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Modulation of NF-κB – A novel approach for the development of anticancer drugs

Santosh G Rathod
santoshgrathod1506@gmail.com
Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra

Ajay D Kshirsagar
ksagar.ajay@gmail.com
Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra

Shashikant Dhawale
shashiprathmesh@gmail.com
Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra

ABSTRACT

Worldwide cancer is the leading cause of death; leukocytes within tumors and at the sites of chronic inflammation provided the first indication of a possible link between inflammation and cancer. Inflammation plays a crucial role at different stages of tumor growth via. transcription factors and inflammatory mediators such as TNF, IL's, chemokines COX-2, STAT3and NF-κB. Nuclear factor-kappa B (NF-κB) has been one of the most extensively investigated transcription factors for its role in cancers. The NF-κB signaling pathways are vital in the initiation and progression of cancer which can act as a node of pharmacological interference in the management of tumor. However, NF-κB is an essential player in the immune response against various cancer developments; hence inhibition of NF-κB seems to be always important in the treatment of various malignancies. The application of an NF-κB inhibitor may prove useful in anticancer therapy by converting anti-apoptosis effect of NF-κB into apoptotic nature. Therefore, current review focuses on the role of NF-κB in Inflammation Induced cancer (IIC) and prospects for developing of a novel treatment for inflammation-related cancer.

Keywords: *Inflammation-induced cancer, Apoptosis, NF-κB signaling pathways*

1. INTRODUCTION

Cancer is the leading cause of death globally, Dr. Rudolf Virchow, in 1863 observed leukocytes within tumors and hypothesized that malignant neoplasm gives first sign of a possible link between inflammation and cancer (1). Inflammation plays a crucial role at different stages of tumor development through transcription factors and inflammatory mediators like NF-κB, STAT3 etc. (Fig.1). Among these, nuclear factor-kappa B (NF-κB) and STAT3 are the major pathways for inflammation-induced cancer (2). In the mammalian cells, several distinct NF-κB activation pathways are present. Among them, the classical or canonical pathway has been well studied.

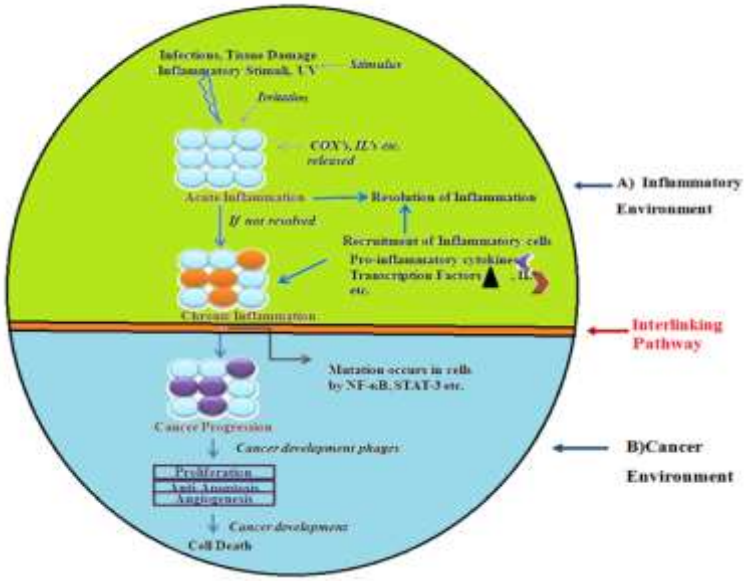

Fig. 1: Interlinking pathway of Inflammation-Related Cancer

(Abbreviations: IL's, Interleukins; NF-κB, Nuclear Factor kappa B; STAT3, signal transducers and activators of transcription-3)

In this pathway; lipopolysaccharides, tumor necrosis factor α or interleukin-1 activate their respective receptors. Through a variety of adapter proteins and signaling kinases which leads to an activation of I*κ*B kinase β in the IKK complex, further it can phosphorylate inhibition of kappa B α on S32 and S36 Serine residues and prerequisite for its subsequent polyubiquitination, and results in proteasomal degradation of inhibition of kappa B α, which further translocate to nucleus and activate target gene transcription (3).

