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Lung and Systemic Inflammation in COPD

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1. Introduction

Nuclear factor-κB (NF-κB) is a nuclear transcription factor first recognized in 1986 by Sen and Baltimore. Its name derives from the fact that it was first diagnosed in the nuclei of B cells [1- 3] bound to an enhancer element of the immunoglobulin kappa light chain gene [4]. At that time, NF-κB was primarily thought to be a B-cell–specific transcription factor, but it was afterward found to be present in every cell type [5]. NF-κB has been implicated in the regulation of host inflammatory [6-8] and immune responses [9-11], cell adhesion [12], developmental signals [13], cell proliferation, differentiation [14, 15] and in defending cells from apoptosis [16, 17]. In addition, it plays important roles in cellular growth properties by encoding cytokines, chemokines and receptors required for neutrophil adhesion and migration, thus increasing the expression of specific cellular genes [18].

Physical and chemical damage to the lung causes an inflammatory response, thus defending the lung against the causative agents. Inflammation initiates a series of cellular procedures which lead to healing the injury; however, if resolving the inflammatory response is inefficient, the result is a chronic situation. Numerous pathophysiologic conditions and inhaled air pollutants are identified as generating stable stimulation of phagocytic cells, leading to the amplification of proinflammatory cytokines, and mediating chronic inflammation in the lung [19].

Many studies have reported the role of NF-kB in inflammation and proven the association of NF-κB with human inflammatory lung diseases. The point of this short review is to summarize what is known about the molecular biology and activation pathway of NF-κB and to highlight the role of NF-κB in the pathogenesis of inflammatory lung disease, as well as in asthma, COPD, ARDS, and cystic fibrosis.

1.1 Molecular pathway of NF-κB and its activation

In mammals, the NF-κB highly conserved protein family is composed of five members, p50 (precursor protein: p105), p52 (precursor protein: p100) [20, 21], p65 (RelA), c-Rel, and

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RelB [22]; these are encoded by NFKB1, NFKB2, RELA, REL, and RELB, respectively [23], which share the so-called N-terminal Rel homology domain (RHD), responsible for DNA binding and homo- and heterodimerization [24, 25]. Various combinations of dimeric complexes bind to κB sites within the DNA, where they directly regulate transcription of target genes [26]. The major form of NF-κB in cells is a p50/RelA heterodimer [27]. The diverse Rel/NF-κB proteins exhibit different abilities to shape dimers [4], dissimilar preferences for different κB sites [28, 29], and distinct abilities to interact with inhibitory subunits known as IκBs. Because different Rel/NF-κB complexes can be induced in different types of cells and via different signals, they can cooperate in diverse ways with other regulatory proteins and transcription factors to control the expression of particular gene sets [30].

In their unstimulated state, NF-κB dimers can be found in the cytoplasm of a large variety of cells as an inactive complex controlled by their interaction with the κB family of inhibitor proteins (IκB) [31, 32]. They block NF-κB nuclear localization sequences and thus cause its cytoplasmic retention [33, 34]. Numerous IκBs have been identified; there are three typical IκB proteins, IκBα [35], IκBβ [36] and IκBε [37], and two atypical IκB proteins, Bcl-3 [38] and IκBζ, which act in a different way [39]. The precursor proteins p100 (NFKB2) and p105 (NFKB1) also act as inhibitory molecules [40].

Most mediators that activate NF-κB are involved in the phosphorylation-induced degradation of IκB. Phosphorylation of IκB by the multisubunit IκB kinase (IKK) complex in N-terminal regulatory domain at two critical serine residues (S32 and S36) [41] results in the ubiquitination and subsequent degradation of IκB by the 26S proteasome [42-44]. Free NF-κB dimmers translocate into the nucleus, where they bind to specific promoters and affect gene transcription [45, 46].

