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Review Article

The role of the transcription factor NF-kB in the pathogenesis of inflammation and carcinogenesis. Modulation capabilities

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Abstract

The nuclear factor kappa B (NF-kB) signaling module is a complex and highly interconnected molecular network with important functions in all nucleated cells. Most chronic diseases caused by lifestyle factors appear to be related to inflammation. The NF-kB plays a major role in the pathogenesis of the inflammation and its intimate molecular mechanism. This transcription factor participates in the evolution of diabetes and its complications. In T1D (Type 1 Diabetes), proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor (TNF), and CD40L secreted by immune cells in islets induce the activation of NF-kB in β-cells through both canonical and noncanonical roads. NF-kB activation increases the expression of genes, including TNF-α, IL-1β, IL-6, MCP-1, and ICAM-1, that initiate and promote atherosclerosis. In particular, the severity and lethality of acute lung injury or acute respiratory distress syndrome (ALI/ARDS) caused by pneumonia or sepsis is primarily associated with an NF-kB-mediated "cytokine storm," in which massive polymorphonuclear (PMN) extravasation and the subsequent release of cytokines cause rapid deterioration due to widespread inflammation and coagulation. Nuclear translocation of NF-kB p65 can induce the transcription of several genes involved in the induction of EMT (epithelial-to-mesenchymal transition). This has been confirmed in various types of cancer, including brain, breast, lung, and gastric cancer. Cutaneous T-cell lymphoma (CTCL) encompasses a group of lymphoproliferative disorders characterized by invasive neoplastic T cells in the skin and various clinical prognoses. In the early stages of CTCL, NF-kB activation and cell proliferation are stimulated by the autocrine production of TNFα, leading to increased NF-kB activation and resistance to apoptosis. Bladder cancer is the second most common genitourinary cancer and is often recurrent and/or chemoresistant after tumor resection. NF-kB is a transcription factor that plays a critical role in normal physiology and bladder cancer. Bladder cancer patients have pathologically active NF-kB induced by proinflammatory cytokines, chemokines, and hypoxia, enhancing carcinogenesis and progression of the disease.

Keywords

transcription factor NF-kB, inflammation, chronic diseases, breast cancer, T-cell cutaneous lymphoma, urothelial carcinoma

Nature of the transcription factor NF-kB

NF-kB was discovered by Ranjan Sen and Baltimore in 1986 (Sen and Baltimore 1987). It has since been found to have a broad role in gene induction in various cellular responses, particularly in the immune system. NF-kB (nuclear factor kappa B) belongs to transcription factors that are known to regulate a wide range of processes—a number of immune cell functions, mechanisms related to cell proliferation and oncogenesis, neuroprotection and long-term memory, stem cell differentiation, and development processes. (Kaltschmidt et al. 2021) The NF-kB family consists of five different subunits: p65 (RelA), RelB, c-Rel, p50 (p105/NFkB1), and p52 (p100/NFkB2). These proteins share an N-terminal Rel-homology domain (RHD), which is responsible for dimerization, DNA binding, and nuclear translocation. Individual NF-kB subunits can form homo- and heterodimers that can bind to promoter kB sites and modulate the transcription of NF-kB-dependent genes (Oeckinghaus and Ghosh 2009; Giridharan and Srinivasan 2018). The nuclear factor kappa B (NF-kB) signaling module is a complex and highly interconnected molecular network with important functions in all nucleated cells. NF-kB can be viewed as an evolutionarily conserved system that allows cells to cope with many types of stress, ranging from inflammatory stimuli to oxidative, nutritional, and even physical stressors (Hayden and Ghosh 2012; Zhang et al. 2017). Patterns of NF-kB activation over time, or activation dynamics, convey information about the identity of the stimulus and coordinate the subsequent inflammatory response. Various ligands can induce distinct dynamics of NF-kB nuclear translocation that facilitate the accurate transmission of information from extracellular signals to the expression of responsive genes (Kellogg et al. 2017; Sheu and Hoffmann 2022). Activation of NF-kB reshapes the accessible chromatin landscape of the cell and regulates gene expression induced by any stimulus (Cheng et al. 2021; Daniels et al. 2023). A better understanding of the mechanism underlying the pathological activation of NF-kB in individual diseases is crucial for the design of more specific and effective pharmacotherapeutic strategies (Liu et al. 2017).

Inflammation and NF-kB

Inflammation is a host defense response to infection and tissue damage characterized by a series of responses, including vasodilation and chemotaxis of immune cells and plasma proteins to the site of infection or tissue damage. Inflammation can be acute or chronic (Chen et al. 2017; Fritsch and Abreu 2019; Michels da Silva et al. 2019; Zhang et al. 2019). Chronic inflammatory diseases are the most important cause of death in the world. The World Health Organization (WHO) defines chronic diseases as the greatest threat to human health. Globally, 3 out of 5 people die due to chronic inflammatory or closely related inflammatory diseases, such as stroke, chronic respiratory diseases, heart disease, cancer, obesity, and diabetes (Barcelos et al. 2019; Deepak et al. 2019; Tsai et al. 2019).

