REVIEW

Nuclear Factor-κB: a Key Regulator in Health and Disease of Lungs

**Sanjay Batra · Gayathriy Balamayooran ·
Malaya K. Sahoo**

Abstract Rel/NF-κB transcription factors play a key role in modulating the response of immunoregulatory genes including cytokines and chemokines, cell adhesion molecules, acute phase proteins, and anti-microbial peptides. Furthermore, an array of genes important for angiogenesis, tumor invasion and metastasis is also regulated by nuclear factor-κB (NF-κB). Close association of NF-κB with inflammation and tumorigenesis makes it an attractive target for basic research as well as for pharmaceutical industries. Studies involving various animal and cellular models have revealed the importance of NF-κB in pathobiology of lung diseases. This review (a) describes structures, activities, and regulation of NF-κB family members; (b) provides information which implicates NF-κB in pathogenesis of pulmonary inflammation and cancer; and (c) discusses information about available synthetic and natural compounds which target NF-κB or specific components of NF-κB signal transduction pathway and which may provide the foundation for development of effective therapy for lung inflammation and bronchogenic carcinomas.

Keywords NF-κB · Inflammation · Cancer · Lung

Introduction

Nuclear factor-κB (NF-κB) was first identified as a B-cell transcription factor protein that binds to the immunoglobulin heavy chain and the kappa light chain enhancers (Sen and Baltimore 1986, 1987). It is now known to comprise a family of ubiquitous proteins conserved from the fruit fly *Drosophila melanogaster* to humans. NF-κB controls the expression of more than 400 genes involved in a plethora of functions, such as immunoreceptor expression and expression of chemokines, cytokines, cell adhesion molecules, proliferation, transformation, apoptosis, angiogenesis, oxidative stress, invasion, and metastasis (Baeuerle and Henkel 1994; Giuliani et al. 2001; Kim et al. 2006; Lee and Burckart 1998). Extensive research has been carried out in the last few years to understand the role of NF-κB in inflammation and cancer in order to design strategies for blocking excessive NF-κB activity. This article focuses on NF-κB signaling pathways, emphasizing their role during pulmonary inflammation and cancer and their modulation with therapeutic agents.

Five mammalian NF-κB family members have been characterized and cloned. These are RelA (p65), RelB, c-Rel, NF-κB 1 (p50/p105), and NF-κB 2 (p52/p100) (Barkett and Gilmore 1999; Dutta et al. 2006; Ghosh et al. 1998; Hayden and Ghosh 2004; Jeong et al. 2004; Mercurio and Manning 1999; Nabel and Verma 1993; Pahl 1999; Shishodia and Aggarwal 2004). NF-κB family members share a highly conserved 300 amino acid Rel homology domain (RHD), responsible for their dimerization, binding to DNA and IκB (inhibitor of NF-κB) (Blank et al. 1992; Chen and Ghosh 1999; Gilmore 1990, 2006; Hayden and Ghosh 2004; Perkins and Gilmore 2006). The N-terminal part of the RHD contains the DNA-binding domain, whereas close to the C-terminal end of the RHD lies the nuclear localization sequence (NLS) which is essential for the transport of active NF-κB complexes into the nucleus. NF-κB proteins can be further subdivided into two groups: RelA, RelB and c-Rel which contain potent transactivation domains (TDs) within sequences C-terminal

S. Batra (✉) · G. Balamayooran · M. K. Sahoo
Department of Pathobiological Sciences,
School of Veterinary Medicine, Louisiana State University,
Baton Rouge, LA 70803, USA
e-mail: sbatra@lsu.edu

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to the RHD are included in first group whereas, p50 and p52 which do not possess TDs and, therefore, cannot act as sole transcriptional activators comprise the second group. The TDs consist of abundant serine, acidic and hydrophobic amino acids which are essential for transactivation activity (Mercurio and Manning 1999; Perkins 2007; Wang and Baldwin 1998; Zhong et al. 1997).

The RHD of all Rel proteins (except Rel B) contains a phosphorylation site for PKA (25 aa N-terminal to the NLS). Phosphorylation of this site may be required for nuclear localization of the Rel proteins and/or may be involved in the transcriptional activity and DNA-binding (Scheinman et al. 1995; Wissink et al. 1997; Zhong et al. 1997). NF-κB is localized in cytoplasm associated with IκB inhibitory proteins in inactive form. Family members of IκB family include-IκBα, IκBβ, IκBγ (derived from the C-terminal of p100), IκBε, BCl-3, pp40 (a chicken homolog), cactus (a Drosophila homolog), and avian swine fever virus protein p28.2 (Baldwin 1996; Barkett and Gilmore 1999; Hatada et al. 1992; Hayden and Ghosh 2004). The balance of localization of NF-κB is dependent on IκBα degradation which leads to the exposure of masked NLS of p65 and also reduces the contribution of nuclear export sequence of IκBα (Arenzana-Seisdedos et al. 1997; Johnson et al. 1999). NF-κB functions only as a dimer, the most abundant activated dimeric form consists of a p50 or p52 subunit and a p65 subunit. However, NF-κB dimer composition depends on cell type, nature of stimulus or lag time after initial exposure to stimuli (Barkett and Gilmore 1999; Hayden and Ghosh 2004; Perkins 1997; Saccani et al. 2003). Homo- or heterodimers of p50 and p52 have been reported to repress κB site-dependent transcription in vivo (Lernbecher et al. 1993), possibly by competing with other transcriptionally active dimers (e.g., p50/RelA) for DNA binding. Interestingly, κB-site-dependent transcriptional activation by p50/p50 has been demonstrated in vitro (Lin et al. 1995).
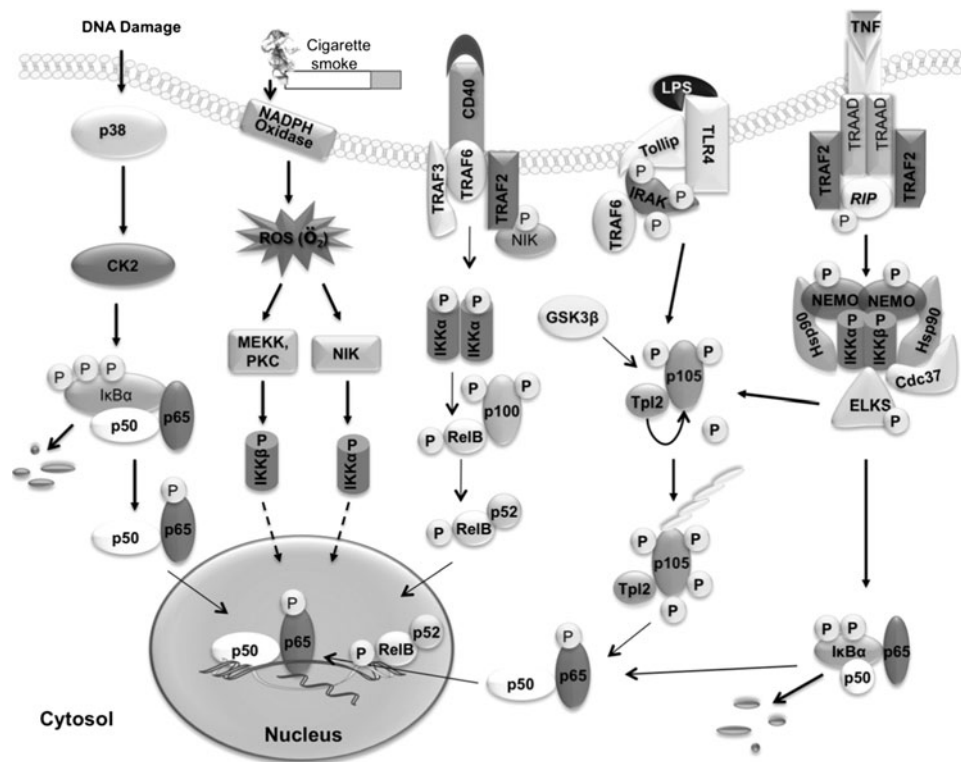
NF-κB Signaling Pathways