A variety of upstream extracellular signals, including tumor necrosis factor alpha (TNF-α) [47-50], lipopolysaccharide [51], virus infection (human T-cell leukemia virus, HIV1) [52-54], ionizing radiation [55], interleukins such as IL-1β [48], epidermal growth factor (EGF) [3], mitogens [56], bacteria [52], reactive oxygen species (ROS) [48], environmental hazards such as cigarette smoke [57], and physical and chemical stresses [58], activate the IKK complexes, which are comprised of three subunits: IKKα, IKKβ, and IKKγ/ NEMO. IKKα and IKKβ are catalytic subunits, and IKKγ functions as a regulatory subunit [59-61].

Numerous genes associated with the inflammatory process include proinflammatory cytokines (such as TNF-α), cell adhesion molecules (such as intercellular adhesion molecule 1) [62, 63], or assumed NF-κB binding sites in their promoters that can amplify the inflammatory response and enhance the time of chronic inflammation. NF-κB also induces the expression of enzymes whose proteins have a connection to the pathogenesis of the inflammatory procedure, such as inducible cyclooxygenase (COX-2) [18], which generates prostanoids, and the inducible type of nitric oxide synthase (iNOS), which manufactures nitric oxide (NO) [64, 65]. These facts emphasize the significance of NF-κB as a regulator of inflammatory gene activation and indicate it as a predominant choice for targeted inactivation. In fact, diverse techniques intended to improve or suppress the inflammatory process related to determined pathologies have already been directed at obstructing the biological actions of NF-κB (Figure 1).

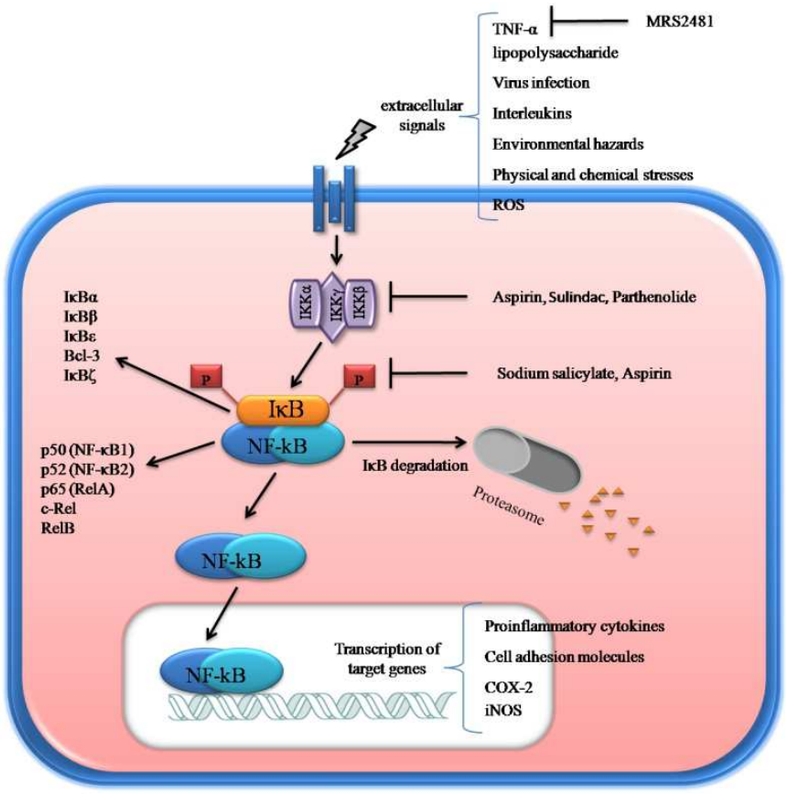

Fig. 1. Schematic representation of NF-κB activation in inflammatory disease. A variety of upstream extracellular signals activate the IKK complexes, which are comprised of 3 subunits: IKKα, IKKβ, and IKKγ. Phosphorylation of IκB by the IKK complex in the N-terminal regulatory domain at two critical serine residues results in the ubiquitination and subsequent degradation of IκB by proteasome. Free NF-κB dimmers translocate into the nucleus, where they bind to specific promoters and affect gene transcription of such molecules as proinflammatory cytokines, cell adhesion molecules, COX-2, and iNOS. Some drugs and agents are able to suppress NF-κB activation via different pathways. Aspirin and sodium salicylate block IkB phosphorylation and degradation. Sulindac, Parthenolide, Aspirin inhibit activation of the NF-kB pathway by suppressing IKK activity and MRS2481 inhibit TNF-α.