Most chronic diseases caused by lifestyle factors appear to be related to inflammation, too. The NF-kB has a key function in the regulation of the human immune system, and its dysregulation is associated with many chronic diseases, including asthma, cancer, diabetes, rheumatoid arthritis, inflammation, and neurological disorders. (Kunnumakkara et al. 2020). NF-kB is a central inducer of proinflammatory genes and regulates multiple aspects of the innate and acquired immune response (Liu et al. 2017). NF-kB induces the expression of various proinflammatory genes, including those encoding cytokines and chemokines, and a number of inflammatory mediators in various types of innate immune cells (Ghosh and Karin 2002; Hayden and Ghosh 2011). It plays a critical role in regulating the survival, activation, and differentiation of nearly all types of immune cells—especially inflammatory T-cells, such as CD4+ T-helper cells (Hayden and Ghosh 2011). NF-kB is involved in the generation of the so-called Treg cells. Nuclear factor kappa B regulates the inflammasome—these are intracellular multiprotein complexes assembled in response to PAMPs and DAMPs that activate inflammatory caspases and play an important role in regulating the composition of the intestinal microbiota. Dysregulation in inflammasome activation contributes to the development of autoimmune and various inflammatory diseases (Kumar et al. 2011).

According to Chang and co-authors, butyrate, one of the most abundant short-chain fatty acids (SCFA) in the microbiome, activates the IL-6 gene (Chang et al. 2014).

Figure 1. Role of NF-kB in inflammation.

Since IL-6 has been shown to be involved in the development of inflammation, insulin resistance, and β-cell dysfunction, activation of IL-6 would increase the risk of those respective disorders occurrence (Akbari and Hassan-Zadeh 2018). In addition, butyrate, as well as propionate, has been shown to induce NF-kB activity (Lakhdari et al. 2011). Since excessive NF-kB activation can lead to insulin resistance, metabolites that activate NF-kB would increase disease risk (Andreasen et al. 2011). For example, Frasinariu and colleagues found that gut-derived bacterial products—lipopolysaccharides (LPS) and unmethylated CpG DNA—were able to penetrate the intestinal mucosa and activate the Toll-like receptor (TLR) signaling pathway in patients with nonalcoholic fatty liver disease and other liver diseases due to weakened barriers (Frasinariu et al. 2013). Since TLRs affect NF-kB activation, which is associated with inflammation, gut "leaking" may be the cause of microbiome dysbiosis (Kawai and Akira 2007).

Table 1. Chronic diseases associated with high activity of NF-kB.

NF-kB	**Cardiovascular disease**	Heart failure, Atherosclerosis, Cardiac hypertrophy,
	Pulmonary disease	Asthma, Chronic obstructive pulmonary, Idiopathic pulmonary fibrosis, ARDS, COVID19
	Endocrine disease	Metabolic syndrome, Diabetes type I and II (diabetic neuropathy, diabetic retinopathy)
	Gastrointestinal disease	Helicobacter pylori- associated gastritis, Crohn's disease, Ulcerative colitis
	Neurology disease	Alzheimer's disease, Multiple sclerosis, Headache
	Autoimmune disease	Rheumatoid arthritis, Systemic lupus erythematosus, Type I diabetes, Multiple sclerosis, Inflammatory bowel disease

Diabetes

Diabetes, especially type 2, is one of the most common chronic diseases in the world, affecting more than 463 million people worldwide (9.3%). Projections indicate that if the increasing trend of recent decades continues, 700 million (10.9%) people will be diabetic by 2045 (Magliano and Boyko 2021). Type 2 diabetes (T2D), which accounts for 90% of diabetes cases, is characterized by systemic chronic low-grade inflammation, insulin resistance, and impaired insulin-producing β-cell function and survival (Pereira and Santani 2009). NF-kB activation is a key event in the pathogenesis of diabetes and its complications (Patel and Santani 2009). In T1D, proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor (TNF), and CD40L secreted by immune cells in islets induce the activation of NF-kB in β-cells through both canonical and noncanonical pathways (Eizirik et al. 2009). Although in vitro and in vivo models of T1D show that activation of the canonical NF-kB pathway in β-cells is generally deleterious, little is known regarding the role of the noncanonical NF-kB pathway in diabetes (Meyerovich et al. 2018).