Classical Pathway

NF-κB signaling occurs through classical and non-classical pathways. In the classical pathway, tumor necrosis factor α (TNF-α) stimulation leads to activation/phosphorylation of IκB kinase (IKK) complex which then phosphorylates two N-terminal serine residues of IκB proteins. The IKK complex comprised IKKα, IKKβ and a regulatory subunit of IKKγ which is an NF-κB essential modulator (NEMO) (Mercurio et al. 1999; Rothwarf et al. 1998; Yamaoka et al. 1998). IKKα and IKKβ form homo or hetero dimers. Although IKKα and IKKβ cooperate for IκB

phosphorylation, these kinases differ in the signal they mediate. IKKα and IKKβ have 52% amino acid homology with similar structural organization including kinase domain, leucine zipper and helix-loop-helix domains (Delhase et al. 1999; DiDonato et al. 1997; Li et al. 1999; Mercurio et al. 1997; Regnier et al. 1997; Woronicz et al. 1997; Zandi et al. 1997). MAP kinase domain of these proteins consists of closely spaced serine residues at positions 176 and 180 in IKKα and positions 177 and 181 in IKKβ. Phosphorylation of these serine residues by upstream kinases activates IKK kinase (DiDonato et al. 1997; Vanden Berghe et al. 1998; Zandi et al. 1997). Signals which induce NF-κB activity cause phosphorylation of IκB's, subsequently leading to their dissociation and degradation thereby allowing NF-κB proteins to enter the nucleus and induce gene expression (Fig. 1). The ubiquitination and subsequent degradation of IκB's are mediated by the multicatalytic ATP-dependent 26S proteasome complex, the evidence for which was provided by the experiments with peptide aldehyde inhibitors of the proteasome, e.g., calpain inhibitor I (ALLN) (Karin and Ben-Neriah 2000).

Alternate Signaling Pathways of NF-κB

Besides the classical pathway, the alternate pathway is triggered by cytokines such as lymphotoxin, B-cell activating factor, CD40 ligand or viruses such as Epstein–Barr virus and T-cell leukemia virus. This pathway is NEMO independent and relies on the recruitment of TNF receptor associated factor (TRAF) proteins to the membrane and on NF-κB inducing kinase (NIK), which activates IKKα homodimer whose substrate is p100 (Xiao et al. 2001, 2004). Phosphorylated p100 undergoes ubiquitination and is cleaved to generate NF-κB protein p52 which moves to the nucleus as a heterodimer with RelB (Fig. 1). The third pathway classified as atypical is independent of IKK but still requires proteasome and is triggered by DNA damage (Kato et al. 2003). UV radiation induces IκBα degradation via proteasome but the targeted serine residues are located within C-terminal cluster, which is recognized by p38 activated casein kinase 2 (Fig. 1). Besides IκBα and p100, IκBβ is also targeted for phosphorylation at Ser19 and Ser23 by IKK complex which triggers its degradation. TNF-α and IKK phosphorylate p105 at Ser927 and Ser932 and lead to its ubiquitination and processing into p50. In addition, glycogen synthase kinase 3β phosphorylates p105 at Ser903 and Ser907 which primes on IKK-mediated phosphorylation of p105 and its subsequent degradation (Fig. 1). Besides classical and alternate pathways for NF-κB activation, exposure of epithelial surface of lungs to cigarette smoke leads to increased NADPH oxidase derived reactive oxygen species (ROS) production which also plays

Fig. 1 Activation of NF-κB through different signaling pathways. The classical pathway of NF-κB activation involves TNF-α binds to TNFR1 and recruits the adaptors like TRAF2, TRADD and RIP to the membrane. These changes mediates the activation of IKK complex and subsequent phosphorylation of IκBα leading to its degradation. P65/p50 heterodimer is released and migrates to nucleus and activates target genes. The alternative pathway is triggered by DNA damage and is dependent on p38 and CK2 activation. Another alternate pathway of NF-κB activation is triggered by binding of CD40 ligand to its receptor. Recruitment of TRAF proteins leads to the activation of NIK and IKKα which causes processing of inhibitory protein p100 resulting in release of p52 which forms homodimers with RelB. Activation of NF-κB through TLR4 mediated pathway stimulated by LPS. Cigarette smoke activates NF-κB by inducing ROS production

a major role in the activation of NF-κB via NIK or MEKK/PKC-mediated pathways (Fig. 1).

NF-κB Activation

Activation of NF-κB is mediated through number of divergent stimuli. These include proinflammatory cytokines (e.g., TNF-α, interleukin (IL)-1, -2, -4, -8, -12, -15, -17 and -18), lipopolysaccharides (LPS), viral proteins, T- and B-cell mitogens, bacteria, viruses, double-stranded RNA, physical (asthma, hyperglycemia, acute lung injury, hemorrhage, proteinuria, biotin deficiency, etc.) and chemical stresses (including ionizing radiation, high fat diet, obesity, etc.), oxidative stress (superoxide ion, hydrogen peroxide, peroxynitrile radicals, nitric oxide (NO), etc.), environmental hazards including exposure to lead, extremes of pH, cigarette smoke, arsenic, silica particles, fatty acids, heat shock proteins (e.g., Hsp60), a number of chemotherapeutic agents, metals and physiological markers. Depending on the stimulus, the

mechanism of NF-κB activation involves overlapping and non overlapping steps.