1.2 Asthma

Asthma is a chronic inflammatory disease [65, 66] of the airway accompanied by reversible bronchial hyperreactivity. Increased numbers of Th2 lymphocytes [67] and eosinophils in the airway can cause chronic inflammatory response, leading to asthma [68, 69]. In addition to the existence of inflammatory cells in the airway, these patients expose changing levels in structure of airway, termed remodeling [69, 70]. As cited above, NF-κB is one of the most important transcription factors involved in the expression of wide groups of inflammatory proteins, including cytokines, adhesion molecules, and enzymes, which themselves are implicated in the pathogenesis of asthma [71]. Translocation of NF-κB and its binding activity increases in airway specimens from asthmatics, in airway epithelial cells obtained from bronchial mucosal biopsies, and in alveolar macrophages extracted from sputum.

Results show that the agents that are coordinate with deterioration of asthma generally activate NF-κB. Viral infections, allergens [72], and ozone, all of which can cause activation of NF-κB, are related to aggravation of asthma [73].

Viral infections of the upper respiratory airway might intensify asthma by activation of NF-κB. In cell cultures of bronchial epithelial cells, rhinovirus causes induction of oxidative stress and NF-κB activation and increases expression of IL-8, which can in turn participate in neutrophil recruitment into the upper respiratory tract. Respiratory syncytial virus (RSV) has been involved in stimulation of NF-kB and consequent expression of IL-8 and IL-1 in human type II–like alveolar epithelial cells (A549 cells). Thus NF-κB seems to be activated during replication of RSV (Table 1)[73].

In vitro research has revealed that allergens activate NF-κB in bronchial epithelial cells of asthmatic patients. For example, exposure to aerosolized ovalbumin causes profound activation of NF-κB and transcription of inducible nitric oxide synthase in the respiratory tract of sensitized Brown Norway rats [73]. Mice lacking the NF-κB subunits p50 or c-Rel exhibit less airway inflammation in response to an antigen challenge, signifying the fundamental role of NF-κB in allergic respiratory disease [68].

Furthermore, activation of NF-κB has also been illustrated in animal models of allergic airway inflammation in airway epithelium. However, inhibition of NF-κB activation in airways did not ameliorate airway hyperresponsiveness, a key characteristic of asthma. These findings reveal that NF-κB activation in airway epithelium is essential to the airways in response to allergen activity via recruitment of inflammatory cells but also exhibits a different segregation between hyperresponsiveness and airway inflammation [68].

Airway irritants such as ozone may also exacerbate asthma symptoms and trigger inflammation through NF-κB activation. Exposure of A549 cells to ozone affects activation of NF-κB and transcription of IL-8. Another study revealed that rats exposed to ozone subsequently show time- and dose-dependent activation of NF-κB and modulate penetration of neutrophils and monocytes into lavageable airspace via expression of CXC and CC chemokines, respectively [73].

Cre/lox molecular techniques have been examined whether inhibiting NF-κB expression only in airway epithelial cells in a mouse model would diminish levels of airway remodeling. In selective airway epithelial cells frominhibitor of κB kinase β (Ikkβ) knockout mice, peribronchial fibrosis had considerably reduced levels of TGF-β in BAL, and numbers of cells had positive peribronchial TGF-β1. Airway epithelial Ikk-β ablation also leads to reduction in levels of mucus and eosinophils in the airway [69].

Reduction in expressions of NF- κB-regulated chemokines such as eotaxin-1 and Th2 cells can diminish airway inflammatory response in the airway as well. These findings support the key role of NF-κB pathway the in bronchial epithelium and its significance in the process of remodeling [69].