Late complications due to poorly controlled diabetes are diabetic retinopathy, neuropathy, and nephropathy. They can lead to serious disability and reduce the quality of life. Diabetic retinopathy (DR), a major microvascular complication of diabetes mellitus (DM), is the leading cause of blindness in adults (Tang and Kern 2011; Wang et al. 2017; Gedebjrg et al. 2018). Diabetic retinopathy (DR) is often considered a consequence of chronic inflammatory stress, which results from persistent and clinically unobtrusive activation of multiple deleterious cascades in response to abnormal metabolic memory (Forrester et al. 2020). Hyperglycemia and the associated hypertonic environment increase the production of angiotensin II (Ang-II), which, together with increased oxidative stress and AGEs, stimulates the expression of nuclear factor (NF)-kB (Medeiros et al. 2014). Cells in the inner and outer nuclear layers, ganglion cell layer, and retinal pericytes are activated by these stimuli, leading to phosphorylation of an NF-kB inhibitory protein and its rapid degradation, followed by release of NF-kB (Jiang et al. 2015). NF-kB is present in almost all cell types and has broad biological and inflammatory activities, including promoting gene transcription of several cytokines and chemokines. The increased activity of -glial cells, -caspase 1, and -caspase 3 activation, together with hypoxia, stimulates glial Müller cells, endothelial cells, macrophages, and neutrophils to increase interleukin (IL)-1β expression (Hangai et al. 1995; Oeckinghaus et al. 2011). Overactivated NF-kB leads to altered gene expression of VEGF, PDGF, and endothelin-1, as well as the release of various cytokines, including TNF-α, IL-1β, and IL-6. These processes ultimately lead to endothelial apoptosis and abnormal angiogenesis (Patel and Santani 2009; Kitada et al. 2019).

In a study by Joussen et al., meloxicam (a COX-2 inhibitor) reduces endothelial nitric oxide synthase (eNOS) levels, inhibits NF-kB activation in the diabetic retina, and partially reduces TNFα levels. (Joussen et al. 2002) Selective inhibition of NF-kB also results in reduced retinal capillary degeneration and expression of inflammatory proteins (Nagai et al. 2007).

A study by Wang et al. in diabetic mice showed that inhibition of Müller cell VEGF significantly reduced the expression of TNFα, ICAM-1, and NF-kB. Retinal leukostasis implicated in the pathogenesis of diabetic retinopathy is also mediated by VEGF, too (Wang et al. 2010).

Administration of phosphomannopentaose sulfate (PI-88) (a sulfonated oligosaccharide that inhibits heparanase) resulted in inhibition of leukostasis and preservation of electroretinogram (ERG) changes in diabetic rats, suggesting that it may reverse retinal dysfunction by reducing VEGF expression (Ma et al. 2009). Inhibition of NF-kB activation by dehydroxymethylepoxyquinomycin experimentally reduces diabetes-induced retinal leukostasis and ICAM-1 and VEGF expression (Nagai et al. 2007).

ChIP-seq and luciferase analysis showed the possible functions of the HMGB1 (high-mobility group box 1) transcription factor, and IKB-α was one of the binding sites of HMGB1. In vivo and in vitro results show high expression of HMGB1 and NF-kB and low expression of IKB-α in diabetic retinopathy (DR), and the expression of IKB-α and NF-kB is regulated by HMGB1. Furthermore, cellular assays showed that HMGB1 inhibited cell proliferation and promoted apoptosis. In conclusion, the results of this study indicate that HMGB1 can affect the NF-kB pathway through IKB-α, thereby influencing DR pathogenesis, and HMGB1 inhibition may provide a new concept for the treatment of DR (Liang et al. 2019).

Receptor activator of NF-kB (RANK) expression is increased in podocytes of patients with diabetic nephropathy. However, the relevance of RANK to the pathobiology of diabetic nephropathy remains unclear. To evaluate the role of podocyte RANK in the development of diabetic nephropathy, a mouse model of podocyte-specific depletion of RANK (RANK-/-CreT) and a model of podocyte-specific overexpression of RANK (RANK TG) were used, and diabetes was induced in these mice with streptozotocin. Depletion of podocyte RANK was found to alleviate albuminuria, expand the mesangial matrix, and thicken the basement membrane, whereas overexpression of RANK worsened these parameters in streptozotocin-treated mice. Furthermore, streptozotocin-induced oxidative stress was increased in RANK overexpression but decreased in RANK-depleted mice (Ke et al. 2021).

Ahmed S. et al. conducted a diosmin study designed to evaluate various biochemical parameters, oxidative stress markers, and proinflammatory cytokine levels in alloxan-induced diabetic Wistar rats. Diosmin treatment significantly decreased blood glucose and plasma insulin levels and increased body weight compared to control untreated diabetic rats. The increased level of malondialdehyde (MDA) and the decreased levels of superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), and nitric oxide (NO) were significantly restored after 28 days of diosmin treatment. The diosmin treatment group also restored normal kidney tissue architecture, which was confirmed by histopathological examination. Furthermore, oral administration of diosmin showed a significant normalization of NF-kB level, proving its essential role in maintaining kidney function (Ahmed et al. 2016).