Phosphorylation

Various kinases phosphorylate p65 in cytoplasm or in nucleus which is stimuli and/or cell type specific. Protein kinase A phosphorylates p65 at Serine276 during IκB degradation and is essential for the recruitment of CREB-binding protein/p300 to p65 for active transcription. Mitogens- and stress-activated protein kinase-1 also phosphorylate p65 at Serine276 following TNF stimulation (Vermeulen et al. 2003). In addition, protein kinase C-ζ-mediated phosphorylation at serine311 of p65 is required for the recruitment of CREB-binding protein and RNA polymerase II to the IL-6 promoter (Duran et al. 2003; Ikeda et al. 2000; McKay and Cidlowski 2000; Shenkar et al. 2001; Tabakin-Fix et al. 2004). The phosphorylation of Serine529 by casein kinase II and Serine536 by IκB kinases following TNF and LPS stimulation increases the transcriptional activity of NF-κB. Serine276 is within the

RHD, which is involved in dimerization, whereas the Serines529 and 536 are in the C-terminal transactivation domain. Moreover, threonine phosphorylation of p65 at residue 254 has been shown to be required for Pin1 association and the increase in p65 stability. It is not known if these phosphorylations are mutually exclusive or whether all three are required for active transcription.

Recent studies have revealed that besides phosphorylation a multitude of other posttranslational modifications in this signaling system including acetylation, nitrosylation, ubiquitination, neddylation and sumoylation also play significant role in regulating the function of NF-κB (Mabb and Miyamoto 2007).

Acetylation

The crystal structure of the p50/p65 heterodimer bound to κB-DNA reveals that lysine 122 and 123 are the only residues that contact the DNA in the minor groove amongst p65 residues involved in DNA binding (Chen and Ghosh 1999). Although acetylation of other lysine residues of the p65 subunit which includes Lys218, Lys221 and Lys310 also plays a significant role in DNA-binding capacity (Chen et al. 2002) and transcriptional regulation of NF-κB. Acetylation of Lys122 and Lys123 within p65 has been shown to reduce NF-κB affinity to κB-DNA (Kiernan et al. 2003). Other studies have proposed that acetylation of p65 protects it from IκBα-mediated inhibition, however, histone deacetylase 3 (HDAC3)-mediated deacetylation of p65 renders it prone to IκBα-mediated interaction leading to its export from the nucleus (Glozak and Seto 2007).

Methylation

Inducible methylation and demethylation of p65 on residues Lys218 and Lys221 in response to IL-1β or TNF-α, or when NF-κB is constitutively activated, by the chromatin-remodeling enzymes FBXL11 and NSD1 have been reported earlier (Lu et al. 2010). These post-translational modifications profoundly affect the function of NF-κB. Interestingly, the same lysine residues can be methylated or acetylated, depending on the specific cellular context. The ways in which lysine methylation and acetylation are controlled to finely regulate NF-κB activity in normal and tumor cells, and the mechanisms that control the timing, location, intensity, residue specificity, and type of modification, are important issues for future research. This supports the notion that the differential posttranslational modifications of NF-κB which occur in response to different signals, such as phosphorylation, acetylation, and the methylation reported here, may specify different promoter-specific responses to activated NF-κB (Perkins 2006), leading to signal-specific downstream effects in response to different regulators, in different cell types, and in different specific contexts (Perkins and Gilmore 2006). It was demonstrated that Set9 methylates p65 at Lys37, Lys315 and Lys316 and regulates transcriptional activity of p65 (Ea and Baltimore 2009; Yang et al. 2009a). Methylated p65 localizes in nucleus and regulates the stability of DNA-p65 complexes thereby affecting the recruitment of p65 to the promoter. The differences in in vitro findings from different groups have been attributed to the use of different epitope tags in generating recombinant p65 fragments.

Lung Inflammation

NF-κB is a critical transcription factor for host immune mechanisms both in innate and adaptive responses. Activation of NF-κB transcription factors upregulates number of proinflammatory proteins, such as cytokines, chemokines, cell adhesion molecules and proteases which help to recruit leukocytes and degrade the bacteria. Chemokines and adhesion molecules serve to recruit and activate immune cells such as neutrophils, eosinophils, macrophages, and lymphocytes (Poynter et al. 2002) to the site of inflammation. NF-κB regulated proteins include eotaxin (Hein et al. 1997), IL-6 (Sanceau et al. 1995), IL-8 (Harant et al. 1996), macrophage-inflammatory protein-2 (MIP-2) (Driscoll et al. 1995), granulocyte–macrophage colony-stimulating factor (Dunn et al. 1994), inducible NO synthase (Kleinert et al. 1996), intercellular adhesion molecule 1 (ICAM-1) (Roebuck et al. 1995), cyclooxygenase-2 (Schmedtje et al. 1997), and TNF-α (Collart et al. 1990; Shakhov et al. 1990). Respiratory tract infection has remained a leading cause of death worldwide among all the infectious diseases (Mizgerd 2008). Pneumonia is an important concern worldwide as it causes mortality in adults and in children. Pneumonia can be caused by a variety of microbes, such as bacteria, viruses and fungi. Bacteria or virus induce a variety of genes, most of them are regulated by the κB sites in the DNA which bind to NF-κB transcription factors subsequent to pulmonary infection (Balamayooran et al. 2010).

Bacterial Infection

Toll-Like Receptor-Mediated Activation of NF-κB

NF-κB activation via Toll-like receptor 4 (TLR4)-mediated signaling plays an important role during *Haemophilus pneumoniae* infection (Lim et al. 2008), whereas MD-2, a key molecule in TLR4-mediated signaling is shown to regulate NF-κB activation during pulmonary *Escherichia coli* infection (Cai et al. 2009b). Protection of mice by endogenous NF-κB during *E. coli* (Alcamo et al. 2001;

Mizgerd et al. 2003) and pneumococcal pneumonia has been reported earlier (Quinton et al. 2007). TIRAP also plays an essential role in the NF-κB regulation during *E. coli* infection (Jeyaseelan et al. 2005). Similarly, TRIF is important for the TLR3 and TLR4-mediated signaling and is essential for late NF-κB activation during pulmonary *E. coli* (Jeyaseelan et al. 2007), *Pseudomonas aeruginosa* (Power et al. 2007) and *Klbesiella pneumoniae* infection (Cai et al. 2009a) (Fig. 2). LPS-induced expression of chemokines KC and MIP-2 is not significantly affected by TNFR1 deficiency, however, expression of both the chemokines is almost entirely inhibited by combined deficiency of TNFR1 and RelA. The LPS-induced increase in pulmonary ICAM-1 expression has been shown to be reduced by the deficiency of TNFR1 alone and more prominently by TNFR1 and RelA combined deficiency (Jones et al. 2005). These observations reveal that RelA isoform of NF-κB promotes the coordinated expression of cell adhesion molecules and chemokines essential to neutrophil immigration in response to bacterial LPS in the lungs (Sawa et al. 2008; Shan et al. 2002). An in vitro study showed that *Legionella pneumophila* induced the degradation of IκBα and activated NF-κB. Inhibition of IKK blocked *L. pneumophila*-induced prostaglandin E(2) release and COX-2 expression via NF-κB and TNF-α pathway and thus significantly contribute to the host response in Legionnaire's disease (N'Guessan et al. 2007). A study with macrophages from p47$^{phox-/-}$ (a component of NADPH oxidase complex) mice confirmed that redox signaling was necessary for maximal TLR4-dependent NF-κB activation during *P. aeruginosa* infection (Sadikot et al. 2004).