The Constitutive activation of NF-κB, which is defined as persistence of NF-κB in the nucleus, is shown in a wide variety of tumor types, such as lymphoma, liver cancer, lungs cancer, breast cancer etc. (4). The NF-κB and STAT3 co-operatively regulate a number of target genes including anti-apoptotic as well as cycle control genes. Moreover, they also synergistically control a common set of genes encoding for cytokines and chemokines (5). NF-κB and STAT3 are constitutively active in most cancers, such as gastric carcinoma, multiple myeloma and chronic lymphocytic leukemia (6).

Research aimed at developing IKKβ/NF-κB inhibitors is currently flourishing (7). This review emphasizes about NF-κB that links inflammation and cancer, signaling pathways which can causes IIC, role of NF-κB inactivation in various types of cancer, interlink between major transcription factor such as NF-κB and STAT3 in inflammation-induced cancer, mechanism that underline the pro-death activity of NF-κB and what are the major strategies which involves in NF-κB inhibition for development of novel and as an ideal therapy.

2. NUCLEAR FACTOR KAPPA B (NF-κB)

Nuclear factor-*κ*B (NF-*κ*B) was first identified in 1986 by some researcher, as a transcription factor that binds to a 10 bp DNA element in kappa immunoglobulin light-chain enhancer in B cells thereby coining the abbreviation NF-κB (8). The mammalian NF-κB family consists of 5 members viz: NF-κB1 (p50/p105), NF-κB2 (p52/p100), c-Rel, RelA (p65) and RelB. Among these RelA, c-Rel and RelB are synthesized in mature forms (contain a transactivation domain, which interacts with transcriptional apparatus). On the other hand, NF-κB1 (p50/p105) and NF- κB2 (p52/p100) are synthesized in precursor forms i.e.p100 and p105, which contain C-terminal ankyrin repeats and proteolyzed by the proteasome resulting in the production of mature proteins (p50 and p52). Both p50 and p52 contain a DNA binding domain but lack a transactivation domain. However, when p50 or p52 are bound to a member containing a transactivation domain, such as p65 or RelB, they constitute a transcriptional activator (3). NF-*κ*B proteins are characterized by the presence of a highly conserved 300 amino acid Rel homology domain that is located toward the N terminus of the protein, and which is responsible for DNA binding, dimerization, and interaction with specific inhibitory factors known as IκB proteins (9).

NF-κB is active in the nucleus and is inhibited through its sequestration in the cytoplasm by an inhibitor of kappa B (IκB). There are seven IκB family members – IκB*α*, IκB*β*, IκB*γ*, IκB*ε*, and BCL-3 and the precursor proteins p100 and p105; which are characterized by the presence of five to seven ankyrin repeats (10). I*κ*Bs bind to NF-*κ*B dimmers and sterically block the function of their nuclear localization sequences, thereby causing their cytoplasmic retention. In, un-stimulated cells, NF-κB–IκB complex can also shuttle between the cytoplasm and the nucleus, but the nuclear export of the complex is more efficient and hence, the NF-κB–IκB complex is mainly cytoplasmic in resting cells. Most NF-κB activating agents stimulate the phosphorylation-induced degradation of I*κ*B. On the other hand, Bcl-3 (member of the IκB family) may interact with p50 or p52 homodimers contain a transactivation domain acts as a transcriptional co-activator (11).