As cited above, expression of some cytokines and adhesion molecules as a result of NF-κB activation exacerbates inflammation in airway cells. For example, tumor necrosis factor alpha (TNF-α) is a cytokine produced by macrophages and associated with inflammation. It increases the expression of adhesion molecules for recruitment of immune cells to damaged tissue. TNF-α may also be involved in expression of intercellular adhesion molecule 1

(ICAM-1). It has been illustrated that epithelial upregulation of ICAM-1, which has an important role in cellinteraction, exists in asthmatics. Active bronchial asthma is matched by an amplified level of soluble ICAM-1 in serum and thereby is associated with the pathogenesis of asthma. When rhinoviruses activate NF-κB, it amplifies the gene expression ofICAM-1 in bronchial epithelial cells, because rhinovirus utilizes ICAM-1 as a cellular receptor [73].

1.3 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow obstruction which is irreversible. COPD is a complex of two chronic lung diseases: chronic bronchitis and emphysema both caused mainly by a familiar irritant, cigarettes [74]. The inflammatory response in smokers' lungs is not fully understood [75]. One theory is that cigarette smoke disturbs the oxidant/antioxidant balance by induction of oxidative stress, which stimulates activation of redox-sensitive transcription factors such as NF-κB. Transcription factors, including NF-κB (Table 1) and activator protein 1 (AP-1), have a key role through gene transcription of wide range of inflammatory cytokines that cause airway inflammation, including TNF-α interleukin (IL)-8, and interleukin (IL)-6 [41, 76]. As well, NF-κB has been demonstrated to be a mediator of cigarette smoke effects on gene transcription in various cell types. Its activated dimer has been revealed to be induced in bronchial biopsies of smokers [77].

Previous studies have reported that cigarette smoke increases DNA damage in lung fibroblasts and human bronchial epithelial cells; however, this does not lead to necrosis or apoptosis. Lung fibroblasts and human bronchial epithelial cells are capable of repairing DNA damage and forming colonies after sub-culturing in normal medium. Cigarette-smoke-induced DNA damage is involved in modulating cell survival or apoptosis via numerous signaling pathways. It has been elucidated that NF-κB plays a significant role in mediating cell survival [78].

Transcription of genes is not only dependent upon transcription factor bindings; it is also related to the alteration of core histone proteins which adjust the availability of the genome to cofactors and nuclear factors. Octamers are composed of two copies of each histone core protein, H2A, H2B, H3, and H4, and DNA covers them. Post-translational modification of N-terminal side chains of each histone cause conformational changes via phosphorylation, methylation and acetylation[76].

Histone acetyltransferases (HATs) acetylate lysine residues in histones, neutralize their positive charge, and lead to chromatin relaxation, increasing binding of transcription factors and RNA polymerase II, which unwinds DNA and increases gene amplification [76].

The imbalance of acetylation/deacetylation and increase in acetylation might cause transcription of proinflammatory genes mediated by NF-κB and therefore initiate chronic inflammation. Consequently, the imbalance of histone acetylation/deacetylation may have a role in the inflammatory response in "susceptible" smokers who progress toCOPD [76].

When NF-κB translocates into the nucleus and acetylates histone H4, the sequence leads to DNA relaxation and transcriptional accessibility. Research has shown that smoking cessation in patients suffering from COPD causes increased histone H3 acetylation,

illustrating that the stability of the inflammation in the lungs in COPD after smoking cessation may be regulated by H3 acetylation. As cited above, this study shows that cigarette smoking affects chromatin remodeling in the lungs [76]. Smoking has been found to reduce expression of IκB protein dramatically and thus affects regulation of NF-κB. Unexpectedly, in ex-smokers with COPD, a notable depletion of IκBα has been detected. Nevertheless, the NF-κB DNA binding in these patients was similar to that in nonsmokers [76]. Other investigations confirm the enhanced activation of NF-κB in cigarette smoke. Cigarette-smoke-exposed Guinea pigs increase expression of IL-8 in response to NF-κB activation. Furthermore, studies of smokers and number of pack-years reveal a positive correlation with NF-κB activation. Smokers with COPD and currently healthy smokers both increase DNA binding activity of NF-κB [76]. NF-κB expression and its translocation in lung tissue and sputum increase in COPD patients in comparison with non-smoking controls, and this seems to be related to exacerbation [79].