NLR-Mediated Activation of NF-κB

In vitro experiments have demonstrated that NF-κB activation by *Streptococcus pneumoniae* is dependent on NOD2 and mediated by protein kinases IRAKs (IL-1 receptor activated kinase). NOD2 also senses intracellular *S. pneumoniae* in macrophages upon phagocytosis and induces cytokine production via NF-κB pathway (Opitz et al. 2004). In a recent study with combined deficiency of TNF-α and IL-1 signaling, reduced NF-κB activation and chemokines expression were observed during pulmonary infection by *S. pneumoniae* compared to *E. coli* showing the importance of TNF-α and IL-1 (Quinton et al. 2007). Using heat-killed *Staphylococcus aureus* Kapetanovic et al. (2007) showed that NOD1 and NOD2-mediated signaling is important for cytokine production via NF-κB activation (Fig. 2).

These observations reveal that both extracellular and intra-cellular pattern recognition receptors regulate NF-κB through MyD88-dependent and independent pathways triggered by variety of pathogens.

Cell-Specific Responses of NF-κB Signaling

Regarding cell specific response, it is important to discuss the role of both hematopoetic and non-hematopoietic cells.

Fig. 2 Respiratory pathogens activate complex signaling pathways via Toll-like receptors (TLR) and Nod-like receptors leading to the activation of NF-κB

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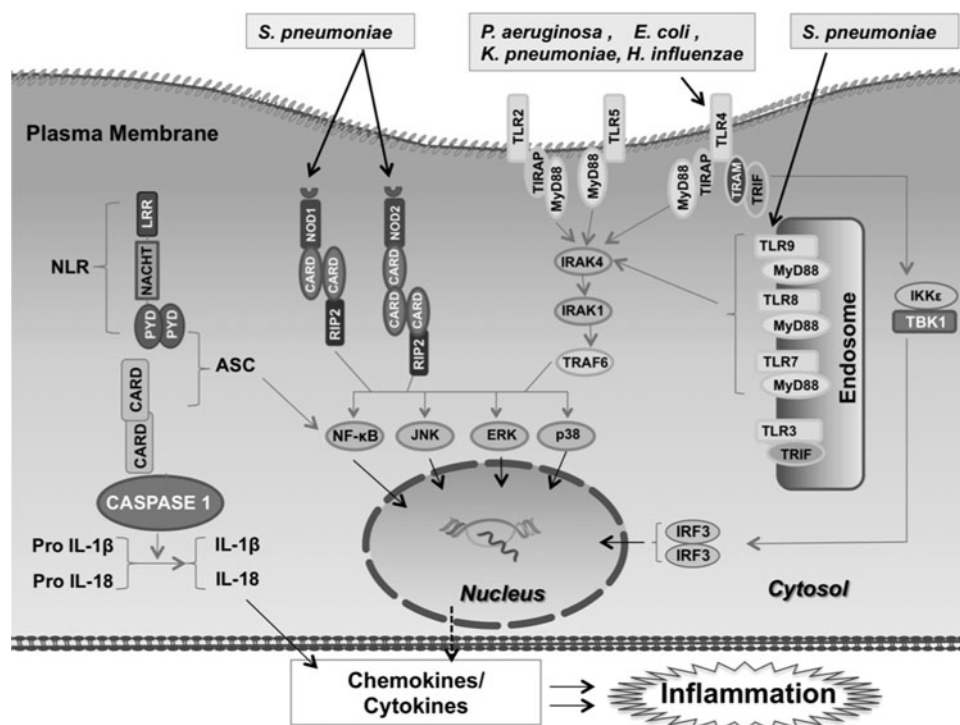
Neutrophils purified from bone marrow cells and bone marrow-derived macrophages (BMMs) from CXCL2 and CCR2 gene deficient mice were unable to activate NF-κB signaling subsequent to pulmonary infection with gram negative bacteria. MD-2 has been shown to be expressed in both these cell types and is important for neutrophil-mediated inflammation. MD-2 regulates NF-κB driven TNF-α, MIP-2, and IL-6 in the lungs following LPS challenge (Cai et al. 2009b). BMMs modulate lung inflammation upon *K. pneumoniae* infection via ELR$^+$CXC chemokine KC-mediated activation of NF-κB and MAPKs (Cai et al. 2010). In addition, signals from both hematopoetic and non-hematopoietic cells are essential to control *P. aeruginosa* replication. During initial phase of infection, MyD88 expression in resident cells plays a vital role in chemokine production and controlling infection whereas early TNF-α and IL-1β production was also dependent on MyD88 signaling in bone marrow cells (Hajjar et al. 2005). Another study with RelA deficient airway epithelial cells resulted in observations leading to decreased cytokine expression, alveolar neutrophil influx, and lung bacterial killing during *S. pneumoniae* infection (Schmeck et al. 2004). Furthermore, mice expressing a dominant-negative form of IκBα in airway epithelial cells also showed impaired bacterial killing in the lungs implicating importance of NF-κB activation during pneumonia. Using transgenic mice expressing mutated IκBα (IκBα_{SR}) exclusively in airway epithelial cells which acts as repressor of NF-κB, Poynter et al. (2003) demonstrated the role of airway epithelial cells in regulating secretion of cytokines/chemokines during intranasal administration of LPS. Koay et al. (2002) used liposome-encapsulated clodronate to deplete macrophages and study the role of macrophages in the pathogenesis of neutrophilic lung inflammation in response to intraperitoneal (i.p.) LPS. The observations from this study revealed the involvement of both pulmonary and extrapulmonary macrophage pool in controlling LPS-induced pulmonary inflammation. Intra tracheal administration of clodronate (for macrophage depletion) resulted in reduced NF-κB-binding activity, cytokines/chemokines production and ICAM-1 expression. Together, these findings conclusively reveal the importance of NF-κB-mediated signaling in both hematopoetic and non-hematopoietic cells (Lentsch et al. 1999). Comprehensive mechanisms that involve in NF-κB activation by different bacterial species are shown in Fig. 2 and Table 1.

Viral Infection

Respiratory syncitial virus (RSV) is a ubiquitous human respiratory tract pathogen known to produce severe lower respiratory tract infections. During RSV infection, NF-κB has shown to regulate the expression of an array of proteins such as chemokines, transcriptional regulators, intracellular proteins regulating translation and proteolysis, and secreted proteins (complement components and growth factor regulators) (Tian et al. 2002). Furthermore, NF-κB activation is a prerequisite for influenza viral infection. It has been shown that cells with low NF-κB activity were resistant to influenza viral infection and they become susceptible upon activation of NF-κB. Primary human cells and lung cancer cell lines (A549 and U1752) were used in this study to elucidate that blocking of NF-κB significantly impaired influenza viral infection in these cells. This group also showed that vaccinia virus infection in these cells was independent of NF-κB activation demonstrating the specificity of NF-κB pathway (Nimmerjahn et al. 2004). Interestingly, severe acute respiratory syndrome coronavirus (SARS-CoV) M suppresses NF-κB activity through a direct interaction with IKKβ, resulting in lower COX-2 expression and SARS pathogenesis (Fang et al. 2007). Idiopathic pulmonary fibrosis is a chronic progressive lung disorder of unknown etiology which is associated with a gamma herpesviral infection. Studies have also shown that inhibition of NF-κB reduces viral load and ameliorates profibrotic events (Krug et al. 2010). In addition during rhino viral infection in humans, MUC5AC a major mucin produced by bronchial epithelial cells is induced via NF-κB pathway (Hewson et al. 2010) (Table 1).

