Beginning with its discovery in 1986 and continuing through the present, transcription factor NF-kappa B (NF-kB) has attracted widespread interest based on its unusual regulation, the variety of stimuli that activate it, the diverse genes and biological responses that it controls, the striking evolutionary conservation of structure and function among family members and its apparent involvement in a variety of cellular responses. The NF-kB family contains p50, p52, p65 (RelA), c-Rel, and RelB proteins, which form various homo- and heterodimers. Of them, the most common active forms are p50/RelA or p52/RelA heterodimer. Dimerization of various NF-kB subunits produces complexes with different DNA-binding specificities and transactivation potential. Each member of the NF-kB family has a conserved N-terminal region called Rel-homology domain (RHD), which contains the dimerization, nuclear localization, and DNA-binding domains (Fig.1). The p50 and p52 proteins are formed by the proteolytic degradation of their precursor proteins p105 and p100 respectively. Among the five members of NF-kB family, proteins p65, RelB and c-Rel contain a C-terminal transactivation domain, which strongly activate the transcription of the target genes. Other members of the family, such as p50 and p52 proteins, lack the transactivation domain but the homo-dimers of these proteins still bind to the NF-kB consensus sites in DNA, and hence act as transcriptional repressor by blocking the consensus sites. While p50 and p65 proteins are ubiquitously expressed, the expression of other members of NF-kB family proteins is mostly restricted to hematopoietic cells and the cells of immune system. In addition the transcription of RelB, c-Rel and p105 is regulated by NF-kB.

NF-kB activation

In most cell types, inactive NF-kB complexes are sequestered in the cytoplasm via their interaction with inhibitory proteins known as I kappa Bs (IxBs). In response to multiple stimuli, including cytokines, viral and bacterial pathogens, and stress-inducing agents, the latent cytoplasmic NF-kB/IxB complex is activated by the proteolytic cleavage of IxBs, leading to the release of the NF-kB transcription factor into the nucleus. Once translocated, NF-kB binds to specific DNA sequences called NF-kB sites, located in the promoters of target genes, and activates their transcription.

Abbreviations used:

- NF-kB: Nuclear factor-kappa B
- IxB: I kappa B
- IKB: Inhibitor of kappa B
- IL: Interleukin
- TNF: Tumor necrosis factor
- NIK: NF-kB-inducing kinase
- NEF: Nuclear factor of activated T-cells
- MEK: Mitogen-activated protein kinase kinase
- MEKK: Mitogen-activated protein kinase kinase kinase
- NEMO: NF-kB essential modulator
- ICAM: Intercellular adhesion molecule
- VCAM: Vascular cell adhesion molecule
- COX: Cyclooxygenase
- iNOS: Inducible nitric oxide synthase
- RHD: Rel-homology domain
- LTR: Long terminal repeat
- IP: Incontinence pigmenti
- RA: Rheumatoid arthritis
- RANTES: Regulated activation in normal T cells, expressed, and secreted
- NSAIDS: Non-steroidal anti-inflammatory drugs
activated by phosphorylation on conserved serine residues at the N-terminal portion of IκB; this modification occurs at Ser 32 and Ser 36 in the case of IκBa. Phosphorylation targets IκBα for ubiquitination by the SCF-ubiquitin ligase complex, which leads to degradation of the inhibitory subunit by the 26S proteasome. This process activates NF-κB, which then translocates to the nucleus and binds to its cognate DNA-binding site (5'-GGGRNNYYCC-3') in the promoter or enhancer regions of specific genes (Fig. 2).

Fig. 1—Members of the NF-κB and IκB families of proteins. The arrow points indicate the endoproteolytic cleavage sites of p100/p52 and p105/p50. The number of amino acids in each protein is shown on right. (RHD, Rel-homology domain; N, nuclear localization sequence; TAD, transactivation domain; LZ, leucine-zipper motif; GRR, glycine-rich region; ANK, ankyrin repeat domain).

