and metastasis. Chemokines (e.g. CXCR3 and CXCR4) were expressed at a higher proportion in metastases than in primary tumors of CRC patients. NF-κB regulates the expression of CXCR3 and CXCR4, which play a pivotal role in CRC metastasis to LNs and distant organs (liver and lung). CXCR3 enhances CRC metastasis preferentially to LNs with poor prognosis and patients with CXCR3-positive CRC exhibit significantly shorter survival than those with CXCR3-negative CRC patients. CXCR4 is associated with distant metastasis of CRC, whereas CXCR3 strengthens the CXCR4 mediated distant metastasis [79].

In IBD, its inflammatory milieu promotes the development of CAC. Cytokines (TNF-α, IL-6, IL-1) derived from myeloid cells activate NF-κB in IEC, which produces in response numerous cytokines, growth factors and chemokines/receptors (CXCR3, CXCR4, CXCL9, CXCL12) attracting immune cells and fibroblasts, thus creating a vicious circuitry [71, 80]. Clinicopathological studies correlated the expression of NF-κB, hypoxia inducible factors (HIF), VEGF and Bcl-3 with proliferation, angiogenesis, decreased survival and poor clinical outcome [81, 82]. All these studies showed that NF-κB is involved in every aspect of intestinal carcinogenesis, from initiation to metastasis [21].

For better understanding of the role of NF-κB in inflammation and in tumorigenesis, commonly used mouse model of IBD-related CAC involves administration of azoxymethane (AOM) followed by repeated administration of dextran sodium sulfate (DSS) ingestion [83]. In AOM/DSS Model, tumor development was investigated in mice lacking IKKβ expression restricted to myeloid cells or intestinal epithelial cells. These mice exhibited decline in tumor load, with a decrease in tumor size and decrease in inflammation compared to tumors in WT mice [84]. This suggests that cytokines of inflammation might target epithelium thus promoting the expansion of transformed cells in an NF-κB dependent manner, the expression of most of cytokines and growth factors characterizing the inflammatory process and involved in tumor progression relies on NF-κB activation in immune cells [85]. More importantly, IKKβ/IκBα/NF-κB pathway is required for the induction and maintenance of epithelial mesenchymal transition (EMT) in mouse model [86]. EMT is a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to initiation of metastasis for cancer progression. Together all these statements show that NF-κB have a diversity of functions that are required for CRC promotion and CRC maintenance.

Inhibition of NF-κB as a therapeutic strategy

The commonly used treatment in cancer is radiotherapy and chemotherapy in addition to surgery. Development of resistance is the cause of treatment failure and mortality in most cancers. Recent study suggests that the NF-κB pathway may contribute to the development of this resistant. Resistant cancers show more aggressive growth potential and have worse prognosis. Several lines of evidence have shown that chemotherapy and radiotherapy in-

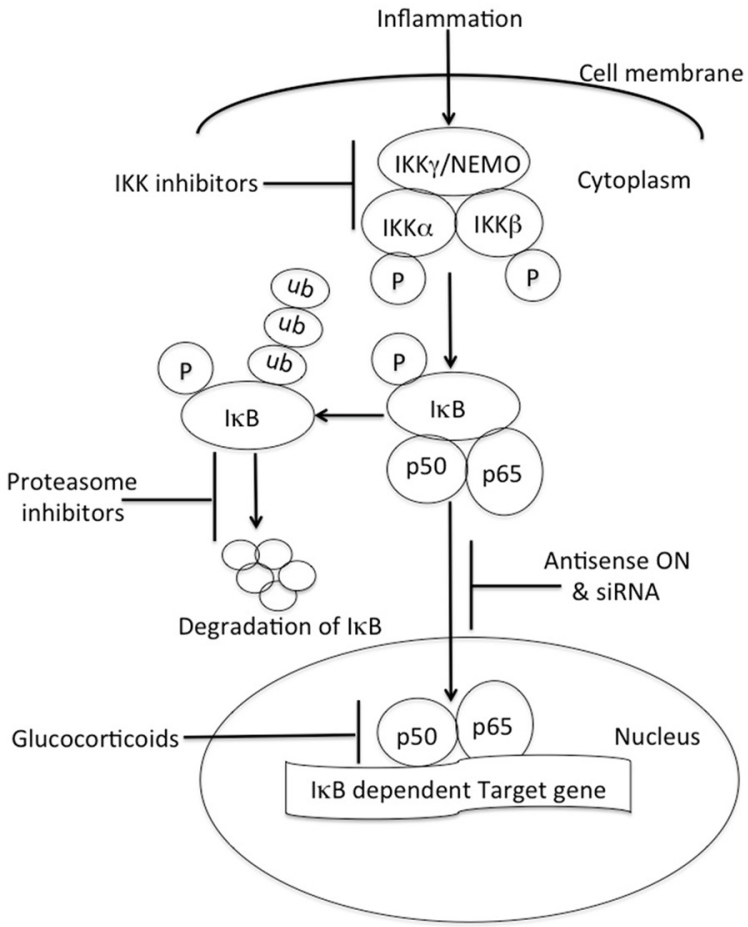

Figure 3. Inhibition of NF-κB Signaling Pathway. NF-κB activation pathway: Blockade shapes show the molecular targets of drugs to inhibit NF-κB activation.