Considering these pivotal roles of NF-κB during viral infections, it is increasingly becoming an important therapeutic target molecule.

Cigarette Smoke-Induced Inflammation

Cigarette smoke (CS) is a potent stimulus of inflammation in the lungs as it contains more than over 4,000 different compounds (Burns 1991). Bioactive LPS is one of the major components in the CS that may contribute to the pathogenesis (Hasday et al. 1999). CS is the main etiological factor in the pathogenesis of chronic obstructive pulmonary disease (COPD), causing oxidative stress, a key feature in smoking induced lung inflammation. CS provokes severe inflammation that results in the NF-κB-dependent production of cytokines, such as TNF-α and IL-6, and the recruitment of neutrophils to the lungs leading to acute lung injury or emphysema (Churg et al. 2002; Deng et al. 2002; MacNee et al. 1989). Studies have also shown that CS not only induces inflammation in the lungs but also reduces the pulmonary host defence and make the respiratory system more prone to infections. Smokers incur twofold to fourfold increased risk to invasive pneumococcal disease and increased risk of influenza and tuberculosis infections (Arcavi and Benowitz 2004). It has

Table 1 Regulation of NF-κB during bacterial and viral infection of lungs

NF-κB subunit	Infection	Regulators	Host immune defense
p50	*Escherichia coli* (Mizgerd et al. 2003)		↑
RelA	*Streptococcus pneumoniae* (Alcamo et al. 2001)		↑
p50/RelA (NF-κB)	*Escherichia coli* (Cai et al. 2009b; Jeyaseelan et al. 2005; Jeyaseelan et al. 2007)	TLR4, MD-2, TRIF, TIRAP	↑
p50/RelA (NF-κB)	*Streptococcus pneumoniae* (Alcamo et al. 2001; Opitz et al. 2004; Quinton et al. 2007; Schmeck et al. 2004; Wang et al. 2008)	TLR9, NOD1, NOD2, TNF-α, IL-1	↑
p50/RelA (NF-κB)	*Haemophilus pneumoniae* (Frantz et al. 1994).	TLR4	↑
p50/RelA (NF-κB)	*Pseudomonas aeruginosa* (Jeyaseelan et al. 2006; Power et al. 2007; Sadikot et al. 2004)	TLR4, TRIF, p47 $^{\text{phox}}$	↑
p50/RelA (NF-κB)	*Klbesiella pneumoniae* (Jeyaseelan et al. 2006)	TRIF	↑
p50/RelA (NF-κB)	*Streptococcus pneumoniae* (Wang et al. 2008)	Morphine (exogenous)	↓
p50/RelA (NF-κB)	RSV (Tian et al. 2002)	IκB	↑
NF-κB	Influenza virus (Nimmerjahn et al. 2004)	(active NFκB promote influenza virus)	↑
p50	Gamma herpes virus (Krug et al. 2010)	(p50 is required for virus reactivation)	↑
NF-κB	Rhino virus (Hewson et al. 2010)	MAPK	↑
NF-κB	SARS virus (Corona virus) (Fang et al. 2007)	IKKβ	↓

TIRAP Toll/IL-1R domain-containing adaptor protein, *TRIF* Toll/IL-1 receptor domain-containing adaptor inducing IFN-β

been reported earlier that bacterial burden in CS-exposed mice was increased 24 and 48 h post-infection and this was accompanied by a more pronounced clinical appearance of illness, hypothermia, and increased lung homogenate cytokines IL-1β, IL-6, IL-10, and TNF-α (Phipps et al. 2010). Interestingly, another group has found that CS changes the bacterial colony in the oral cavity to gram negative bacilli and thus potentiate the chances of aspiration pneumonia caused by gram negative bacteria (Ertel et al. 1991).

Using NF-κB-decoy oligodeoxynucleotides on long-term CS-induced lung inflammation and pathology in mice, it has been shown that NF-κB plays an important role in the recruitment of macrophages and pulmonary dysfunction in smoke-induced chronic lung inflammation (Li et al. 2009). CS extract activates NF-κB and up-regulates Bcl-XL in human bronchial epithelial cells, and p65 deficiency in the cells leads to CS-mediated cell death suggesting that activation of NF-κB regulates cell survival following DNA damage by CS (Liu et al. 2008).

CS-Mediated ROS Production and NF-κB Activation

NADPH oxidase-derived ROS production upon the exposure of epithelial surface of lungs to CS also plays a major role in the activation of NF-κB (Yao et al. 2007) (Fig. 1). Studies have shown that LPS and *P. aeruginosa*-induced lung NF-κB activation was impaired in knockout mice for NADPH oxidase member proteins such as p47$^{\text{phox}}$ and gp91$^{\text{phox}}$ (Koay et al. 2001). Sadikot et al. (2004) have demonstrated that the

activation of RelA subunit of NF-κB was decreased in the lungs of p47$^{\text{phox}-/-}$ and gp91$^{\text{phox}-/-}$ mice compared with wild-type (WT) mice in response to CS exposure. In contrast, other report demonstrated that NADPH deficiency enhances LPS-induced acute inflammatory responses in vivo (Zhang et al. 2009). Furthermore, a low i.p. dose of LPS [5 µg/g body weight (bw)], equally induced pulmonary NF-κB activation in p47$^{\text{phox}-/-}$ and WT mice, however, 20 µg/g bw, i.p. dose of LPS-mediated NF-κB activation was lower in p47$^{\text{phox}-/-}$ mice (Koay et al. 2001). In support of these observations, another report showed that susceptibility to cigarette smoke-induced lung inflammation and emphysema was significantly enhanced in mice genetically ablated of NADPH oxidase (p47$^{\text{phox}}$ and gp91$^{\text{phox}}$) (Yao et al. 2008). These contradictory findings clearly state that low dose of LPS does not induce NF-κB activation via ROS, or that mice deficient in NADPH oxidase components can compensate this defect by either xanthine oxidase (Faggioni et al. 1994; Nakai et al. 2006) or mitochondria-mediated ROS production (Boczkowski et al. 1999; Ritter et al. 2003). Interestingly, variations in LPS doses, difference in observation times and use of different animal models may also play an important role in differential regulation of NF-κB.