Fig. 2—NF-κB activation pathway. NF-κB heterodimers (p50/RelA) are sequestered in the cytoplasm by IκB inhibitory proteins (IκBa). Stimulation by divergent agents leads to the activation of signaling cascades converging on the IKK complex. Phosphorylation of IκBa by activated IKK is a signal for its ubiquitination and proteasome-dependent degradation. This event unmasks NF-κB, which is then free to translocate to the nucleus, where it binds to κB elements and activates the transcription of a variety of genes involved in various cellular responses.
NF-κB activation represents the terminal step in a signal transduction pathway leading from the cell surface to nucleus. A seminal event in the activation of NF-κB is the phosphorylation of IκB, which is mediated by a multimeric complex, referred to as the IκB kinase (IKK) complex. The IKK complex consists of two catalytic subunits (IKKα and IKKβ) and the NF-κB essential modulator alternatively referred to as NEMO or IKKγ. Although IKKγ is not itself a kinase per se, it is absolutely essential for NF-κB activation by multiple stimuli. Activation of a predominant form of IKKβ is mediated via phosphorylation of either IKKα or IKKβ by the upstream kinases, including NF-κB-inducing kinase (NIK) and MEKK1 of the MAP3K family. The activated IKK complex recruits IκB proteins and phosphorylates them at serine residues.

In the classical pathway, the activation of IKK is considered a major mechanism of NF-κB activation, however, in certain cases such as in response to short-wave UV light, peroxanate, H2O2, hypoxia/reoxygenation, nerve growth factor, erythropoietin, and HER-2 protein, the activation of NF-κB does not seem to involve phosphorylation of IκB by IKK or even IκB degradation. A number of NF-κB-regulated target genes involved in immune and inflammatory responses, cellular proliferation, the anti-apoptotic response, and other cellular functions have been identified. NF-κB has also been shown to regulate the expression of anti-inflammatory genes during the resolution of inflammation in vivo. Although, the functionally important NF-κB-binding sites have been located in the promoter/enhancer region of a number of genes, the transcription of individual genes and the amount of transcribed product after NF-κB activation under specific circumstances depend on many factors, including the composition of NF-κB dimers, the nature of the NF-κB-activating stimulus, and the number of consensus sites in the target gene. Additionally, NF-κB works in cooperation with other transcription factors, in particular, activator protein-1 (AP-1).

**Gene deletion studies of NF-κB signaling proteins**

The physiological functions of various proteins of NF-κB signaling pathway have been studied by targeted disruption of individual gene (Fig. 4). These studies have revealed both specific and redundant functions of each member of NF-κB family proteins in the regulation of innate and adaptive immune responses and in the cell survival. The deletion of RelA (p65) gene in mice causes embryonic lethality due to extensive apoptosis in liver, which indicates that the function of RelA (p65) cannot be compensated for by other NF-κB family proteins and is indispensable for the survival of the mouse embryo. Despite the essential role of RelA in prevention of TNF-induced apoptosis in liver, RelA is not involved in the development of T cells. However, RelA−/−T cells showed reduction in the proliferative responses to various stimulators.

On the other hand, mice lacking p50 or RelB are immunodeficient but otherwise develop normally to adulthood. Mice lacking other NF-κB proteins, including c-Rel and p52, also have defective immune functions. The knockout of multiple members of NF-κB family result in even more severe phenotypes, which suggests that there might be some functional redundancy between the NF-κB family members.

The gene-targeting experiments have also revealed the importance of other key components of NF-κB signaling pathways in mouse development. Although, both IKKα and IKKβ are necessary for survival of mouse embryos, their role in embryonic development and survival are quite different. IKKα has a unique function in skin and skeletal development, as well as in B cell maturation, and its absence cannot be compensated for by IKKβ. In contrast, IKKβ appears to play an indispensable role in inducible NF-κB activation in response to pro-inflammatory and pro-apoptotic stimuli. Lack of IKKβ leads to embryonic lethality and liver degeneration in knockout mice similar to RelA knockout mice. Severe liver degeneration and early lethality have also been observed in embryos that are deficient in the IKK-γ/NEMO subunit of IKK complex.