Curcumin (CUR), a natural compound derived from turmeric, exerts beneficial effects on diabetes mellitus, most probably through its interaction with the nuclear factor kappa B (NF-kB) pathway. Research has shown that CUR targets inflammatory mediators in diabetes, including tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), by modulating the NF-kB signaling pathway. CUR exerts its beneficial effects in the management of diabetic complications by regulating signaling pathways such as calcium-calmodulin (CaM)-dependent protein kinase II (CaMKII), peroxisome proliferator-activated receptor gamma (PPAR-γ), NF-kB, and transforming growth factor β1 (TGFB1). CUR reduces oxidative stress (OS), prevents structural kidney damage associated with diabetic nephropathy, and suppresses NF-kB activity. In addition, CUR exhibits a protective effect against diabetic cardiomyopathy, lung injury, and diabetic gastroparesis (Zamanian et al. 2024).

Heart diseases and NF-kB

Heart failure is a clinical syndrome with signs and symptoms that result from functional or structural disorders in the ejection or filling with blood from and to the ventricle (Heidenreich et al. 2022). Increased blood concentrations of endotoxins and cytokines have been reported in heart failure patients during exacerbations, suggesting that endotoxins may activate immune responses during the development of edema (Niebauer et al. 1999). Since NF-kB is activated by endotoxins and cytokines, and this activation leads to the expression of genes encoding cytokines and chemokines, among others, it has been suggested that NF-kB may play a crucial role in cardiovascular diseases and their leading and causative risk factors, such as atherosclerosis and diabetes. Atherosclerosis is the most common contributing factor to ischemic heart disease and stroke and is considered a chronic inflammatory disease (Matsumori 2022). NF-kB contributes to other processes involved in the formation of atherosclerotic plaques, too. NF-kB activation increases the expression of genes, including TNF-α, IL-1β, IL-6, MCP-1, and ICAM-1, that initiate and promote atherosclerosis. NF-kB is detected in the nuclei of macrophages in atherosclerotic lesions, suggesting that NF-kB activation is associated with atherogenesis (Brand et al. 1996). The benefits of targeting inflammation in human atherosclerosis were demonstrated in the Cantos trial, in which treatment with canakinumab, an antibody targeting IL-1β, improved clinical outcomes in patients with a history of myocardial infarction (MI) (Ridker et al. 2017). In addition, clinical trials have shown that the anti-inflammatory agent colchicine reduces the risk of cardiovascular events in patients with recent myocardial infarction or coronary artery disease (Nidorf et al. 2020). Thus, inhibition of NF-kB remains a promising intervention for the prevention of atherosclerosis and its sequelae.

Several therapeutic agents used to treat CVD and diabetes, such as pimobendan and sodium-glucose cotransporter 2 inhibitors (dapagliflozin, empagliflozin), exert anti-inflammatory effects by inhibiting NF-kB activation (Cowie and Fisher 2020; Matsumori 2023). Gemigliptin has been shown to have anti-inflammatory effects by regulating the IKK/NF-kB, MKK7/JNK, and JAK2/STAT1 pathways in macrophages (Lee et al. 2021). Metformin attenuates LPS-stimulated phosphorylation of p65 and JNK1 and regulation of proinflammatory cytokine levels (Woo et al. 2014). Metformin also inhibits the translocation of NF-kB to the nucleus and reverses the LPS-induced decrease in apolipoprotein E expression in macrophages. Inhibition of NF-kB nuclear translocation is mediated by the phosphatidylinositol 3-kinase/Akt pathway. (Isoda et al. 2006). Glucagon-like peptide-1 (GLP-1) receptor ag-

onists inhibit NF-kB activity and reduce inflammatory biomarkers, such as reactive oxygen species, the expression of IL-1β, TNF-α, JNK1, TLR2, TLR4, and SOCS-3 in mononuclear cells, and circulating concentrations of IL-6, MCP-1, MMP-9, and serum amyloid A (Yang et al. 2021).

Interestingly, resveratrol suppresses the TLR4/MyD88/NF-kB signaling pathway in lysophosphatidylcholine-induced injury and inflammation, which may be useful in preventing atherosclerosis. Thus, resveratrol may prevent inflammation and oxidative stress and may be promising as an anti-inflammatory agent in CVD to improve quality of life and reduce the risk of carcinogenesis (Chen et al. 2018).