IKK*α* and IKK*β* are two highly homologous catalytic subunits of multi-subunit protein kinase i.e. IκB kinase, which phosphorylates IκB, and a nonenzymatic regulatory subunit, IKK*γ* (known as NEMO) is required for the activation of IKK*α*/IKK*β* heterodimers in response to proinflammatory cytokines. Phosphorylation of IκB*α* and IκB*β* at two critical serine residues Ser32, Ser36 and Ser19, Ser23 respectively in their N-terminal regulatory domain by the IKK complex, that targets them for rapid polyubiquitination and subsequent degradation by the proteasome (fig.2) (12).After liberation then translocation to the nucleus, NF-κB dimmers further regulated by phosphorylation, acetylation, and interactions with co-activators and co-repressors. NF-κB regulates the transcription of diverse genes encoding cytokines, growth factors, cell adhesion molecules and pro/antiapoptotic proteins (9). Activated NF-κB can then be downregulated through multiple mechanisms including the well-characterized feedback pathway, whereby newly synthesized IκB*α* protein binds to nuclear NF-κB and exports it to the cytoplasm (13).

3. NF-κB SIGNALING PATHWAYS

NF-κB is activated by many stimuli, including pro-inflammatory cytokines (such as TNF-α, IL-1), T and B-cell mitogens, bacteria, lipopolysaccharide, viruses, viral proteins, double-stranded RNA and cellular stresses (such as UV, ionizing radiation, and chemotherapeutic agents). In the mammalian cells, there are three NF-κB activation pathways viz: 1) Classical or Canonical pathway, 2) Non-Canonical pathway and 3) Atypical pathway. Among them, the classical or canonical pathway has been the most studied (Fig.2).

In the canonical NF-κB signaling pathway lipopolysaccharides, interleukin-1 or tumor necrosis factor α activate Toll-like receptors, interleukin-1 receptor, and tumor necrosis factor receptor, respectively. Through several adapter proteins and signaling kinases, they can lead to an activation of IKKβ in the IKK complex, which can then phosphorylate IκBα on S32 and S36 Serine residues. This phosphorylation is a prerequisite for its subsequent polyubiquitination, it results in proteasomal degradation of IκBα. Which further translocate to the nucleus and activate target gene transcription (3). This pathway mostly targets p50: RelA and p50: c-Rel dimmers, depends mainly on IKKβ activity. The classical pathway is essential for activation of anti-apoptotic genes, inflammatory cytokines and various genes that promote cell proliferation, angiogenesis, and metastasis (14).

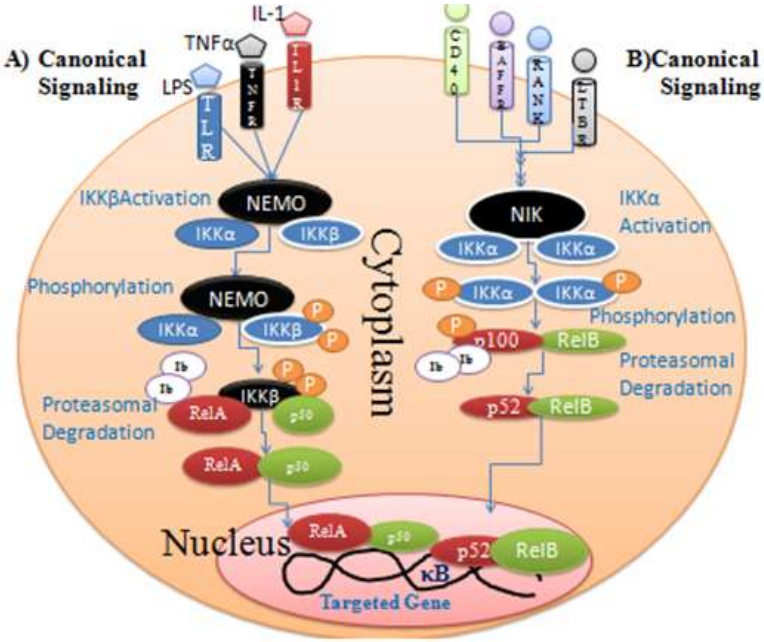

Fig. 2: NF-κB Signaling Pathways

(Abbreviations: LPS, lipopolysaccharides; IL-1, interleukin-1; or TNFα, tumor necrosis factor α; TLRs, Toll-like receptors; IL-1R, interleukin-1 receptor and TNFR, tumor necrosis factor receptor; NEMO, NF-κB essential modulator; IκB, Inhibitor of kappa B;IKK, IκB kinase; κB, kappa B chain; NIK, NF-κB-inducing kinase; BAFFR, B-cell activation factor; CD40,Cluster of Differentiation 40; RANK, Receptor Activator for Nuclear factor kappa B; LTβR, lymphotoxin β-receptor)