**Involvement of NF-κB in human diseases**

The gene knockout studies have clearly established that NF-κB family proteins are essential for development of various tissues and to protect the cells from apoptosis. However, the research done in past decade has shown that abnormal activation of NF-κB is involved in pathogenesis of a number of human diseases including those related to inflammation, enhanced cellular proliferation, viral infection, and genetic diseases (Fig. 5). Although, the complete description of NF-κB-related diseases is beyond the scope of this review, we highlight here the evidences of abnormal activation of NF-κB in some important human diseases.
Fig. 3—NF-κB regulated genes. Genetic and biochemical studies have led to the identification of number of genes which are directly regulated by NF-κB. Many of the NF-κB regulated genes are listed here. It is important to note that activated NF-κB does not lead to increased expression of all target genes. The transcriptional activity of NF-κB depends on many factors including the nature of stimulus, the composition of NF-κB complex, and the activity of several other accessory transcription factors. [NF-κB, nuclear factor-kB; CINC, Cytokine-induced neutrophil chemoattractant; Gro, Growth regulated oncogene; ICOS, Inducible co-stimulator; IFN, Interferon; IL, Interleukin; LT, Lymphotoxin; MCP, Macrophage chemotactic protein; MIP, Macrophage inflammatory protein; LAG, Lymphocyte activation gene; RANTES, Regulated upon Activation Normal T lymphocyte Expressed and Secreted; TCA, T-cell activation; TNF, Tumor necrosis factor; TRAIL, TNF-related-apoptosis-inducing ligand; MHC, Major histocompatibility antigen; NOD, Nucleotide-binding oligomerization domain protein; TAP, transporter associated with antigen processing; LMP, Low molecular mass polypeptide; ICAM, Intercellular adhesion molecule; MadCAM, Mesosalven address cell adhesion molecule; VCAM, Vascular cell adhesion molecule; LBP, Lipopolysaccharide binding protein; PTX, Pentraxin; SAα, Serum amyloid A protein; COX, Cyclooxygenase; CYP2C11, Cytochrome p450 2C11; iNOS, Inducible nitric oxide-Synthase; MAPK, mitogen-activated protein kinase; MsdO, Manganese superoxide dismutase; EGFR, Epidermal Growth Factor Receptor; Lox, Receptor for oxidized low density lipoprotein; Mdr, Multiple drug resistance; NMDA, N-methyl-D-aspartate; PAF, Platelet-activating factor; RAGE, Receptor for Advanced Glycation End products; Bcl, B-cell lymphoma; FADD, Fas-associated death domain protein; FLICE, FADD-like IL-1-converting enzyme; cFLIP, Cellular FLICE interacting protein; IAP, Inhibitors of apoptosis; IEX, Radiation-Inducible immediate-early gene; TRAF, TNF-receptor associated factor; NGQ, NAD(P)H quinone oxidoreductase; BMP, Bone morphogenetic protein; G-CSF, Granulocyte colony stimulating factor; GM-CSF, Granulocyte-macrophage colony stimulating factor; M-CSF, Macrophage Colony Stimulating Factor; EPO, Erythropoietin; IGFIRP, Insulin-like growth factor binding protein; NκR-1, Neurokinin-1 receptor; NK4, Natural killer cell transcript 4; PDGF, Platelet-derived growth factor; TSP, Thrombospondin; THBS, Thrombospondin; VEGF, Vascular endothelial growth factor; Egr, Early growth response; TGF, Transforming growth factor; TIEG, TGF-beta-inducible early gene; ELYS, Embryonic large molecule derived from yolk sac; IRF, Interferon regulatory factor; IκB, Inhibitor of NF-κB; Mill, Molecule possessing ankyrin repeat induced by