Lung diseases and NF-kB

Pulmonary inflammatory diseases such as ALI/ARDS, asthma, idiopathic pulmonary fibrosis (IPF), bronchoalveolar dysplasia (BPD), and chronic obstructive pulmonary disease (COPD) are also characterized by dysregulated NF-kB activation (Rieger-Fackeldy and Hentschel 2008; Ye et al. 2008; Janssen-Heininger et al. 2009; MacNee and Tuder 2009). In particular, the severity and lethality of ALI/ARDS caused by pneumonia or sepsis is primarily associated with an NF-kB-mediated "cytokine storm," in which massive polymorphonuclear (PMN) extravasation and the subsequent release of cytokines cause rapid deterioration due to widespread inflammation and coagulation (Chousterman et al. 2017; Faigenbaum and June 2020).

Chronic obstructive pulmonary disease (COPD) is a major global health problem characterized by pulmonary inflammation and airway remodeling (Christenson et al. 2022). Traditional Chinese medicine, such as the modified Jiawei Bushen Yiqi (MBYF) formula, is used as adjunctive therapy for COPD in China. Pharmacological network analysis suggests that MBYF may act through the IL-17 signaling pathway to regulate inflammatory responses. RNA sequencing and molecular analyses showed that MBYF inhibits neutrophil chemotaxis by downregulating the CXCL1/CXCL5/CXCL8-CXCR2 axis and suppresses IL-17A, IL-17F, and its downstream cytokines, including IL-6, TNFα, IL-1β, and COX2. Furthermore, MBYF inhibited the activation of NF-kB and MAPKs by the IL-17 signaling pathway (Kong et al. 2024).

Liguo Lu et al. reported the therapeutic effects of Lifei decoction in a mouse model of COPD induced by LPS and cigarette smoke. Administration of LD (Lifei decoction) demonstrated significant efficacy in mitigating lung tissue damage in a mouse model while inhibiting activation of the NF-kB inflammatory pathway to reduce levels of pro-inflammatory factors (Lu et al. 2024).

More recently, the SARS-CoV-2 spike protein has been shown to activate NF-kB in multiple cell types, including endothelial cells (ECs) and macrophages (Cao et al. 2021; Robles et al. 2022). These findings suggest a similar role for the NF-kB-dependent cytokine storm in COVID-19-associated ARDS (Chen et al. 2021). The activation, upon infection with COVID-19, of the transcription factor NF-kappa B (NF-kB) in various cells such as macrophages of the lung, liver, kidney, central nervous system, gastrointestinal system, and cardiovascular system results in the production of IL-1, IL-2, IL-6, IL-12, TNF-α, LT-α, LT-β, GM-CSF, and various chemokines. The relationship between NF-kB activation and the expression of SARS-CoV-2 structural and non-structural proteins has also been reported (Zhang et al. 2017; Hariharan et al. 2021).

Immunomodulation of the level of NF-kB activation and inhibitors of NF-kB degradation (IkB), together with TNF-α inhibition, potentially reduces the cytokine storm and alleviates the severity of COVID-19. (DeDiego et al. 2014) Drugs such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) have been found to be inhibitors of NF-kB pathways (Hariharan et al. 2021). Glucocorticoids increase the expression of IkB, which helps to retain NF-kB in the cell cytoplasm. They are also immunomodulating agents that reduce IL-6 production and activity, which in turn decrease cytokine feedback on NF-kB activity (Auphan et al. 1995). Dexamethasone is among the two glucocorticoids (prednisolone being the other) that has an inhibitory effect on the NF-kB pathway (Ye et al. 2020). The demonstrated beneficial role of dexamethasone may be at least partially related to the inhibition of NF-kB activation in critically ill patients with COVID-19 (Horby et al. 2021).

Autoimmune diseases and NF-kB

Autoimmune diseases are clinical syndromes that result from pathogenic inflammatory responses driven by inadequate immune activation by T- and B-cells. Although the exact mechanisms of autoimmune diseases are still elusive, genetic factors play an important role in pathogenesis. Gene modulation can be applied to regulate the levels of interleukins (ILs), tumor necrosis factor (TNF), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), interferon-γ, and other inflammatory cytokines by inhibiting these cytokines expressions using short interfering ribonucleic acid (siRNA) or by inhibiting cytokine signaling using small molecules (Lee et al. 2020). Patients with autoimmune diseases have a higher risk of developing hematologic cancers or solid tumors. Autoimmunity is a poor prognostic factor for these cancers. The risk of developing immune-related adverse events (IrAE) is higher than in the general population. IrAEs occur due to therapy-related cytokine release and T-cell infiltration when these cancers are treated with immunotherapy (Valencia et al. 2019). Most treatments proposed for autoimmune diseases inhibit immune cell activation and inflammatory signaling pathways, such as those activated by cytokines and their receptors. NF-kB has an important role in the pathophysiology of autoimmune diseases (Barnabei 2021). Most widely used drugs that modulate NF-kB activation are glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and some