duces activation of NF-κB, and their constitutive activation is associated with the development of both radioresistant and chemoresistant [87-90]. Inhibition of NF-κB activity (**Figure 3**) in resistant cancers results in resensitization, by increased apoptosis after chemotherapy and radiotherapy. Based on these lines of evidence, it is a reasonable assumption that simultaneous inhibition of NF-κB with chemotherapy and radiotherapy may be of great value in counterbalancing intrinsic, acquired, or induced resistance mechanisms.

Protease inhibitors, which act as an anti-inflammatory, were incidentally discovered as a killer of transformed cells, with minimal effect on normal cells. The final step in NF-κB activation is phosphorylation, ubiquitination, and degradation of IκBα by the 26S proteasome, making protease inhibitors attractive therapeutic agents. Since this discovery it has become a promising field of cancer therapy. Bortezomib (PS-341) has been used for the treatment of multiple myeloma as well as shown to be cytotoxic against a range of human tumor cell lines, including brain, pancreatic, colorectal, lung, breast, and prostate [91-96]. It has also been shown that bortezomib enhances chemotherapy and radiotherapy sensitivity in an NF-κB dependent manner for a variety of cancers.

Nonsteroidal anti-inflammatory drugs (NSAID) may serve as useful therapeutics for a range of inflammatory cancers. Both NF-κB and COX-2 promote activation of each other in a feedforward fashion. Even though its mechanism in inhibition of tumor formation is not yet established, it mainly involves cyclooxygenase-2 inhibition, and as a consequence inhibits inflammatory signaling, decreased NF-κB activity. The role of COX-2 in mitogenic signaling was validated in normal gastric epithelial cells (RGM1) and multiple colon cancers, in which prostaglandin E2 rapidly phosphorylates the EGFR and triggers extracellular signal-regulated kinase 2, stimulating mitogenic signals that support cellular proliferation [97]. Prostaglandins through their stimulation of G-coupled EP receptors have been implicated in multiple oncogenic processes. A recent study shown that celecoxib inhibitor of COX-2 in colorectal carcinoma xenografts resulted in significantly reduced local tumor growth and decreased metastasis in a dose dependent manner [98]. Curcumin decreased COX2 activity and synthesis in human intestinal epithelial cell [99]. Salicylates and aspirin have been shown to directly compete with ATP for IKKβ, inhibiting IKKβ function and preventing NF-κB activation. Recent study proved that patients with colon cancer (with PI3K mutation) treated with aspirin had a 64% reduction in overall mortality and 82% reduction in cancer specific mortality [100]. The evidence suggests that NSAID use for cancer prevention and therapy holds a great promise.

Sulfasalazine, which contains salicylate, is another type of anti-inflammatory agent that is commonly used in ulcerative colitis and rheumatoid arthritis. It has been used to attenuate growth in multiple cancers, including breast, brain, colon, leukemia, and lymphoma [101-105]. At micromolar concentrations sulphasalazine inhibit NF-κB activation by TNF-α, lipopolysaccharide (LPS), and phorbol ester in SW620 colon cancer cells [106].

Glucocorticoid (GC) is a widely prescribed and commonly used medicine for its anti-inflammatory effect by down-regulating pro-inflammatory cytokines, stimulating transcriptional activity of GC receptors (GRs), and by directly inhibiting the NF-κB pathway. Dexamethesone (DEX) acts on endogenous GR, thereby inhibits NF-κB DNA binding and transcriptional activation. DEX pretreatment was an effective chemosensitizer for carboplatin and gemcitabine in multiple mouse xenograft models, including colon, lung, breast, and brain cancers. GC resistance is a common but poorly understood problem in cancer therapy. Refractory NF-κB activation may be a key regulator of resistance [107-109]. This is strongly supported by study on steroid resistance in IBD in which epithelial NF-κB activity is strongly associated with resistance [110]. More studies are needed for better understanding of suppression of GC by NF-κB and to establish the alternative mechanisms of resistance for cancers in which NF-κB may be irrelevant.

Ikkβ-inhibitors is the main regulator to activate NF-κB signaling pathway. Investigators are developing specific IKKβ inhibitors and some small molecule inhibitors are already discovered. Most of those inhibitors are competitive ATP binders that require to activate IKKβ. Some of these are already tried on human cancer cell lines. Those inhibitors include SU6668, PS-1145, ML120B, and BMS-345541. Several drugs also act as an inhibitor of NF-κB, such as arsenic trioxide, manumycin, and celastol. Arsenic trioxide a thiol -reactive compound, inducing apoptosis in several cancers in brain, colon, liver, leukemia, neuroblastoma [111-115]. More research is needed for better understanding the different isoform of IKKβ, their functions in normal physiology and immune regulation. Use of target IKKβ inhibitor will help to prevent development of immunedeficiency in treatment.