lipopolysaccharide; Nur, Orphan receptor of the nuclear receptor; STAT, Signal transducer and activator of transcription; Wt1, Wilms' tumour gene 1; GMV, Cytolesinaviruses; EVB, Epstein-Barr virus; HBV, Hepatitis B virus; HIV, Human immunodeficiency virus; HSV, Herpes simplex virus; HPV, Human Papilloma virus; SIV, Simian immunodeficiency virus; SV-40, Simian virus-40; ADH, Alcohol dehydrogenase; ABC transporter, ATP-binding cassette transporter; ARFRP, ADP-ribosylation factor-related protein; CRAD, cis-retinoicoidandrogen dehydrogenase; ENO, Enolase; GADD45, Glutamic acid decahydroxyan 67; GD3, GD3 synthase; GSTP1-1, Glutathione S-transferase P1-1; HO, Hemoxgenase-2; LOX, Lipoxygenase; L-PGDS, Lipoxygenase type prostaglandin D synthase; MKP, MAP kinase phosphatase; MMP, matrix metalloproteinase; PDE7A1, Phosphodiesterase 7A1; P5, Protein phosphatase 5; PLC, Phospholipase C; PKC, Protein kinase C; PTGIS, Prostaglandin synthase; PGES, prostaglandin E synthase; RACK, Receptor for activated C kinase; TERT, Telomerase reverse transcriptase; AMH, Anti-Müllerian hormone; Gadd45, Growth arrest and DNA damage; CIF, Growth inhibitory factor; BmgH4, High mobility group 14; Mst1, Multiple tumor suppressor; p11, Annexin B ligand; Pax, Paired box; PCID, 6-pyruvyltetrahydropterin synthase; PFK, Phosphofructokinase; mGSTM3, Pregnancy-specific glycophorin; Rho, Receptor-interacting protein kinase; RICK, Rip-like interacting caspase-like apoptosis-regulatory protein kinase; TRP1, Tissue factor pathway inhibitor; UBEM, Ubiquitin conjugating enzyme E2M; UCP, Uncoupling protein]
Cancer — The ability of NF-κB to suppress apoptosis and to induce expression of proto-oncogenes such as c-myc and cyclin D1, which directly stimulate proliferation, suggest that NF-κB may participate in many aspects of oncogenesis. NF-κB also regulates the expression of various molecules such as cell adhesion proteins, matrix metalloproteinases, cyclooxygenase-2 (COX-2), iNOS, chemokines, and inflammatory cytokines, all of which promote tumor cell invasion and angiogenesis. Indeed, constitutive NF-κB activity has been observed in a number of human cancers, including breast cancer, non-small cell lung carcinoma, thyroid cancer, T- or B-lymphocyte leukemia, melanoma, colon cancer, bladder cancer, and several virally-induced tumors, and inhibition of NF-κB abrogates tumor cell proliferation. Chromosomal alterations of NF-κB family genes provide additional evidence for the role of NF-κB in oncogenesis. It has been shown, for example, that genes encoding RelA, c-Rel, NF-κB1 (p105/p50), and NF-κB2 (p100/p52) proteins are all located within breakpoint regions of the genome that are involved in oncogenic rearrangements or amplifications. Although it is widely accepted that inhibition of NF-κB triggers apoptosis in many tumor cell types, there are a few exceptions in which NF-κB activation blocks malignant growth. Inhibition of the NF-κB pathway results in both increased basal frequency of apoptotic cells and the spontaneous development of squamous cell carcinomas. NF-κB and oncogenic Ras both induce cell-cycle arrest in normal human epidermal cells. The cell-cycle arrest by oncogenic Ras can be bypassed by inhibition of NF-κB through the overexpression of IκBα protein, which results in malignant epidermal tissues resembling squamous cell carcinomas. These findings thus suggest that NF-κB can play a different role in the regulation of cell growth in tissue-context-dependent manner.