Caramori and coworkers investigated p65 expression in leucocytes extracted from sputum patients with exacerbated COPD and revealed p65 transcription in macrophages but not in neutrophils [80].

Even though an enhanced proinflammatory molecule whose expression is vitally dependent on NF-κB activation has been formerly described in COPD, the role of NF-κB activation has not been determined. We hypothesize that, through COPD exacerbations, initiation factors including viral and bacterial infections could activate NF-κB, generate cytokines and chemokines, and lead to inflammatory cell penetration of the airways. Sputum immunocytochemistry methods have evidenced activation of p65 in alveolar macrophages through COPD exacerbations [80].

As a sign of oxidative stress activation, Di Stefano and colleagues demonstrated increases in activation of NF-κB in segmental and subsegmental bronchial biopsies in COPD subjects and healthy smokers accompanied by enhanced lipid peroxidation products. They reported increased localization of p65 and its immunoreactivity in bronchial epithelium but not in submucosa. Nevertheless, they could not diagnose any difference between healthy smokers and COPD smoking subjects [81]. Similarly, Yagi and coworkers investigated IκBα expression by an immunostaining method to measure NF-κB activation indirectly in airway epithelial cells. They revealed increased levels of phosphorylated IκBα in both ex-smokers with COPD and subjects without COPD. Phosphorylated IκBα underwent degradation and freed NF-κB to bind to enhancers of related genes [76].

Inflammatory molecules in COPD cause increased neutrophils and inflammatory agents in the airways and bronchial tissue of patients [79]. Mishra and colleagues reported that NF-κB can be inhibited independently from IκBα and may be inhibited via a peroxisome proliferator-activated receptor α (PPAR-α). The interaction of PPARα with the p65 and c-Jun subunits of NF-κB and AP-1, respectively, may block their activation, suppressing expression of cytokines such as IL-6 [76].

1.4 Cystic fibrosis

Cystic fibrosis (CF) is a chronic inflammatory airway disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Lung disease in CF expresses a profoundly proinflammatory phenotype related to increased constitutive

viscosity of respiratory secretions and chronic lung infection by *Pseudomonas aeruginosa* and other bacterial species, resulting in considerable morbidity in cystic fibrosis subjects followed by the lack of innate immune responses [73].

Pseudomonas aeruginosa supposedly causes activation of NF-κB and may play an important role in overproduction of mucin caused by the increase in MUC2 mucin transcription (Table 1) [73]. Even though there is not enough data in vivo, enhanced activation of NF-κB and amplification of IL-8 can be observed in bronchial epithelial cells that display CFTR mutations (IB3 cells) in comparison with normal bronchial epithelial cells line (C38 cells). To decrease sputum viscosity in CF patients, inhibition of NF-κB activation might be a useful procedure for decreasing airway inflammation and improve lung function [82]. These findings show that CFTR mutations are related to modification of NF-κB levels and airway inflammation [73]. Another research revealed that, in either wild-type (WT) or mutant (CFTR) isogenic bronchial epithelial cell lines infected by *Pseudomonas aeruginosa*, transcriptional changes occur in cytokine production. For example, NF-κB activates transcription of four -regulated cytokines include ICAM-1, CXCL1, IL-8 and IL-6, but protein expression in both cell lines involves only enhancement of IL-6 and IL-8 expressions. Inhibition of NF-κB prior to countering t *Pseudomonas aeruginosa* revealed different levels of dependence on NF-κB for expression of the cytokines [83].