In the non-canonical Signaling pathway, NF-κB-inducing kinase activates to IKKα through activation of B-cell activation factor, CD40, receptor activator for nuclear factor kappa B or lymphotoxin β-receptor. These activated IKKα then further phosphorylate p100 on S866 and S870 serine residues. This phosphorylation leads to proteasomal processing to p52 due to polyubiquitination of p100. The alternative or non-canonical pathway leads to the selective activation of p52: RelB dimers by inducing the processing of p100 precursor protein (15).

Translocation of NEMO to nucleus taken place under genotoxic stress, where it is sumoylated and subsequent ubiquitinated in the atypical NF-κB signaling pathway, this pathway is mediated by Ataxia Telangiectasia Mutated checkpoint kinase. Ataxia Telangiectasia Mutated and NEMO can then come back to the cytosol where they activate IKKβ (3).

4. NF-κB ACTIVATION in IIC

Several recent studies proposed that activation of NF-κB in the carcinogenic promotion and progression stages. The proliferative stage of the immortal cancer cell is represented by promotional stage and progression is determined by anti-apoptosis, angiogenesis, proliferation, invasion, and metastasis (Fig.3) (16).

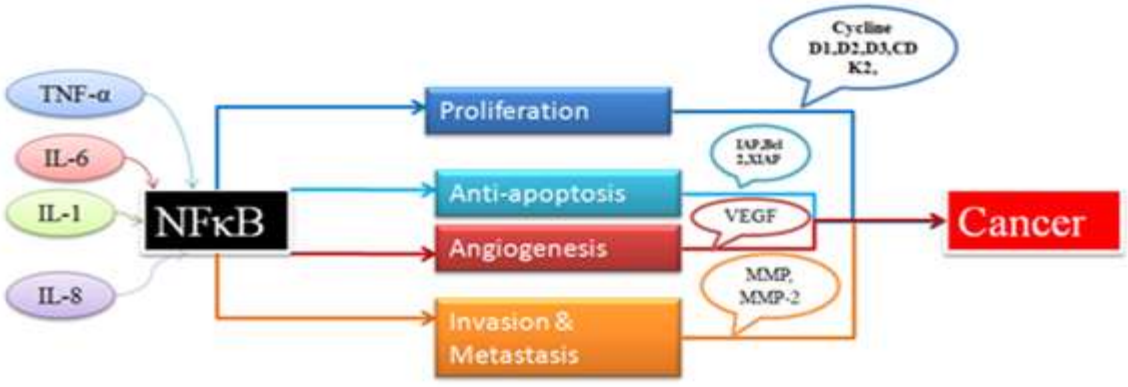

Fig. 3: NF-κB Activation in IIC

(Abbreviations: IAP, Inhibitor of Apoptosis Proteins; VEGF, Vascular Endothelial Growth Factor; MMP, Matrix Metallo Proteinases)

Constitutive activation of NF-κB, which is defined as persistence of NF-κB in the nucleus, is shown in a wide variety of tumor types, such as lymphoma, liver cancer, lung cancer, breast cancer, etc (17). Besides, it is activated in response to tobacco, alcohol, irradiation, stress, obesity, infectious agents, dietary agents and environmental stimuli that commonly contribute to carcinogenesis by controlling the expression of the genes that link with proliferation, invasion, angiogenesis, and metastasis of cancer. Based on this evidence, NF-κB is believed to be closely connected to the whole process of tumorigenesis (18).