CS-Mediated HDAC Regulation and NF-κB Activation

The other key players to regulate transcriptional activity of NF-κB are histone deacetylases (HDACs). HDACs play an important role in maintaining the balance of histone acetylation/deacetylation and/or transcriptional activity of pro-

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Table 2 Regulation of NF-κB during lung cancer by endogenous and exogenous agents

	NF-κB regulation	Probability of tumorigenisis	Type	References
Endogenous regulators				
p53	↑	↑	NSCLC	Rodin and Rodin 2000
K-Ras (oncogenic Ras)	↑	↑	Lung adenocarcinoma	Meylan et al. 2009; Tang et al. 2006
Exogenous regulators				
CS	↑	↑	Lung carcinoma	Liu et al. 2008; Tang et al. 2006
Benzopyrene in CS	↑	↑	Lung carcinoma	Shishodia et al. 2003
PPARβ/δ agonist	↑	↑	NSCLC	Han et al. 2008
Exogenous regulators/treatment options				
Pyrrolidine dithiocarbonate	↓			Frode-Saleh and Calixto 2000
Calpain-1 inhibitor	↓			Lancaster et al. 2001
SiRNA	↓			Chen et al. 2008
Bortezomib	↓			Denlinger et al. 2004; Mortenson et al. 2004
Farnesol like agents	↑			Joo and Jetten 2010

PPARβ/δ peroxisome proliferator-activated receptor-$\beta\delta$, *CS* cigarette smoke, *NSCLC* non-small cell lung cancers

inflammatory genes in cells by the removal of acetyl groups from lysine residues at the N-terminal ends of core histone and also of non-histone proteins. CS-mediated reduction in HDAC2 has been associated with increased RelA activation (Yao et al. 2007). It has also been observed that RelA interacts with HDAC2 and becomes available or retained in the nucleus for pro-inflammatory gene transcription when HDAC2 is decreased (Yang et al. 2009b). Therefore, understanding the mechanism of regulation of HDAC2 could provide scope for therapeutic modulation of steroid resistance in CS-induced lung inflammation.

CS causes immunosuppression in smokers because most of the constituents in CS are toxic to the cells. These components break the innate immune barriers in the respiratory system, thereby making it vulnerable to infections. Some components like LPS stimulate innate immune cells such as alveolar macrophages and epithelial cells to produce pro-inflammatory mediators such as chemokines and cytokine. Furthermore, constitutive CS exposure causes progressive damage to innate immune barrier thereby stimulating inflammation. Therefore, chronic CS exposure makes the vicious cycle to go on. This is the reason why although CS is immunosuppressive at the same time inflammatory (Mehta et al. 2008; Sopori 2002). However, investigations to elucidate the related molecular mechanisms are still warranted.

Role of NF-κB in Lung Cancer

More than one million people worldwide die from lung cancer each year, which is the leading cause of cancer mortality worldwide. Intimate association exists between chronic inflammation and promotion of cancer as evidenced by tumor infiltration of immune cells with poor clinical outcome (Coussens and Werb 2002).

Bronchogenic Carcinomas

Lung cancers, also known as bronchogenic carcinomas, are broadly classified into two types: small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC). SCLC comprises about 20% of lung cancers and is the most aggressive and rapidly growing of all lung cancers. NSCLC are the most common lung cancers, accounting for about 80% of all lung cancers (Meylan et al. 2009). Immuno-histochemically higher expression of nuclear of NF-κB/p65 was observed in SCLCs as compared with NSCLCs (Tang et al. 2006). Peroxisome proliferator-activated receptor-$\beta\delta$ agonist induced proliferation of NSCLC cells by inhibiting the expression of phosphate and tensin homolog deleted on chromosome 10 (PTEN) which stimulates PI3K/Akt and NF-κB signaling (Han et al. 2008) (Table 2). Targeting the NF-κB signaling pathway may also help sensitize cancer cells to TNF-related apoptosis-inducing ligand (TRAIL, also known as Apo2L). Using a complementary gene therapy modality, it was demonstrated that combination treatment with Ad5hTRAIL and AdIKKβKA induced significant apoptosis of TRAIL-resistant A549 cells, suggesting that dual gene therapy strategy involving exogenous TRAIL gene expression with concurrent IKK inhibition may be a promising gene therapy modality to treat lung cancer (Aydin et al. 2010).

CS and Bronchogenic Carcinomas

Environmental factors such as tobacco smoke and genetic susceptibility interact to influence carcinogenesis. The gas

phase of CS contains free radicals such as superoxide radicals, hydroxyl radicals and hydrogen peroxide, which potentially can activate NF-κB (Shishodia et al. 2003). Benzopyrene, another potent carcinogen of CS, can also activate NF-κB, but by an unknown mechanism (Shishodia et al. 2003) (Table 2). NF-κB activation plays an important role in lung cancer pathogenesis and is a suitable target for the development of new lung cancer therapies and chemoprevention strategies (Meylan et al. 2009). It has been shown that nuclear RelA and IκBα are potential markers of NSCLC and associated with poor prognosis. In addition, CS can induce DNA damage and cell cycle arrest without leading to apoptosis, but also stimulates NF-κB-DNA binding activity and up-regulates Bcl-XL (Liu et al. 2008). This group suggested that by damaging the DNA and inhibiting apoptosis through NF-κB, CS can cause epigenetic changes and/or somatic cell mutations that can lead to lung cancer.

Inflammation and Cancer

Recurrent or chronic inflammation may induce or increase the susceptibility to tumorigenesis by damaging the DNA, eliciting reparative proliferation and creating a stromal tissue enriched with inflammatory and growth signal molecules. Persistent inflammation causes constitutive stress to the tissue and modifies its growth signal leading to metaplastic tissue which will eventually become neoplastic (Coussens and Werb 2002). Chronic inflammation may involve unresolved acute inflammation or evolve over a period of time without a clinical manifestation of acute inflammation. Chronic inflammation is characterized by cellular influx predominantly with macrophages and lymphocytes, multiple permeable small blood vessels, fibrosis and necrosis. Activated macrophages and lymphocytes produce cytokines and chemokines which further amplify the inflammatory signal will result in concurrent tissue destruction and repair (Balkwill 2004).

Chemokines which comprise the largest family of cytokines lead to migration and activation of leukocytes to sites of infection and also in tumor stroma. In addition, chemokines also stimulate cells causing a release of proteolytic enzymes which help in digesting the extracellular matrix. These alterations open up migratory path for inflammatory cells thereby leading to tumor growth and metastasis. Furthermore, increased production of reactive oxygen and nitrogen species is cardinal feature of inflamed tissues. Nitric oxide and its products have been shown to cause DNA mutations, inhibition of apoptosis, DNA and protein damage and induce angiogenesis. Alveolar macrophages, neutrophils, lymphocytes, fibroblasts, and endothelial cells all mediated release of cytokines, chemokines, and growth factors may act to promote epithelial

dysfunction and malignant progression. Epithelial abnormalities induced by smoking may also lead to abnormal inflammatory responses and as initiators of deregulated inflammation. Roles of chemokines IL-8/CXC ligand (CXCL)8 (Yuan et al. 2000), and CXCL5, in human NSCLC have been demonstrated earlier (White et al. 2003). In vitro and in vivo expressions of both CXCL8 and CXCL5 are regulated by COX-2 in NSCLC. Another report demonstrated that COX-2 up-regulates the expression of these chemokines by activating NF-κB nuclear translocation, which led to enhanced NSCLC tumor growth and angiogenesis in vivo (Pold et al. 2004; Williams et al. 1999). Multiple signaling pathways including MAPK and NF-κB can lead to regulation of CXCR2. Alterations in CXCR2 level lead to regulation of cell cycle, apoptosis, and angiogenesis. Interestingly, inhibition of CXCR2 blocked the expansion of early alveolar neoplastic lesions (Wislez et al. 2006).