Gene therapy is a challenging technology that uses viral delivery of NF-κB inhibitors to tumor cells. Adenoviral delivery of IκBα-super repressor (IκBα-SR), a synthetic nondegradable IκBα, in LoVo colorectal cancer cells abrogated NF-κB activation and sensitized previously resistant cells to both TNF-α and CPT-11 induced killing [116]. This technology needs further investigation to determine viral specificity for tumor cells and thereby for better understanding of off-target abrogation of NF-κB in healthy cells.

Conclusion

For the last few decades NF-κB has become a target focus of cancer study because of its relation in carcinogenesis and inflammation. Tumor-promoting inflammation has been recognized as one of the hallmarks of cancer that may precede tumor initiation, creating a favorable microenvironment in which mutated cells can survive [117]. Studies on animal models found that chronic inflammation creates a good field for tumor initiation. IBD is a form of chronic inflammation and its one of the life threatening complication is CRC. As NF-κB is suspected to play a key role in between inflammation and carcinogenesis, this could be a target of treatment for CRC. The major drawback will be the unanticipated adverse effects, long-term immune suppression, because of its complex signaling pathway is involved in many physiological functions, including immune regulation, development, and cell cycle control. It can be presumed that complete inhibition of NF-κB may predispose patients to immunosupression and unforeseen adverse effects. Up to date no NF-κB inhibitor is clinically approved for the patients to treat cancer, as their potency or effectiveness is not yet clear. Because of their therapeutic profiles and adverse effects, the duration and time of NF-κB inhibition may vary. Further research is needed for investigating specific NF-κB inhibitor for treatment of targeted cancer cells. This has opened another venue to prevent the carcinogenesis by inhibiting or blocking inflammation contributing to the development of IBD related CRC.

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References

[1] Chung FH, Lee HH and Lee HC. ToP: a trend-of-disease-progression procedure works well for identifying cancer genes from multi-state cohort gene expression data for human colorectal cancer. PLoS One 2013; 8: e65683.

[2] Huber S, Gagliani N, Zenewicz LA, Huber FJ, Bosurgi L, Hu B, Hedl M, Zhang W, O'Connor W Jr, Murphy AJ, Valenzuela DM, Yancopoulos GD, Booth CJ, Cho JH, Ouyang W, Abraham C and Flavell RA. IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. Nature 2012; 491: 259-263.

[3] Dube PE, Yan F, Punit S, Girish N, McElroy SJ, Washington MK and Polk DB. Epidermal growth factor receptor inhibits colitis-associated cancer in mice. J Clin Invest 2012; 122: 2780-2792.

[4] Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G and Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001; 411: 603-606.

[5] Park JH, Wacholder S, Gail MH, Peters U, Jacobs KB, Chanock SJ and Chatterjee N. Estimation of effect size distribution from genome-wide association studies and implications for future discoveries. Nat Genet 2010; 42: 570-575.

[6] Barrett JC, Lee JC, Lees CW, Prescott NJ, Anderson CA, Phillips A, Wesley E, Parnell K, Zhang H, Drummond H, Nimmo ER, Massey D, Blaszczyk K, Elliott T, Cotterill L, Dallal H, Lobo AJ, Mowat C, Sanderson JD, Jewell DP, Newman WG, Edwards C, Ahmad T, Mansfield JC, Satsangi J, Parkes M, Mathew CG, Donnelly P, Peltonen L, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Duncanson A, Jankowski J, Markus HS, Mathew CG, McCarthy MI, Palmer CN, Plomin R, Rautanen A, Sawcer SJ, Samani N, Trembath RC, Viswanathan AC, Wood N, Spencer CC, Barrett JC, Bellenguez C, Davison D, Freeman C, Strange A, Donnelly P, Langford C, Hunt SE, Edkins S, Gwilliam R, Blackburn H, Bumpstead SJ, Dronov S, Gillman M, Gray E, Hammond N, Jayakumar A, McCann OT, Liddle J, Perez ML, Potter SC, Ravindrarajah R, Ricketts M, Waller M, Weston P, Widaa S, Whittaker P, Deloukas P, Peltonen L, Mathew CG, Blackwell JM, Brown MA, Corvin A, McCarthy MI, Spencer CC, Attwood AP, Stephens J, Sambrook J, Ouwehand WH, McArdle WL, Ring SM and Strachan DP. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nat Genet 2009; 41: 1330-1334.

[7] Hagemann T, Balkwill F, Lawrence T. Inflammation and cancer: a double-edged sword. Cancer Cell 2007; 108: 300-1.

[8] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008; 454: 436-44.

[9] Baeuerle PA, Henkel T. Function and activation of NF-kappa B in the immune system. Annu Rev Immunol 1994; 12: 141-79.