NF-κB activation further upregulates major inflammatory factors, such as TNFα, IL-6, IL-1, IL-8, which are potent activators for NF-κB. Therefore it is believed that NF-κB and inflammation play a positive role to induce cellular and DNA damage, to promote cell proliferation and transformation. NF-κB is engaged in tumorigenesis by the promotion of cell proliferation and suppression of cell death. NF-κB controls some key cell cycle regulatory genes, including cyclin D1, cyclin D2, cyclin D3, cyclin E1, c-myc, CDK2, CDK4 and CDK6 (fig.3) (19).

The anti-apoptotic function of NF-κB is mainly achieved through the transcriptional regulation of an array of anti-apoptotic proteins, which can be divided into two groups. The first group mainly includes an inhibitor of apoptosis proteins, Ciap1, Ciap2, XIAP and CFLIP (20). The second group mainly refers to Bcl-2 family members, including Bcl-2 and Bcl-xL (21). The production of important antiapoptotic proteins has been demonstrated to occur during the carcinogenic promotion (22). NF-κB also regulates expression of several angiogenic factors. Macrophages and tumor cells are responsible to produce vascular endothelial growth factor under the control of NF-κB activation (23) and vascular endothelial growth factor promotes the proliferation and migration of endothelial cells. During the inflammation, leukocytes regulate the expression of the chemokine IL-8 by NF-κB and IL-8 having a role in a blood vessel for their growth factor in tumor tissue (24). Therefore, NF-κB is a main key player in IIC promotional stages, depending upon its role, it can be stimulated or inhibited in the treatment of malignancies.

Cancer invasion and metastasis strongly influence a patient's prognosis, and changes in the extracellular matrix as a result of inflammation. An inflammatory cell produces Matrix metalloproteinase's, which are key players in the degradation of extracellular matrix and basement membranes, so having important in tumor invasion. NF-κB activation can lead to regulation and expression of gelatinases (MMP-2 and MMP-9), these are prognostic factors in many solid tumors. The clinical application of an MMP inhibitor aimed at preventing metastasis is expected in the treatment of malignancies (25).

5. COLLABORATION BETWEEN NF-κB and STAT3: AN OPPORTUNITY

Global chromatin binding surveys revealed that STAT3 binds at least 3,000 different gene promoters and the number of genes targeted by NF-κB family members is even larger. During tumorigenesis, NF-κB and STAT3 control both distinct and overlapping groups of genes. This can be explained in part by the distribution of NF-κB and STAT3 binding sites in the regulatory regions of such genes. For instance, a gene that contains both NF-κB and STAT3 binding sites may be regulated by both factors in a cooperative manner (5).In addition to binding to adjacent sites in the control regions of shared target genes, RelA/p65 and p50 (NF-κB family members), found to physically interact with STAT3 (26). This interaction may result in either specific transcriptional synergy or repression of NF-κB/STAT3 regulated genes. There are several scenarios for the STAT3: NF-κB interaction. First, STAT3, sensibly in its unphosphorylated form can bind to NF-κB complex with IκB, displace IκB from NF-κB and facilitate NF-κB activation and nuclear entry even in the absence of conventional IKK signaling (5). Second, certain NF-κB induced inhibitory proteins, such as IκBζ, can bind to STAT3 and inhibit its binding to DNA (27). Third, STAT3 may interact with p65 RelA/p65 in the nucleus and recruits the p300 histone acetylase (HAT) to the complex that increases its nuclear retention and thereby prolong its transcriptional activity. This means that STAT3 can prolong the presence of active NF-κB in the nucleus but it is unable to in the absence of upstream NF-κB activating signals Since NF-κB activation is tightly regulated (28).

The activation and interaction between STAT3 and NF-κB are observed in different human cancers such as colon, stomach, and liver cancers. The interaction between these two transcription factors plays a very important role in regulating the communication between inflammatory cells and cancerous cells. They can also control the capacity of pre-neoplastic and malignant tumor cells to resist immune surveillance by regulating apoptosis, angiogenesis, and tumor invasion. By understanding the molecular mechanisms of NF-κB and STAT3 cooperatively in carcinogenesis will provide opportunities for the design of novel anticancer drugs (29).