Cancer is a complex disease involving diverse causes, developmental stages, cell targets and etiologies. It is rooted from and compounded by some degree of genomic instability. Cancer cells share common features that override normal controls on proliferation and homeostasis. In certain systems, the upregulation of NF-κB is associated with advanced stages of oncogenesis, supporting its role in tumor progression. NF-κB activates the expression of genes important for invasion and metastasis which include angiogenic factors like vascular endothelial growth factor (VEGF), proteolytic enzymes such as matrix metalloproteinases, and urokinase plasminogen activator (uPA) (Kunsch and Rosen 1993; Li et al. 1998; Libermann and Baltimore 1990; Novak et al. 1991; Sovak et al. 1997). Elevated circulating levels of both uPA and uPA receptor were found in NSCLC patients with terminal disease (Henneke et al. 2010; Veale et al. 1990). The role of IκB in oncogenesis was first proposed by over expression studies on the antisense IκBα transcripts that transformed mouse NIH3T3 cells to tumorous cells (Beauparlant et al. 1994). Persistent nuclear NF-κB DNA binding and transactivation activity in many human tumors clearly reveal the defective IκB activity. Simultaneously, inverse correlation of IκB levels with oncogenesis has been reported by other groups. These results are consistent with other reports which show that activation of IKK leads to the destruction of IκB factors (Devalaraja et al. 1999; Newton et al. 1999). Thus, IκBα in these studies has been proposed to act as a tumor suppressor to control the oncogenic activation of NF-κB.

Studies reporting reduced cancer risks in patients on anti-inflammatory drugs and the causative roles of proteolytic enzymes, the transcription factor NF-κB, and cytokines such as TNF in potentiating inflammation-based cancer extensively supports this relationship (Coussens and Werb 2002; Greten et al. 2004; Pikarsky et al. 2004). The

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switching from non-transformed to cancer cells can be epigenetic in response to transient inflammatory signals via a positive feedback loop involving NF-κB and STAT3. STAT-3 directly activates miR-21 and miR-181b-1, which inhibit PTEN and CYLD tumor suppressors, leading to increased NF-κB activity required to maintain the transformed state. These STAT3-mediated regulatory circuits are required for the transformed state in diverse cell lines and tumor growth in xenografts, and their transcriptional signatures are observed in colon adenocarcinomas. Thus, the epigenetic switch involving miR-21, miR-181b-1, PTEN, and CYLD is part of the positive feedback loop that underlies the epigenetic switch which links inflammation to cancer via NF-κB (Iliopoulos et al. 2010).

In pulmonary diseases, the greatest risk for lung cancer is associated with COPD. Tobacco smoking is considered the major cause for COPD. Tobacco smoking provides persistent network of inflammatory stimuli for COPD and this gives the environment for epithelial–mesenchymal transition and cancer progression (Engels 2008; Sasco et al. 2004; Smith et al. 2006). This will eventually lead to loss of host immune functions to both infections and tumor formation.

NF-κB as Therapeutic Target: Pharmacological and Dietary Inhibitors

The mechanism by which inflammation affects the apoptosis is centered around NF-κB, which can be activated by diverse stimuli including proinflammatory cytokines, infectious agents and cellular stresses (Wang and Cho 2010). Therefore, the NF-κB signaling pathway has also provided a focus for pharmacological intervention in cancer where the pathway is often constitutively active and plays a key role in the disease. Concomitantly, NF-κB inhibition by pharmacological and molecular means sensitizes cancer cells with active NF-κB to chemically induced oxidative stress and death (Meng et al. 2010). More than 750 inhibitors of the NF-κB pathway have been identified, including a variety of natural and synthetic molecules. These compounds include antioxidants, peptides, small RNA/DNA, microbial and viral proteins, small molecules, and engineered dominant-negative or constitutively active polypeptides (Gilmore and Herscovitch 2006) (Table 2). Several of these molecules act as general inhibitors of NF-κB induction, whereas others inhibit specific pathways of induction. The NF-κB pathway can be targeted by inhibition of proteasome function to prevent IκB degradation, degradation-resistant IκB proteins, glucocorticoid-mediated repression of the NF-κB pathway, nonsteroidal anti-inflammatory drugs, and other immunosuppressive agents. Cyclopentenone prostaglandins and natural products such as flavonoids also inhibit the NF-κB pathway (Yamamoto and Gaynor 2001).

Bortezomib/Velcade is a highly specific inhibitor of the proteasome, and is currently approved for treatment of multiple myeloma (Richardson et al. 2004). Similarly disulfiram, olmesartan and dithiocarbamates can also inhibit the NF-κB signaling cascade in a similar manner (Cvek and Dvorak 2007). Bortezomib is a dipeptidyl boronic acid that can selectively and specifically inhibit 26S proteasome. By inhibiting proteasome, bortezomib reduces NF-κB activity and Bcl-2 and Bcl-xL levels thereby leading to growth arrest of cancer cells, impaired angiogenesis, decreased metastasis and increased susceptibility to chemotherapy (Table 2). It is the first Food and Drug Administration (FDA) approved proteasome inhibitor. It has been evaluated for frontline and second line therapy for NSCLC and SCLC. Bortezomib as a monotherapy and in combination with other cytotoxic drugs has shown promising results. Bortezomib, although being a FDA approved drug for multiple myeloma, it's efficacy in different other cancers such as mantle cell and follicular non-Hodgkin's lymphoma, peripheral T-cell lymphoma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, prostate cancer, ovarian cancer is still being evaluated. Nevertheless in combination with other drugs, bortezomib shows some degree of activity while keeping toxicity in manageable range. To date, at least 534 clinical trials using bortezomib alone or in combination have been registered in the US (source: clinicaltrials.gov database, accessed 18 Feb 2011) against almost all resistant cancers including solid tumors such as melanoma, malignant glioma, kidney, colon, breast, lung, pancreas and head or neck cancers, as well as hematological malignancies. The 33 studies of phase I and II, that are particularly looking for its use in lung cancer, mainly NSCLC at various stages and treatment conditions, have decided its dose and tolerability in addition to efficacy. Bortezomib has also been evaluated as a co-treatment with other chemotherapies such as docetaxel, cetuximab (Lilenbaum et al. 2009); pemetrexed (Scagliotti et al. 2010); carboplatin, paclitaxel or radiotherapy (Edelman et al. 2010); gemcitabine, cisplatin (Voortman et al. 2007) and docetaxel (Lara et al. 2006). A study using Bortezomib plus gemcitabine/carboplatin resulted in a notable survival benefit in patients with advanced NSCLC in phase I (Davies et al. 2008) and phase II trials (Davies et al. 2009).