[10] Barnes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. N Engl J Med 1997; 336: 1066-71.

[11] Karin M, Lin A. NF-kappaB at the crossroads of life and death. Nat Immunol 2002; 3: 221-7.

[12] Perkins ND. The diverse and complex roles of NF-kappaB subunits in cancer. Nat Rev Cancer 2012; 12: 121-132.

[13] Baeuerle PA, Baltimore D. I kappa B: a specific inhibitor of the NF-kappa B transcription factor. Science 1988; 242: 540-6.

[14] Yamazaki S, Muta T, Takeshige K. A novel IkappaB protein, IkappaB-zeta, induced by proinflammatory stimuli, negatively regulates nuclear factor-kappaB in the nuclei. J Biol Chem 2001; 276: 27657-62.

[15] Lai JH, Horvath G, Subleski J, Bruder J, Ghosh P, Tan TH. RelA is a potent transcriptional activator of the CD28 response element within the interleukin 2 promoter. Mol Cell Biol 1995; 15: 4260-71.

[16] Beg AA, Sha WC, Bronson RT, Ghosh S, Baltimore D. Embryonic lethality and liver degeneration in mice lacking the RelA component of NF-kappa B. Nature 1995; 376: 167-70.

[17] Ivanov VN, Lee RK, Podack ER, Malek TR. Regulation of Fas-dependent activation-induced T cell apoptosis by cAMP signaling: a potential role for transcription factor NF-kappa B. Oncogene 1997; 14: 2455-64.

[18] Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF-[kappa]B activity. Annu Rev Immunol 2000; 18: 621-63.

[19] Aggarwal BB. Nuclear factor-kappaB: the enemy within. Cancer Cell 2004; 6: 203-8.

[20] Schiemann B, Gommerman JL, Vora K, Cachero TG, Shulga-Morskaya S, Dobles M, Frew E, Scott ML. An essential role for BAFF in the normal development of B cells through a BCMA-independent pathway. Science 2001; 293: 2111-4.

[21] Pomerantz JL, Baltimore D. Two pathways to NF-kappaB. Mol Cell 2002; 10: 693-5.

[22] Senftleben U, Cao Y, Xiao G, Greten FR, Krähn G, Bonizzi G, Chen Y, Hu Y, Fong A, Sun SC, Karin M. Activation by IKKalpha of a second, evolutionary conserved, NF-kappa B signaling pathway. Science 2001; 283: 1495-9.
[23] Senftleben U, Karin M. The IKK/NF-kappa B pathway. Crit Care Med 2002; 30: S18-26.
[24] Keats JJ, Fonseca R, Chesi M, Schop R, Baker A, Chng WJ, Van Wier S, Tiedemann R, Shi CX, Sebag M, Braggio E, Henry T, Zhu YX, Fogle H, Price-Troska T, Ahmann G, Mancini C, Brents LA, Kumar S, Greipp P, Dispenzieri A, Bryant B, Mulligan G, Bruhn L, Barrett M, Valdez R, Trent J, Stewart AK, Carpten J, Bergsagel PL. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. Cancer Cell 2007; 12: 131-44.
[25] Annunziata CM, Davis RE, Demchenko Y, Bellamy W, Gabrea A, Zhan F, Lenz G, Hanamura I, Wright G, Xiao W, Dave S, Hurt EM, Tan B, Zhao H, Stephens O, Santra M, Williams DR, Dang L, Barlogie B, Shaughnessy JD Jr, Kuehl WM, Staudt LM. Frequent engagement of the classical and alternative NF-kappaB pathways by diverse genetic abnormalities in multiple myeloma. Cancer Cell 2007; 12: 115-30.
[26] Saitoh Y, Yamamoto N, Dewan MZ, Sugimoto H, Martinez Bruyn VJ, Iwasaki Y, Matsubara K, Qi X, Saitoh T, Imoto I, Inazawa J, Utsunomiya A, Watanabe T, Masuda T, Yamamoto N, Yamaoka S. Overexpressed NF-kappaB-inducing kinase contributes to the tumorigenesis of adult T-cell leukemia and Hodgkin Reed-Sternberg cells. Blood 2008; 111: 5118-29.