disease-modifying drugs. For example, sulfasalazine acts on the nuclear translocation of NF-kB. Mesalamine inhibits post-transcriptional modifications of p65 (Brüstle et al. 2012). TPCA1 2-[(aminocarbonyl)amino]-5 - (4-fluorophenyl)-3- thiophenecarboxamide, another inhibitor of NF-kB, also inhibits STAT3 as well as reduces the production of cytokines such as TNF-α, IL-6, and IL-8 (Nan et al. 2014). Another inhibitor, 3-s[(dodecylthiocarbonyl)methyl]-glutarimide (DTCM-glutarimide), exhibits in vivo anti-inflammatory activity and an inhibitory effect on receptor activator of nuclear factor-kB ligand (RANKL)-induced osteoclast differentiation in bone and mouse brain-derived macrophages (Koide et al. 2015).

Inhibitors have been developed that act specifically on the subunits of the immunoproteasome and are a promising strategy for the treatment of autoimmune diseases. The immunoproteasome is specifically expressed in hematopoietic cells and is induced during the inflammatory process (Ettari et al. 2016). KZR-616, a dual immunoproteasome β5i/β2i selective inhibitor developed by Kezar Life Sciences, was recently approved for Phase II clinical trials for the treatment of several autoimmune diseases. Besides these approaches targeting kinase or protease complexes involved in NF-kB activation, another design approach directly targets NF-kB binding to DNA with synthetic DNA oligodeoxynucleotides (ODNs). This approach has not yet been used in patients, but its effectiveness has been shown in mouse models of colitis or arthritis (Amstein et al. 2023).

Carcinogenesis and NF-kB

Epithelial-to-mesenchymal transition (EMT) is a well-known mechanism responsible for tumor cell invasiveness and metastasis formation. A number of molecular pathways can regulate the EMT mechanism in cancer cells, and nuclear factor-kappaB (NF-kB) is one of them. Nuclear translocation of NF-kB p65 can induce the transcription of several genes involved in the induction of EMT. This has been confirmed in various types of cancer, including brain, breast, lung, and gastric cancer. After induction of NF-kB-driven EMT, there is a significant decrease in E-cadherin levels, while N-cadherin and vimentin levels undergo an increase. Furthermore, the NF-kB/EMT axis is involved in mediating drug resistance in tumor cells. Thus, suppression of the NF-kB/EMT axis may also promote the sensitivity of cancer cells to chemotherapeutic agents (Mirzaei et al. 2022).

Breast cancer is the second deadliest disease and the leading cause of cancer-related deaths in women (Arnold et al. 2020). Breast cancer (BC) is caused by aberrant tumor suppressor genes and oncogenes regulated by transcription factors (TFs) such as NF-kB. (Pavitra et al. 2023). NF-kB is a key TF that links inflammation to cancer. It has been shown to be involved in tumorigenesis in breast cancer and resistance to endocrine therapy. NF-kB plays an essential role in the management of inflammation, proliferation, and survival of cell lines (Lin et al. 2022; Cheng et al. 2023; Koerner et al. 2023; Que et al. 2023). As a result, NF-kB is a compelling target for therapeutic intervention in BC. NF-kB inhibitors can reduce NF-kB activity and improve the outcomes of BC treatment (Abdin et al. 2021). Furthermore, IKK-related kinases are important regulators of NF-kB, and their inhibitor IKK16 was more effective than gefitinib (an EGFR inhibitor) in reducing the viability of triple-negative breast cancer (TNBC) cell lines. Therefore, the combination of IKK16 with gefitinib resulted in a synergistic antiproliferative effect (Yi et al. 2022). In a mouse model, thalidomide is known to inhibit tumor growth by inhibiting angiogenesis and necrosis of BC tumor cells. (Wang et al. 2020) In addition, NF-kB inhibitors can be used alone or in combination with other breast cancer therapies, such as chemotherapy and radiation therapy. Extensive animal and human studies are needed to fully understand the effectiveness and potential side effects of NF-kB inhibitors for the treatment of breast cancer.