6. NF-κB IN APOPTOSIS OF CANCER CELLS AND PRO-DEATH ACTIVITY

Although NF-κB is best known for its ability to antagonize programmed cell death, it should be noted that it can be pro-apoptotic in certain cells and in response to certain stimuli (30). Apoptosis is another corridor of programmed cell death; controlled and energy-dependent process, its deregulation can lead to cancer, autoimmune and degenerative diseases; explaining the increasing interest in elucidating the apoptosis pathways for disease etiology and therapeutic modulation. It occurs through the intrinsic and extrinsic pathway (fig.4 & 5). Caspase is an enzyme responsible for initiation of apoptosis process, it can be modulated by several endogenous cellular factors like, inhibitors of apoptosis proteins, having baculovirus inhibitor repeat domain which binds & inhibits active caspase (31).

There are distinct NF-κB transcriptional targets that were implicated in caspase activation by modulating the mitochondrial and death receptor apoptotic pathways through p53 tumor suppressor, death receptor Fas, TNFα, TRAIL receptors DR4, DR5, DR6 and the pro-apoptotic Bcl-2 family members Bcl-xS and Bax. A recent study shows the interesting way whereby the typically anti-apoptotic NF-κB subunit RelA can behave as a pro-death factor in response to certain stimuli (32).

Intrinsic pathway or the mitochondrial pathway

This pathway mainly activated through mitochondria via the loss of growth factor signals or DNA damage, oxidative stress, hypoxia, or chemotherapeutic drugs. Mitochondrial intermembrane space contains many proteins that involved in cell death induction, i.e. cytochrome C and apoptosis-inducing factors. All stimuli cause the change in the inner mitochondrial membrane permeability, loss of mitochondrial transmembrane potential and release of pro-apoptotic proteins from the intermembrane space into the cytosol. After release into the cytoplasm, cytochrome C stimulates apoptosome formation (a complex including apoptotic protease-activating factor) followed by activation of caspase 9. The 'initiator' caspase 9 causes the activation of the 'executioner' caspases (3, 6, 7), which cleave vital substrates, resulting in cellular death (Fig.4). The intrinsic pathway is controlled by interactions between proapoptotic and antiapoptotic members of the Bcl-2 protein family. (33)

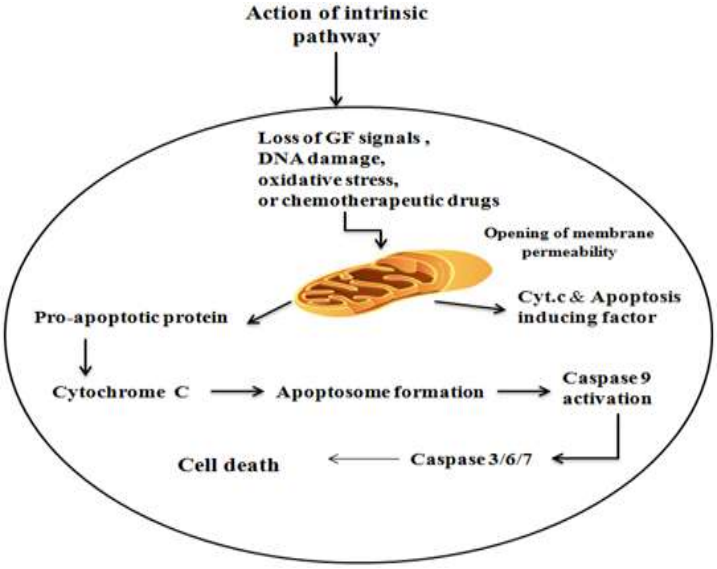

Fig. 4: Intrinsic Apoptosis Pathway

Extrinsic pathway

The extrinsic pathway is regulated by the transmembrane death receptors through specific ligands released by other cells. Death receptors may belong to the tumor necrosis factor family (TNF) and have a cysteine-rich extracellular subdomain called the "death domain" (DD), which plays a significant role in transmitting the death signal from the cell surface to the intercellular pathways. There are, six death receptors are present, including TNF receptor 1, Fas, DR3, TNF-related apoptosis-inducing ligand receptor 1 (TRAIL-R1), TRAIL-R2 and DR6.