[27] Mannick EE, Bravo LE, Zarama G, Realpe JL, Zhang XJ, Ruiz B, Fontham ET, Mera R, Miller MJ, Correa P. Inducible nitric oxide synthase, nitrotyrosine, and apoptosis in Helicobacter pylori gastritis: effect of antibiotics and antioxidants. Cancer Res 1996; 56: 3238-43.
[28] Zhang R, Kang KA, Kim KC, Na SY, Chang WY, Kim GY, Kim HS, Hyun JW. Oxidative stress causes epigenetic alteration of CDX1 expression in colorectal cancer cells. Gene 2013; 524: 214-9.
[29] Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. Int J Cancer 2007; 121: 2373-80.
[30] Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 2012; 338: 120-3.
[31] Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, Iwakura Y, Oshima K, Morita H, Hattori M, Honda K, Ishikawa Y, Hara E, Ohtani N. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 2013; 499: 97-101.
[32] Gewirtz AT, Rao AS, Simon PO Jr, Merlin D, Carnes D, Madara JL, Neish AS. Salmonella typhimurium induces epithelial IL-8 expression via Ca(2+)-mediated activation of the NF-kappaB pathway. J Clin Invest 2000; 105: 79-92.
[33] Lavon I, Goldberg I, Amit S, Landsman L, Jung S, Tsuberi BZ, Barshack I, Kopolovic J, Galun E, Bujard H, Ben-Neriah Y. High susceptibility to bacterial infection, but no liver dysfunction, in mice compromised for hepatocyte NF-kappaB activation. Nat Med 2000; 6: 573-7.
[34] Rayet B, Gélinas C. Aberrant rel/nfkb genes and activity in human cancer. Oncogene 1999; 18: 6938-47.
[35] Wang CY, Cusack JC Jr, Liu R, Baldwin AS Jr. Control of inducible chemoresistance: enhanced anti-tumor therapy through increased apoptosis by inhibition of NF-kappaB. Nat Med 1999; 5: 412-7.
[36] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357: 539-45.
[37] Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860-7.
[38] Pasparakis M. Role of NF-κB in epithelial biology. Immunol Rev 2012; 246: 346-58.
[39] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010; 140: 883-99.
[40] Kanai T, Totsuka T, Uraushihara K, Makita S, Nakamura T, Koganei K, Fukushima T, Akiba H, Yagita H, Okumura K, Machida U, Iwai H, Azuma M, Chen L, Watanabe M. Blockade of B7-H1 suppresses the development of chronic intestinal inflammation. J Immunol 2003; 171: 4156-63.
[41] MacDonald TT, Monteleone G, Pender SL. Recent developments in the immunology of inflammatory bowel disease. Scand J Immunol 2000; 51: 2-9.
[42] Totsuka T, Kanai T, Iiyama R, Uraushihara K, Yamazaki M, Okamoto R, Hibi T, Tezuka K, Azuma M, Akiba H, Yagita H, Okumura K, Watanabe M. Ameliorating effect of anti-inducible costimulator monoclonal antibody in a murine model of chronic colitis. Gastroenterology 2003; 124: 410-21.
[43] Ekbom A, Helmick CG, Zack M, Holmberg L, Adami HO. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. Gastroenterology 1992; 103: 954-60.
[44] Ligibel J. Lifestyle factors in cancer survivorship. J Clin Oncol 2012; 30: 3697-704.
[45] Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, Colditz GA. Comparison of risk