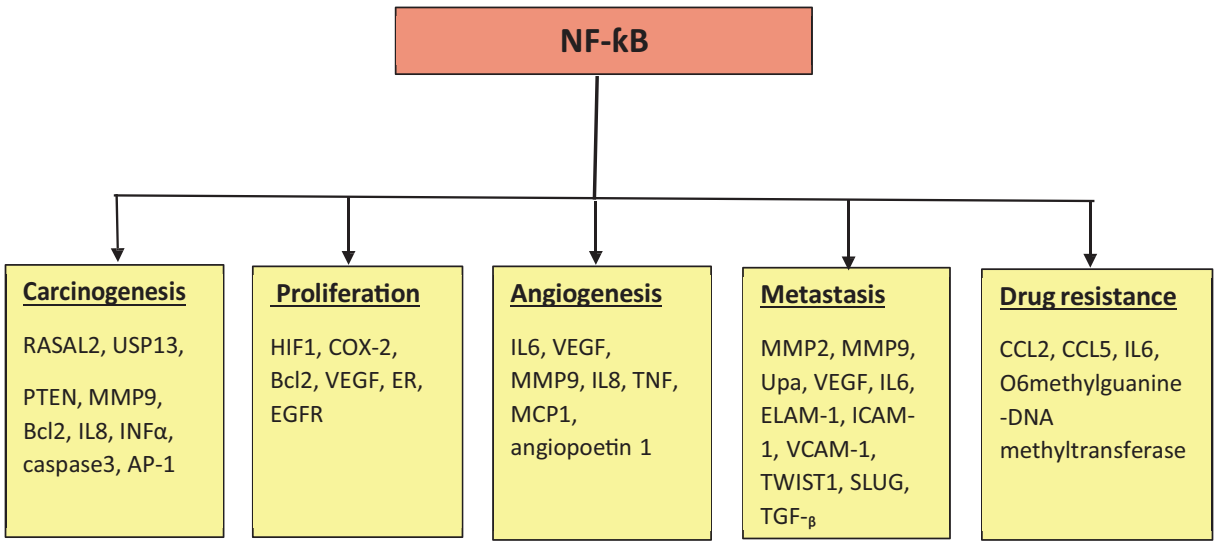

Figure 2. Involvement of NF-kB in carcinogenesis, proliferation, angiogenesis, metastasis, and drug resistance.

Recent research progress in understanding many aspects of the NF-kB signaling cascade demonstrates strong support for possible interactions between NF-kB signaling and lung tumorigenesis. Highly selective monoclonal antibodies have also shown potent action by inhibiting NF-kB signaling in lung cancer alone or in combination with other antiproliferative agents (Rasmi et al. 2020). Another important aspect to consider when using NF-kB inhibitors is a thorough understanding of the cancer stage or treatment phase. Currently, NF-kB inhibitors such as bortezomib and carfilzomib are some of the most powerful therapeutically useful drugs on the market (Freitas and Fraga 2018). In lung cancer models, EGCG (epigallocatechin-3-gallate) modulates the expression of microRNAs that can regulate NF-kB and MAP kinase pathways (Cheng et al. 2020).

The transmembrane protein tetraspanin1 (TSPAN1) potently inhibits in vitro migration and invasion as well as in vivo metastasis of nasopharyngeal carcinoma (NPC) cells by interacting with the IKBB protein. In addition, TSPAN1 is essential to prevent over-activation of the NF-kB pathway in TSPAN1-overexpressing NPC cells. Furthermore, decreased expression of TSPAN1 is associated with NPC metastasis and poor prognosis of NPC patients. These results reveal the suppressive role of TSPAN1 against NF-kB signaling in NPC cells to prevent NPC metastasis. Its therapeutic value warrants further investigation (Wang et al. 2024).

The NF-kB transcription factor family plays a critical role in lymphocyte proliferation and survival. Consequently, aberrant activation of NF-kB has been described in various lymphoid malignancies, including diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, and adult T-cell leukemia. Several factors, such as persistent infections (e.g., with Helicobacter pylori), the pro-inflammatory cancer microenvironment, self-reactive immune receptors, as well as genetic defects altering the function of key signaling effectors, contribute to the constitutive activity of NF-kB in these malignancies. (Grondona et al. 2018) Antiapoptotic effects of NF-kB inhibition may confer chemotherapy resistance in lymphoid malignancies. Inhibition of NF-kB activation represents an attractive therapeutic option in many lymphoid malignancies (Nakanishi and Toi 2005).