Fig. 4 — Effect of genetic deletion of NF-κB signaling proteins in mice. Genes that encode members of the NF-κB signaling pathway have been deleted by homologous recombination in mice. These mice models indicate the distinct roles of the NF-κB signaling proteins in regulation of innate and adaptive immune responses, lymphocyte functions and cell survival.
AIDS—Although, NF-kB activation during viral infection has been interpreted as a protective response of the host to viral infection, some viruses including HIV have evolved strategies to interfere with NF-kB activation to evade the immune response. The promoter/enhancer region of HIV-1 LTR contains two adjacent NF-kB binding sites that play a central role in inducible HIV gene expression. High levels of viral gene expression and replication result in part from the activation of NF-kB, which in addition to orchestrating the host inflammatory response also activates the HIV-1 long terminal repeat (LTR). Indeed, transdominant mutants of IκBa that block NF-kB induction also inhibit de novo HIV-1 infection in T cells by interfering with viral replication, suggesting that NF-kB promotes the pathogenesis of HIV-1 in infected cells.

Asthma—Asthma is a chronic inflammation of the bronchial tubes (airways) that cause swelling and narrowing (constriction) of the airways. The pathogenesis of asthma involves persistent expression of a broad array of genes, such as those encoding pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes. Most of these genes contain the consensus NF-kB binding sites within their promoters suggesting that NF-kB plays a major role in the initiation and perpetuation of allergic inflammation. Indeed, increased NF-kB activity has been observed in the key locations in the airways of asthmatic patients and animal models of asthma. Furthermore, agents, such as allergens, ozone, and viral infections, which are associated with exacerbation of asthma, stimulate activation of NF-kB. Higher activation of NF-kB has been observed in vitro in asthmatic bronchial epithelial cells on exposure to certain allergens known to cause asthma. Treatment of A549 cells (a human type II-like alveolar epithelial cell) with ozone increases the activation of NF-kB and the transcription of the IL-8 chemokine. About 80% of asthma exacerbations in school-aged children

![Fig. 5—Major physiological and pathological roles of NF-kB. Different studies indicate that NF-kB family proteins are essential for normal T and B cell development and their proliferation (indicated in green), but its deregulation leads to various diseases (indicated in red).](image-url)
and half of all asthma exacerbations in adults are associated with viral upper respiratory infection, and the majority of viruses isolated are rhinoviruses. Rhinoviruses activate NF-κB in various cell types and induce the expression of ICAM-1 in bronchial epithelial cells. ICAM-1, besides playing an important role in the recruitment of inflammatory cells, also acts as a receptor for rhinovirus. Respiratory syncytial virus (RSV), which is also involved in the perpetuation of asthma phenotypes, is also a potent inducer of NF-κB and expression of IL-8 gene in A549 cells. The activation of NF-κB also induces the proliferation of airway smooth muscle cells that results in further airway narrowing and hyper-responsiveness in asthmatic subjects. Moreover, inhaled glucocorticoids are first-line of treatment of asthma. Glucocorticoids are potent inhibitors of NF-κB activation in mice and cultured cells. Glucocorticosteroids have also been shown to inhibit the activation of NF-κB in asthmatic patients. Beside corticosteroids, recent evidence also supports the beneficial effects of other NF-κB inhibitory molecules in asthmatic animals.