factors for colon and rectal cancer. Int J Cancer 2004; 108: 433-42.
[46] Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell 2006; 124: 823-35.
[47] Arai N, Mitomi H, Ohtani Y, Igarashi M, Kakita A, Okayasu I. Enhanced epithelial cell turnover associated with p53 accumulation and high p21WAF1/CIP1 expression in ulcerative colitis. Mod Pathol 1999; 12: 604-11.
[48] Nenci A, Becker C, Wullaert A, Gareus R, van Loo G, Danese S, Huth M, Nikolaev A, Neufert C, Madison B, Gumucio D, Neurath MF, Pasparakis M. Epithelial NEMO links innate immunity to chronic intestinal inflammation. Nature 2007; 446: 557-61.
[49] Atreya I, Atreya R, Neurath MF. NF-kappaB in inflammatory bowel disease. J Intern Med 2008; 263: 591-6.
[50] Rogler G, Brand K, Vogl D, Page S, Hofmeister R, Andus T, Knuechel R, Baeuerle PA, Schölmerich J, Gross V. Nuclear factor kappaB is activated in macrophages and epithelial cells of inflamed intestinal mucosa. Gastroenterology 1998; 115: 357-69.
[51] Neurath MF, Fuss I, Schürmann G, Pettersson S, Arnold K, Müller-Lobeck H, Strober W, Herfarth C, Büschenfelde KH. Cytokine gene transcription by NF-kappa B family members in patients with inflammatory bowel disease. Ann N Y Acad Sci 1998; 859: 149-59.
[52] Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, Kagnoff MF, Karin M. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell 2004; 118: 285-96.
[53] Kojima M, Morisaki T, Sasaki N, Nakano K, Mibu R, Tanaka M, Katano M. Increased nuclear factor-kB activation in human colorectal carcinoma and its correlation with tumor progression. Anticancer Res 2004; 24: 675-81.
[54] Shimizu T, Marusawa H, Endo Y, Chiba T. Inflammation-mediated genomic instability: roles of activation-induced cytidine deaminase in carcinogenesis. Cancer Sci 2012; 103: 1201-6.
[55] Marusawa H, Takai A, Chiba T. Role of activation-induced cytidine deaminase in inflammation-associated cancer development. Adv Immunol 2011; 111: 109-41.
[56] Takai A, Marusawa H, Minaki Y, Watanabe T, Nakase H, Kinoshita K, Tsujimoto G, Chiba T. Targeting activation-induced cytidine deaminase prevents colon cancer development despite persistent colonic inflammation. Oncogene 2012; 31: 1733-42.
[57] Prasad S, Ravindran J, Aggarwal BB. NF-kappaB and cancer: how intimate is this relationship. Mol Cell Biochem 2010; 336: 25-37.
[58] Aggarwal BB, Sung B. NF-kB in cancer: a matter of life and death. Cancer Discov 2011; 1: 469-71.
[59] Srinivasula SM, Ashwell JD. IAPs: what's in a name? Mol Cell 2008; 30: 123-35.
[60] Luo JL, Kamata H, Karin M. IKK/NF-kappaB signaling: balancing life and death--a new approach to cancer therapy. J Clin Invest 2005; 115: 2625-32.
[61] De Smaele E, Zazzeroni F, Papa S, Nguyen DU, Jin R, Jones J, Cong R, Franzoso G. Induction of gadd45beta by NF-kappaB downregulates pro-apoptotic JNK signalling. Nature 2001; 414: 308-13.
[62] Guttridge DC, Albanese C, Reuther JY, Pestell RG, Baldwin AS Jr. NF-kappaB controls cell growth and differentiation through transcriptional regulation of cyclin D1. Mol Cell Biol 1999; 19: 5785-99.
[63] Chen C, Edelstein LC, Gélinas C. The Rel/NF-kappaB family directly activates expression of the apoptosis inhibitor Bcl-x(L). Mol Cell Biol 2000; 20: 2687-95.
[64] Hanada T, Yoshimura A. Regulation of cytokine signaling and inflammation. Cytokine Growth Factor Rev 2002; 13: 413-21.
[65] Goldring MB, Otero M, Tsuchimochi K, Ijiri K, Li Y. Defining the roles of inflammatory and anabolic cytokines in cartilage metabolism. Ann Rheum Dis 2008; 67 Suppl 3: iii75-82.
[66] Fernández-Majada V, Aguilera C, Villanueva A, Vilardell F, Robert-Moreno A, Aytés A, Real FX, Capella G, Mayo MW, Espinosa L, Bigas A. Nuclear IKK activity leads to dysregulated notch-dependent gene expression in colorectal cancer. Proc Natl Acad Sci U S A 2007; 104: 276-81.
[67] Rahman KM, Ali S, Aboukameel A, Sarkar SH, Wang Z, Philip PA, Sakr WA, Raz A. Inactivation of NF-kappaB by 3,3'-diindolylmethane contributes to increased apoptosis induced by chemotherapeutic agent in breast cancer cells. Mol Cancer Ther 2007; 6: 2757-65.
[68] Loch T, Michalski B, Mazurek U, Graniczka M. Vascular endothelial growth factor (VEGF) and its role in neoplastic processes. Postepy Hig Med Dosw 2001; 55: 257-74.
[69] Huang S, DeGuzman A, Bucana CD, Fidler IJ. Nuclear factor-kappaB activity correlates with growth, angiogenesis, and metastasis of human melanoma cells in nude mice. Clin Cancer Res 2000; 6: 2573-81.
[70] Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? Biochem Pharmacol 2006; 72: 1605-21.
[71] Vaiopoulos AG, Papachroni KK, Papavassiliou AG. Colon carcinogenesis: Learning from NF-kappaB and AP-1. Int J Biochem Cell Biol 2010; 42: 1061-5.