Nonsteroidal anti-inflammatory drugs and glucocorticoids have shown activity against different cancer models through the induction of apoptosis and growth arrest, which is most possibly due to inhibition of NF-κB (Yamamoto and Gaynor 2001). Cyclosporin A and tacrolimus (FK-506) are immunosuppressive agents used in organ transplantation to prevent graft-versus-host disease. These agents can

prevent NF-κB activation under specific conditions by inhibiting the activity of calcineurin, a calcium- and cal-modulin-dependent serine/threonine phosphatase (Frantz et al. 1994; Meyer et al. 1997; Venkataraman et al. 1995). Proteasome inhibitors such as peptide aldehydes, including MG101, MG132, and MG115, make up a class of agents that inhibit the protease activity of the proteasome, while other class, including lactacystin, block protein degradation activity by acylating a threonine residue in one of the key proteasome subunits.

Natural compounds like edible plant-derived flavonoids exhibit a variety of biological activities, including suppression of inflammation, cancer chemoprevention, and protection from vascular disease. Reports suggest that the properties of the flavonoids quercetin, resveratrol, myricetin, fisetin and apigenin may be mediated through downregulation of the NF-κB pathway (Holmes-McNary and Baldwin 2000; Tsai et al. 1999). Thiocolchicoside, a semisynthetic colchicoside from the plant *Gloriosa superba*, inhibits proliferation of leukemia, myeloma, squamous cell carcinoma, breast, colon, and kidney cancer cells, induces apoptosis and suppresses formation of tumor colonies, through inhibition of NF-κB and NF-κB-regulated gene products (Reuter et al. 2010). One of the more extensively studied compounds in this group is curcumin, a diferuloylmethane derived from turmeric, which has been shown to suppress NF-κB activation and NF-κB-dependent gene expression (Anto et al. 2002; Mukhopadhyay et al. 2001; Shishodia et al. 2005). Nimbolide, a triterpenoid isolated from *Azadirachta indica*, enhanced the apoptosis induced by inflammatory cytokines and chemotherapeutic agents in tumor cells. This limonoid abrogated the expression of proteins associated with cell survival (Bcl-2, Bcl-xL, IAP-1, and IAP-2), proliferation (cyclin D1), invasion (MMP-9), and angiogenesis (VEGF), by inhibition of NF-κB activation, induced by carcinogens and inflammatory stimuli (Gupta et al. 2010). Naturally occurring isothiocyanates such as allyl isothiocyanate, benzyl isothiocyanate (BITC), phenethyl isothiocyanate and sulphoraphane have been shown to offer protection against chemically induced cancers in experimental animals (Conaway et al. 2002; Fimognari and Hrelia 2007; Hecht 2000). BITC treatment led to decrease in NF-κB transcriptional activity and κB-DNA binding of p65 in BITC-treated pancreatic cancer cell lines, B×PC-3 and Capan-2 cells, while decreasing NF-κB/p65 phosphorylation at Ser536. This was concomitant with reduced HDAC activity and cyclin D1 expression (Batra et al. 2010).

Agents which can interfere with dimerization of NF-κB family members can also be possible therapeutic targets in near future (Gilmore and Herscovitch 2006). In vitro use of trans-dominant p50 mutants in this line has already been reported, however further studies in this area of intervention are still warranted (Logeat et al. 1991). Furthermore, compounds which can target specific posttranslational modification of NF-κB can provide exquisite specificity by regulating its transactivation related to specific gene. Few compounds have been shown to specifically block p65 phosphorylation, these include mesuol (Marquez et al. 2005), pertussis (Iordanskiy et al. 2002), mesalamine (Egan et al. 1999). Another, challenging aspect with regard to therapeutic intervention is to identify the molecules/compounds which can inhibit distinct NF-κB complexes in various experimental models/cell types upon specific stimulation. Preliminary efforts in this respect have been made by Choi et al. 2004 and Isomura and Morita 2006 using antisense oligonucleotides to Rel A. Since RelA is the most common subunit in most of the systems, the effectiveness of this approach in various diseased conditions is not clear and needs further study. Alternatively, low dose multi drug (combined use of inhibitors) approach seems promising as it may target multiple steps of NF-κB pathway with reduced side effects. One of the examples, in this context, will be thiol reactive compounds which can target the upstream kinase IKK of NF-κB as well as DNA binding of this transcription factor. Keeping in view that the pharmacological and natural compounds targeting NF-κB show very encouraging results against various carcinomas, it is quite likely that they can be effective to a measurable degree against lung cancer.

Future Perspectives

Inspite of several advances in the saga of NF-κB, the future progress will certainly be in the direction of resolving mysteries related to regulation of signaling pathways in pathology and disease, and its therapeutic potential using various model systems. Inspite of abundant literature available regarding signaling pathways associated with NF-κB, very scant information is available regarding the role of various dimeric forms of NF-κB family members in different conditions. We can expect to see more reports in this understudied area of NF-κB in recent years. Another area of future investigations would be to explore the possibility of the application of NF-κB inhibitors topically or local use, e.g., during skin inflammation or airway inflammation, respectively. Intervention by external agents to regulate post-translational modification of NF-κB is another area which has been scantily explored.

Numerous reports discuss about the regulation of NF-κB in response to infection with various pathogens. Recent advances using conditional knockout mice may reveal interesting and novel role(s) of NF-κB family members. Besides the complexity in understanding the signaling

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pathways, NF-κB will still remain the focus of therapeutic intervention under various diseased conditions including pulmonary infection and cancer. Furthermore, in future we may expect to see more studies using combined therapy, which may prove to be more effective and beneficial by targeting multiple steps at low doses.

Summary

The transcription factor NF-κB has been linked to several metabolic and inflammatory diseases including various types of cancer and has increased our understanding about the regulation of inflammation and chronic diseases. NF-κB has also been shown to involve in resistance to multiple drug therapy by having various degrees of activity in *induction* such as epigenetic switching, *promotion* by free radical generation and cellular stress responses, and *maintenance* by antagonizing tumor suppressor gene products and apoptosis. In the specific case of lung cancer induced by inflammation due to habitual or environmental causes like cigarette smoking, NF-κB is a pertinent regulatory hub that can be manipulated for better disease management. The major therapeutic challenge in cancer therapy is to determine molecules that destroy only cancer cells and cause minimal harm to somatic cells, as NF-κB is a regulatory molecule in almost all cells. Most of the studies are done in cell cultures and in animal models which do not usually explain the human system and it is extremely difficult to pass the preclinical studies. Therefore, better understanding of NF-κB regulation (post-translational modifications and dimerization in particular) in inflammation and lung cancer is of importance to define promising pharmacological and natural inhibitors for the treatment/management of disease.

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