**Cardiac diseases**—Heart failure is the final consequence of many underlying disease states such as hypertension, cardiac hypertrophy, coronary heart disease, arrhythmia, viral myocarditis, and mutation in cytoskeleton protein encoding genes. Strong evidence suggests that inflammatory response participates in the development of heart failure. Augmented activation of NF-κB and expression of NF-κB-regulated pro-inflammatory genes such as TNF-α, IL-β, IL-6, IL-8, and iNOS have been reported in experimental and human heart failure regardless of etiology. NF-κB plays an almost exclusive role in ischemia/reperfusion and in the early phase of myocardial infarction. In a rat in vivo model of ischemia/reperfusion, NF-κB activity increased biphasically, with peak levels occurring after 15 min and 3 hr. Inhibition of NF-κB by introduction of NF-κB decoy cis element in vivo significantly reduced infarct size in ischemia and reperfusion. Cardiac hypertrophy, which involves increase in cardiac protein synthesis and cell growth, is a major risk factor for heart failure and death. NF-κB seems to play an essential role in the induction of cardiac hypertrophy in response to both biomechanical strain and neurohormonal stimuli. The activation of NF-κB is increased in response to several hypertrophic agonists such as phenylephrine, endothelin-1, angiotension II, and myotrophin in cultured rat primary neonatal ventricular cardiomyocytes, whereas the inhibition of NF-κB reduces cardiac hypertrophy. These studies collectively suggest that the NF-κB signaling pathway may play a critical role in induction and/or manifestation of several heart-related ailments.

**Incontinentia pigmenti**—Until recently, no genetic disease caused by NF-κB dysfunction was known. However, emerging reports suggest that mutations in genes of some of the core components of NF-κB signaling pathway can cause genetic abnormalities in human gender death, which is antenatally lethal in male newborns. Affected females with only one copy of the abnormal gene show skin pigmentation abnormality in four characteristic stages that starts with erythematous skin lesion and ends with hypopigmentation and atrophy. It has been recently shown that IP in humans is caused by deletion of exons 4-10 of IKKγ/NEMO gene, which prevents the expression of functional IKKγ protein and therefore, the NF-κB response. This leads to death in male fetuses, while female fetuses can compensate by selective X-chromosomal inactivation. These findings have been confirmed in male IKKγ/NEMO knockout mice, where the NF-κB activation by pro-inflammatory cytokines is completely blocked. Heterozygous females develop skin lesions with hyper-proliferation and increased apoptosis of keratinocytes.

**Other diseases**—Besides the diseases indicated above, the abnormal activation of NF-κB has been linked with several other diseases such as atherosclerosis, arthritis, inflammatory bowel disease, muscular dystrophy, bone resorption, multiple sclerosis, Alzheimer’s disease, type I and II diabetes, viral infections and inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis. Till recently, it has been suggested that NF-κB might not be involved in the initiation of the pathological state but it plays a major role in the perpetuation of the disease state. However, we have recently observed that in skeletal muscles of mdx mice (a mouse model of Duchenne muscular dystrophy), the DNA-binding activity of NF-κB and the expression of NF-κB-regulated inflammatory cytokines such as TNF-α and IL-1β starts increasing even before the clinical onset of muscular dystrophy. We have also observed that the activation
of NF-κB in many diseased states such as muscular dystrophy and cardiomyopathy, the activation of NF-κB is not associated with the degradation of NF-κB inhibitor protein IκB (our unpublished observations) indicating that different mechanisms might be involved in the activation of NF-κB in some human diseases.

Clinical application of inhibition of NF-κB

From the observations above, one may think that inhibitors of NF-κB possess a great therapeutic potential in individuals with cancer, HIV-1 infection, and a wide variety of inflammatory diseases. In addition to its direct role in tumor development, the activation of NF-κB by chemotherapeutic drugs and ionizing radiation provides a strong anti-apoptotic signal that reduces the efficiency of many common cancer therapies. Therefore, such inhibitors could also have a role in the treatment of many cancers in which aberrant NF-κB activation does not represent one of the underlying causes of the original tumor. A large number of commonly used anti-inflammatory drugs have been shown capable of inhibiting NF-κB, although the efficiency with which this is accomplished in the clinical setting is, in most instances, yet to be demonstrated. Relatively well-defined mechanisms exist to deactivate NF-κB after it has been activated in response to different stimuli, thus serving as molecular 'brakes' to the ongoing NF-κB activation. Both molecular and pharmacological approaches have been used to inhibit the spurious activation of NF-κB in response to inflammatory cytokines and in some disease states.