[72] Terzić J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010; 138: 2101-14.
[73] Sunami Y, Wirth T. Intestinal carcinogenesis: IKK can go all the way. J Clin Invest 2011; 121: 2551-3.
[74] Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell 1998; 93: 705-16.
[75] Kim S, Takahashi H, Lin WW, Descargues P, Grivennikov S, Kim Y, Luo JL, Karin M. Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis. Nature 2009; 457: 102-6.
[76] Maeda S, Omata M. Inflammation and cancer: role of nuclear factor-kappaB activation. Cancer Sci 2008; 99: 836-42.
[77] Karin M, Cao Y, Greten FR, Li ZW. NF-kappaB in cancer: from innocent bystander to major culprit. Nat Rev Cancer 2002; 2: 301-10.
[78] Luo JL, Maeda S, Hsu LC, Yagita H, Karin M. Inhibition of NF-kappaB in cancer cells converts inflammation- induced tumor growth mediated by TNFalpha to TRAIL-mediated tumor regression. Cancer Cell 2004; 6: 297-305.
[79] Murakami T, Kawada K, Iwamoto M, Akagami M, Hida K, Nakanishi Y, Kanda K, Kawada M, Seno H, Taketo MM, Sakai Y. The role of CXCR3 and CXCR4 in colorectal cancer metastasis. Int J Cancer 2013; 132: 276-87.
[80] Grivennikov SI, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. Ann Rheum Dis 2011; 70 Suppl 1: i104-8.
[81] Puvvada SD, Funkhouser WK, Greene K, Deal A, Chu H, Baldwin AS, Tepper JE, O'Neil BH. NF-kB and Bcl-3 activation are prognostic in metastatic colorectal cancer. Oncology 2010; 78: 181-8.
[82] Kwon HC, Kim SH, Oh SY, Lee S, Kwon KA, Choi HJ, Park KJ, Kim HJ, Roh MS. Clinicopathological significance of p53, hypoxia-inducible factor 1alpha, and vascular endothelial growth factor expression in colorectal cancer. Anticancer Res 2010; 30: 4163-8.
[83] Okayasu I, Ohkusa T, Kajiura K, Kanno J, Sakamoto S. Promotion of colorectal neoplasia in experimental murine ulcerative colitis. Gut 1996; 39: 87-92.
[84] Greten FR, Arkan MC, Bollrath J, Hsu LC, Goode J, Miething C, Göktuna SI, Neuenhahn M, Fierer J, Paxian S, Van Rooijen N, Xu Y, O'Cain T, Jaffee BB, Busch DH, Duyster J, Schmid RM, Eckmann L, Karin M. NF-kappaB is a negative regulator of IL-1beta secretion as revealed by genetic and pharmacological inhibition of IKKbeta. Cell 2007; 130: 918-31.
[85] Hayden MS, West AP, Ghosh S. NF-kappaB and the immune response. Oncogene 2006; 25: 6758-80.
[86] Huber MA, Azoitei N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H, Wirth T. NF-kappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. J Clin Invest 2004; 114: 569-81.
[87] Weldon CB, Burow ME, Rolfe KW, Clayton JL, Jaffe BM, Beckman BS. NF-kappa B-mediated chemoresistance in breast cancer cells. Surgery 2001; 130: 143-50.
[88] Arlt A, Vorndamm J, Müerköster S, Yu H, Schmidt WE, Fölsch UR, Schäfer H. Autocrine production of interleukin 1beta confers constitutive nuclear factor kappaB activity and chemoresistance in pancreatic carcinoma cell lines. Cancer Res 2002; 62: 910-6.
[89] Chen X, Shen B, Xia L, Khaletzkiy A, Chu D, Wong JY, Li JJ. Activation of nuclear factor kappaB in radioresistance of TP53-inactive human keratinocytes. Cancer Res 2002; 62: 1213-21.
[90] Fan M, Ahmed KM, Coleman MC, Spitz DR, Li JJ. Nuclear factor-kappaB and manganese superoxide dismutase mediate adaptive radioresistance in low-dose irradiated mouse skin epithelial cells. Cancer Res 2007; 67: 3220-8.
[91] Yin D, Zhou H, Kumagai T, Liu G, Ong JM, Black KL, Koeffler HP. Proteasome inhibitor PS-341 causes cell growth arrest and apoptosis in human glioblastoma multiforme (GBM). Oncogene 2005; 24: 344-54.
[92] Shah SA, Potter MW, McDade TP, Ricciardi R, Perugini RA, Elliott PJ, Adams J, Callery MP. 26S proteasome inhibition induces apoptosis and limits growth of human pancreatic cancer. J Cell Biochem 2001; 82: 110-22.
[93] Coquelle A, Mouhamad S, Pequignot MO, Braun T, Carvalho G, Vivet S, Métivier D, Castedo M, Kroemer G. Cell cycle-dependent cytotoxic and cytostatic effects of bortezomib on colon carcinoma cells. Cell Death Differ 2006; 13: 873-5.
[94] Ling YH, Liebes L, Jiang JD, Holland JF, Elliott PJ, Adams J, Muggia FM, Perez-Soler R. Mechanisms of proteasome inhibitor PS-341-induced G(2)-M-phase arrest and apoptosis in human non-small cell lung cancer cell lines. Clin Cancer Res 2003; 9: 1145-54.
[95] Adams J. The proteasome as a novel target for the treatment of breast cancer. Breast Dis 2002; 15: 61-70.
[96] Williams S, Pettaway C, Song R, Papandreou C, Logothetis C, McConkey DJ. Differential effects of the proteasome inhibitor bortezomib on apoptosis and angiogenesis in human prostate tumor xenografts. Mol Cancer Ther 2003; 2: 835-43.