The binding of transmembrane death receptors with their specific ligands will initiate the extrinsic pathway. After its initiation, death domain bind to the adaptor protein Fas-associated death domain (FADD) to form the death-inducing complex (DISC) with the recruitment of pro-caspase 8. These, pro-caspase 8 is proteolytically activated and acts as the 'initiator' caspase, further activating downstream effectors proteins such as caspase 3 and 7 to initiate apoptosis (Fig.5) (33).

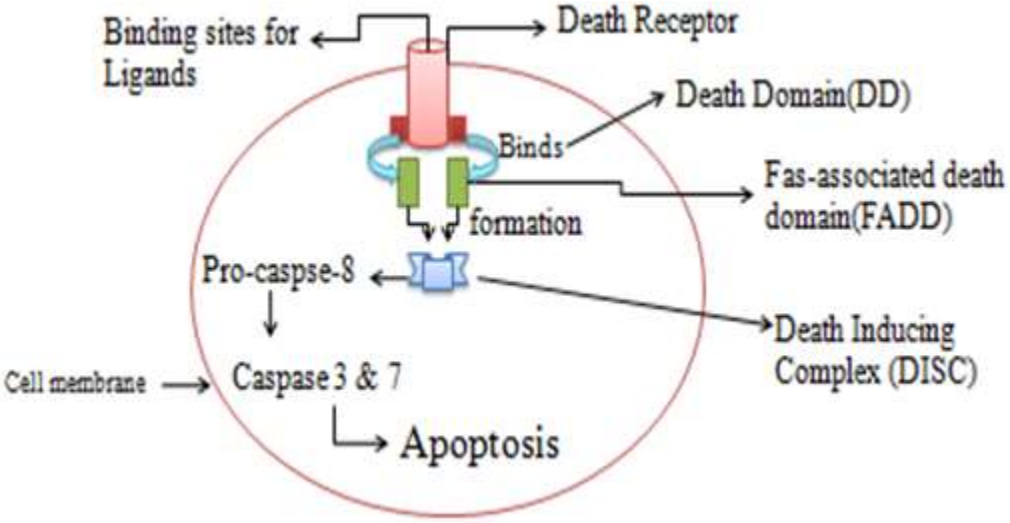

Fig. 5: Extrinsic Apoptosis Pathway

Targeting of RelA to the nucleolus was recently suggested as a novel means to antagonize its transcriptional and anti-apoptotic activities in colorectal cancer cells treated with aspirin, serum deprivation, or UV-C radiation (34). Although others previously reported that aspirin suppresses NF-κB activation by interfering with the activity of the IKK complex (35).

7. THERAPEUTIC APPROACHES FOR TARGETING NF-κB

The pivotal role of the NF-*κ*B pathway in the inhibition of apoptosis, tumor promotion, and progression, and the observation that NF-*κ*B is constitutively activated in a large number of epithelial and hematologic malignancies, strongly suggest that NF-*κ*B inhibitors would be useful in cancer therapy. Strategies for blocking NF-*κ*B include an upstream strategy and an NF-*κ*B targeting strategy (36). The upstream strategy involves blocking the activation of NF-*κ*B signaling pathway using: (a) proteasome inhibitors (such as PS-341- Bortezomib, MG132); (b) IKK inhibitors (such as NSAIDs, sulfasalazine, arsenic trioxide, curcumin, thalidomide); (c) cell-permeable peptides (such as SN-50); (d) antioxidants (such as disulfiram, glutathione) (37); or (e) the recombinant adenovirus-mediated overexpression of the I*κ*B*α* gene. On the other hand, the NF-*κ*B targeting strategy includes: (a) blocking the DNA binding of NF-*κ*B using decoy oligodeoxynucleotides (38); (b) blocking the transactivation of NF-*κ*B using glucocorticoids (39); or (c) interfering with NF-*κ*B mRNA using NF-*κ*B antisense oligonucleotide. So far, one success story is Bortezomib (formerly PS-341), a specific proteasome inhibitor capable of suppression NF-κB activation, has obtained FDA approval for treatment of multiple myeloma (40).