Molecular strategies—Several molecular level strategies exist to inhibit NF-κB activation, including transgenic animals, decoy oligonucleotides, and gene transfer strategies. The first evidence that NF-κB pathway can be inhibited comes from studies of IκBα mutant, which is not phosphorylated by IKK and is not degraded by proteasome. This IκBα mutant have a dominant negative phenotype because it sequesters NF-κB in the cytoplasm and therefore, prevent the induction of specific NF-κB target genes. Adenoviral vectors to deliver this IκBα super-repressor mutant have been effective in RA model systems. Similarly, such vectors reduce the resistance of tumors to chemotherapy in a mouse model. NF-κB has also been shown to be inhibited by intracellular delivery of NF-κB-specific 'decoy' oligodeoxynucleotide (ODN) both in in vitro studies and in various animal models of clinical diseases. The concept of ODN decoy is based on the fundamental principle that transcription factors are capable of binding specific DNA sequences in the promoter regions of genes (i.e., consensus binding sites). This specific binding can occur even in absence of surrounding genomic DNA which forms the basis of electrophoretic mobility shift assay. This same property has been applied to study gene expression by intracellular delivery of 'decoy' ODN that can bind specific transcription factors in an intact cell and inhibit their respective activity.

Pharmacological strategies—A number of pharmacologic agents are known to inhibit NF-κB at one or multiple activation steps of the signaling pathways (Table 1). Our group has contributed significantly to identifying the pharmacological compounds which are potent inhibitors of NF-κB and tumor growth. The immunosuppressive and anti-inflammatory actions of glucocorticosteroids have been shown to be mediated at least in part by the induction of IκBα synthesis. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, sodium salicylate, and leflunomide also inhibit endotoxin- and cytokine-induced nuclear translocation of NF-κB by preventing IκBα phosphorylation and proteolysis. Recently it has been shown that the inhibitory effects of aspirin and sodium salicylate result from the specific inhibition of binding of IKK-β to ATP. Several pharmaceutical companies are now involved in development of novel specific inhibitors of IKK. Some naturally occurring and synthetic inhibitors of ubiquitin-proteasome that can block NF-κB activation by preventing IκB degradation have also been identified. This includes: (a)-lactacystin, a streptomyces metabolite; (b)-peptide aldehydes, such as carboxbenzoxyl-leucinyl-leucinyl-leucinal-H (MG-132); and (c)-boronic acid peptides such as PS-341. Among the proteasome inhibitors, PS-341 is gaining increasing attention as being suitable for in vivo administration and relatively stable at physiological conditions. In phase I clinical trials, PS-341 has been shown to produce a significant antitumor response in chemo-resistant multiple myeloma.

Concluding remark

The NF-κB transcription factor family represents an important group of regulators of a broad range of genes involved in cellular responses to inflammatory and stress signals. Recently, the knockout mouse studies have revealed the key role for this family in
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| Interleukin-10 | Glucocorticoids | Dimethyldithiocarbamate | Prostaglandin | Atractyloside | Anti-inflammatory agents | Cell-signaling inhibitors | IKK inhibitors | Protease inhibitors | Antibody- and enzyme inhibitors | 15-Deoxyspergualin | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deoxy-12,14-PGJ2 | 15-Deo
broad physiological processes, including immune function and metabolism. Further, identification of specific components of the NF-κB signal transduction pathway provides an opportunity to define mechanisms at the biochemical level by which specific members of the NF-κB family are activated. Furthermore, this may identify specific targets for selective inhibition or promotion of NF-κB functions. Additional studies are required on mechanisms regulating specificity and selectivity of NF-κB function, as well as its role in different diseases, prior to potential clinical application.

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