[97] Pai R, Soreghan B, Szabo IL, Pavelka M, Baatar D, Tarnawski AS. Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy. Nat Med 2002; 8: 289-93.

[98] Ninomiya I, Nagai N, Oyama K, Hayashi H, Tajima H, Kitagawa H, Fushida S, Fujimura T, Ohta T. Antitumor and anti-metastatic effects of cyclooxygenase-2 inhibition by celecoxib on human colorectal carcinoma xenografts in nude mouse rectum. Oncol Rep 2012; 28: 777-84.

[99] Plummer SM, Holloway KA, Manson MM, Munks RJ, Kaptein A, Farrow S, Howells L. Oncogene 1999; 18: 6013-20.

[100] Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, Imamura Y, Qian ZR, Baba Y, Shima K, Sun R, Nosho K, Meyerhardt JA, Giovannucci E, Fuchs CS, Chan AT, Ogino S. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J 2012; 367: 1596-606.

[101] Narang VS, Pauletti GM, Gout PW, Buckley DJ, Buckley AR. Suppression of cystine uptake by sulfasalazine inhibits proliferation of human mammary carcinoma cells. Anticancer Res 2003; 23: 4571-9.

[102] Robe PA, Bentires-Alj M, Bonif M, Rogister B, Deprez M, Haddada H, Khac MT, Jolois O, Erkmen K, Merville MP, Black PM, Bours V. In vitro and in vivo activity of the nuclear factor-kappaB inhibitor sulfasalazine in human glioblastomas. Clin Cancer Res 2004; 10: 5595-603.

[103] Ryan BM, Russel MG, Langholz E, Stockbrugger RW. Aminosalicylates and colorectal cancer in IBD: a not-so bitter pill to swallow. Am J Gastroenterol 2003; 98: 1682-7.

[104] Gout PW, Simms CR, Robertson MC. In vitro studies on the lymphoma growth-inhibitory activity of sulfasalazine. Anticancer Drugs 2003; 14: 21-9.

[105] Habens F, Srinivasan N, Oakley F, Mann DA, Ganesan A, Packham G. Novel sulfasalazine analogues with enhanced NF-kB inhibitory and apoptosis promoting activity. Apoptosis 2005; 10: 481-91.

[106] Wahl C, Liptay S, Adler G, Schmid RM. Sulfasalazine: a potent and specific inhibitor of nuclear factor kappa B. J Clin Invest 1998; 101: 1163-74.

[107] Nicholson L, Hall AG, Redfern CP, Irving J. NF-kappaB modulators in a model of glucocorticoid resistant, childhood acute lymphoblastic leukemia. Leuk Res 2010; 34: 1366-73.

[108] Oerlemans R, Vink J, Dijkmans BA, Assaraf YG, van Miltenburg M, van der Heijden J, Ifergan I, Lems WF, Scheper RJ, Kaspers GJ, Cloos J, Jansen G. Sulfasalazine sensitises human monocytic/macrophage cells for glucocorticoids by upregulation of glucocorticoid receptor alpha and glucocorticoid induced apoptosis. Ann Rheum Dis 2007; 66: 1289-95.

[109] Chauhan D, Auclair D, Robinson EK, Hideshima T, Li G, Podar K, Gupta D, Richardson P, Schlossman RL, Krett N, Chen LB, Munshi NC, Anderson KC. Identification of genes regulated by dexamethasone in multiple myeloma cells using oligonucleotide arrays. Oncogene 2002; 21: 1346-58.

[110] Bantel H, Domschke W, Schulze-Osthoff K, Kaskas B, Gregor M. Abnormal activation of transcription factor NF-kappaB involved in steroid resistance in chronic inflammatory bowel disease. Am J Gastroenterol 2000; 95: 1845-6.

[111] Zanotto-Filho A, Braganhol E, Schröder R, de Souza LH, Dalmolin RJ, Pasquali MA, Gelain DP, Battastini AM, Moreira JC. NFκB inhibitors induce cell death in glioblastomas. Biochem Pharmacol 2011; 81: 412-24.

[112] Lee HR, Cheong HJ, Kim SJ, Lee NS, Park HS, Won JH. Sulindac enhances arsenic trioxide-mediated apoptosis by inhibition of NF-kappaB in HCT116 colon cancer cells. Oncol Rep 2008; 20: 41-7.

[113] Ma Y, Wang J, Liu L, Zhu H, Chen X, Pan S, Sun X, Jiang H. Genistein potentiates the effect of arsenic trioxide against human hepatocellular carcinoma: role of Akt and nuclear factor-κB. Cancer Lett 2011; 301: 75-84.

[114] Mahieux R, Pise-Masison C, Gessain A, Brady JN, Olivier R, Perret E, Misteli T, Nicot C. Arsenic trioxide induces apoptosis in human T-cell leukemia virus type 1- and type 2-infected cells by a caspase-3-dependent mechanism involving Bcl-2 cleavage. Blood 2001; 98: 3762-9.

[115] Woo SY, Lee MY, Jung YJ, Yoo ES, Seoh JY, Shin HY, Ahn HS, Ryu KH. Arsenic trioxide inhibits cell growth in SH-SY5Y and SK-N-AS neuroblastoma cell lines by a different mechanism. Pediatr Hematol Oncol 2006; 23: 231-43.

[116] Wang CY, Cusack JC Jr, Liu R, Baldwin AS Jr. Control of inducible chemoresistance: enhanced anti-tumor therapy through increased apoptosis by inhibition of NF-kappaB. Nat Med 1999; 5: 412-7.

[117] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-74.