Nevertheless, combining classical chemotherapeutics with inhibitors of NF-κB activation seems to result in promising synergies. Most anti-cancer drugs are cytotoxic agents that drive proliferating cells into apoptosis by interfering with DNA synthesis. Elevated NF-κB activity in cancer cells provides a survival mechanism by up-regulating anti-apoptotic genes, thereby representing a major causative factor for drug resistance (41). The combination of NF-κB inhibitors with anti-androgen therapy is more responsible for the killing of prostate cancer cells and slower the recurrence of cancer. Whereas, NF-κB inhibitors combined with radiotherapy revealed that, radiation upregulate the NF-κB which is responsible for promoting the cancer cells survival (42).

Many natural products involved in anti-cancer and anti-inflammatory activity have been shown to inhibit NF-κB. Costunolide inhibits the activation of Akt and NF-κB and the expression of antiapoptotic factors of B-cell lymphoma-extra-large and X-linked inhibitor of apoptosis protein in 11Z cells (43), magnolol inhibits ERK1/2 phosphorylation and NF-κB translocation (44). There are many antioxidant compounds such as thiol antioxidants, calcium chelators, vitamin C and E derivatives, and alpha-lipoic acid are used to inhibit hydrogen peroxide- or stimulus-induced NF-κB activation. Presumably, they also act by scavenging reactive oxygen species (45). In addition, inhibitors of mitochondrial electron transport that suppress ROS production (like rotenone) or overexpression of antioxidizing enzymes, such as MnSOD and catalase, can block TNF-α-induced activation of NF-κB. Caffeic acid phenethyl ester, a phenolic antioxidant and a structural relative of flavonoids, may directly interfere with DNA binding by NF-κB. The low dose of aspirin is effective in preventing certain types of cancer, particularly colorectal cancer and also cardiovascular diseases (46). At higher concentrations, aspirin also been blocks NF-κB activity by directly binding and inhibiting the kinase activity of IKKβ by reduction of binding ability to ATP. It also inhibits the proteasomal activity and interferes with degradation of IκB (47). As such, high-dose aspirin therapy may have applications to diseases where NF-κB activity is involved, including cancer, diabetes and heart disease (48). Glucocorticoids inhibit NF-κB signal pathway through inhibition of DNA binding activity, and IKK activity and transactivation (49). Several reports have shown that Cyclosporine A (CsA), an inhibitor of B- and T-cell proliferation by blocking the activity of calcineurin, inhibits NF-κB induction (50).

Several studies proved that NF-κB is responsible for activation of oncogenic factors in inflammation-induced cancer. By inhibiting its activation pathway with anti-inflammatory agents can act as supportive therapy in cancer treatment. Combining anti-inflammatory approaches with anticancer therapy may provide more effective treatment to suppress tumor progression as well as improve the survival rate of patients. These strategies designed to synergize the pro-apoptotic effect of NF-κB rather than trying to inhibit, it can prove to be a better option in the management of malignancies.

8. CONCLUSION

NF-*κ*B is activated by inflammatory stimuli and its constitutive activation plays a critical role in the expression of a large number of genes that regulate immune responses, cell growth, proliferation, survival, apoptosis and pro-apoptotic. Abnormal NF-κB activation leads to the development of inflammation-induced cancer and various disorders. Hence, inhibition of NF-*κ*B signaling appears to be a potential therapeutic target for clinical application in inflammatory and cancer management.

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