Pharmacotherapeutic options for the controlled inhibition of this signaling cascade have been studied in cutaneous T-cell lymphoma (CTCL). Cutaneous T-cell lymphoma (CTCL) encompasses a group of lymphoproliferative disorders characterized by invasive neoplastic T cells in the skin (Berger et al. 2005; Pulitzer 2017). In the early stages of CTCL, NF-kB activation and cell proliferation are stimulated by the autocrine production of TNFα, leading to increased NF-kB activation and resistance to apoptosis. In addition to TNFα, the epidermis of CTCL patients showed increased levels of the NF-kB-dependent cytokines IL-1β and IL-8, demonstrating their role in the pathogenesis of CTCL. Recent studies have shown that malignant T cells and skin lesions from CTCL patients produce the proinflammatory cytokine IL-17, which is also regulated by NF-kB (DiDonato et al. 2012). Several pharmacological agents have been shown to inhibit NF-kB activity and to induce apoptosis in CTCL: Arsenic trioxide (As2O3) is effective against CTCL by reducing the DNA-binding activity of NF-kB and inducing apoptosis (Tun-Kyi et al. 2008). Nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid, sodium salicylate, and diclofenac, which are widely used in the treatment of several inflammatory diseases, induce apoptosis in CTCL cells (Braun et al. 2012). Ara C (cytosine arabinoside) inhibits NF-kB activity by dephosphorylating the p65 subunit, leading to increased apoptosis in CTCL Hut-78 cells (Sreenivasan et al. 2003). The nitric oxide-generating compound sodium nitroprusside (SNP) can induce apoptosis in the CTCL Hut-78 cell line by suppressing NF-kB activity and Bcl-xL expression (Rishi et al. 2007). The 26S protease inhibitor bortezomib (BZ, Velcade) has shown promising antitumor activity. In CTCL cells, proteasome inhibition by BZ inhibited the in vitro DNA binding activity of NF-kB. CTCL Hut-78 zinc-deficient cells show reduced phosphorylation of IKK and IkB, resulting in reduced DNA binding of NF-kB (Zinzani et al. 2007; Kim et al. 2012). Curcumin induces apoptosis in CTCL cells by inhibiting the phosphorylation of IkBα and the DNA-binding activity of NF-kB. Its oxidative effect by generating reactive oxygen species (ROS) and inhibiting the constitutive activity of NF-kB in CTCL Hut-78 cells was also demonstrated (Zhang et al. 2010). Inhibition of the nuclear accumulation of NF-kB p65 and p50 by an IKKb (IKK2) inhibitor (AS6028668) induced a potent apoptotic response in CTCL cell lines and SS patients (Sors et al. 2008).

Bladder cancer is the second most common genitourinary cancer and is often recurrent and/or chemoresistant after tumor resection. Cigarette smoking, exposure to aromatic amines, and chronic infection/inflammation are risk factors for bladder cancer. NF-kB is a transcription factor that plays a critical role in normal physiology and bladder cancer. Bladder cancer patients have pathologically active NF-kB induced by proinflammatory cytokines, chemokines, and hypoxia, enhancing carcinogenesis and progression (Walter et al. 2020). Interestingly, increased NF-kB expression was associated with BCG treatment, reflecting a role for NF-kB in the BCG-mediated immune response. (Kamat et al. 2018) BCG-treated patients with the NF-kB del/del genotype are reported to have a 2.5-fold increased risk of relapse compared with the in/ins genotype (Ahirwar et al. 2010). The association between NF-kB genotype and response to BCG treatment highlights the importance of personalized medicine in bladder cancer therapy (Mukherjee et al. 2015). EGCG was found to inhibit the migration and invasion of T24 human bladder cancer cells through the inhibition of the PI3K/AKT pathway, which further ensured the inactivation of NF-kB and the downregulation of MMP-9 expression, ultimately limiting the metastatic potential of the cells (Qin et al. 2007; Qin et al. 2012). A similar effect was observed in SW-780 bladder cancer cells, where EGCG downregulated NF-kB and MMP-9 expression and triggered cancer cell apoptosis (Luo et al. 2024). EGCG has been tested for synergistic anticancer effects with a commonly used anticancer agent,

doxorubicin (DOX). EGCG was found to enhance the ability of DOX to induce apoptosis. In addition, EGCG enhanced the ability of DOX to prevent bladder cancer cell migration. According to the results of mechanistic studies, the combination of DOX and EGCG suppressed the expression of phosphorylated NF-kB and E3 ubiquitin-protein ligase Mdm2 (MDM2) while increasing the expression of TP53 in tumor cells *in vivo* (Luo et al. 2020).

Conclusion

Dysregulated activation of NF-kB is a leading factor in the pathogenesis of various inflammatory diseases. It is now well accepted that NF-kB serves as a central inflammatory trigger that responds to a wide variety of immune receptors. Targeting the signaling pathway of the NF-kB transcription factor represents an attractive approach for new anti-inflammatory therapies, modulating "universally" and "in the bud" the inflammatory response regardless of the relevant nosological entity. Of course, questions are arising regarding the balance between efficacy and safety, as NF-kB function is required for maintaining normal immune responses and cell survival. Global inhibition of NF-kB signaling can cause severe immune imbalance. A better understanding of the mechanism underlying the pathological activation of NF-kB in individual diseases is crucial for the design of more specific and effective pharmacotherapeutic strategies not only for inflammatory diseases but neoplastic ones as well.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Data availability

All of the data that support the findings of this study are available in the main text.

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