T. Joseph and colleagues demonstrated that in vitro activation of NF-κB in human airway epithelial cells isolated from CF (DeltaF508/DeltaF508) and non-CF (NCF) patients when infected by *Pseudomonas aeruginosa* elevated nuclear levels of IkBα in CF cells, although this increase was transient. They also showed increased baseline translocation of NF-κB to nuclei in primary CF epithelial cell cultures; following *Pseudomonas aeruginosa* infection, activation of IκBα might suppress that of NF-κB [84].

In a systematic search for drugs for therapeutic treatment that may be utilized for inhibition of IL-8 secretion from these cells, a series of amphiphilic pyridinium salts was examined. The most effective of these salts is a (R)-1- phenylpropionic acid ester known as MRS2481. For optimal activity, it has been demonstrated that the ester ought to be joined to the pyridinium derivative by an eight-carbon chain. MRS2481 seems to be able to suppress signaling of the NF-κB and AP-1 to the IL-8 promoter . Another therapeutic feature is that MRS2481 is an effective inhibitor of TNF-α, which leads to suppression of phosphorylation and proteosomal destruction of IκBα (Figure 1). In this way, IκBα is maintained and keeps the IL-8 promoter silent [85]. Another pharmaceutical strategy against the inflammatory phenotype of the CF lung is Parthenolide, which is sesquiterpene lactone derived from the feverfew plant. Numerous researchers have controversially proposed that this compound suppresses the NF-κB pathway by attenuation of IκBα degradation. As we show in Figure 1, parthenolide inhibits IκB kinase, ensuring the stabilization of IκBα in cytoplasm, hence causing inhibition of NF-κB translocation and reduction of following inflammatory responses, so parthenolide can be an effective treatment for the excessive inflammation in CF [86].

another therapeutic medicine, Azithromycin (AZM), has been shown to modulate airway inflammation in CF subjects. AZM suppressed IL-8 expression in a CF cell line. Because the IL-8 gene is transcripted by NF-κB, it can be concluded that this is the probable pathway by which AZM activates NF-κB in the cell line. Such findings indicate the anti-inflammatory

task of this macrolide. Suppression of NF-κB activity reveals other proinflammatory molecules regulated by this factor as an AZM effect relevant to the treatment of CF [87].

1.5 Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is known for enormous infiltration of neutrophils into the lungs accompanied by leak of serum proteins, especially albumin, into the alveolar space, blood loss in the intra-alveolar space, and interstitial edema, all important and frequent signs in exacerbation of ARDS. In spite of the occurrence of ARDS in all over the world, the precise pathophysiology mechanisms remain to be detailed [88].

Varying expression levels of proinflammatory cytokines are associated with the progression of ARDS. overexperssion of proinflammatory cytokines such as TNF-α, IL-6 and IL-8 in the lung has been demontrated in bronchoalveolar lavage (BAL) of ARDS patients and is correlated with poor outcome [88].

Patients with proved ARDS revealed increased activation of NF-κB in alveolar macrophages, in comparison with control subjects without acute lung injury [73]. Because there were no notable increases in the levels of transcription factors, including CREB, AP-I , or SP- I activation, in alveolar macrophages from patients with ARDS, NF-κB is suggested to be a significant upstream regulator for cytokine gene expression in ARDS patients, because of its existence on the enhancer of proinflammatory cytokines (Table 1). The level of subunits p50, p65, and c- Rel decreased in cytoplasm of alveolar macrophages in ARDS subjects, proving the existence of an ongoing stimulus for NF-κB activation. Increased levels of oxygen radicals, proinflarnmatory cytokines, and endotoxin in ARDS might be associated with NF-κB activation. TNF-a and IL-8 are increased in BAL of ARDS subjects [88].

NF-κB activation can alsobe caused by oxygen radicals. Our in vivo data from a hemorrhage-induced murine model of ARDS indicates an outstanding role for xanthine oxidase, a kind of oxygen radical, in stimulation of NF-κB in lung cells [88]. Cytoplasmic and nuclear levels of IκBa are not notibly dissimilar in alveolar macrophages from ARDS subjects and controls, so these findings are rather unexpected, because signals that cause activation of NF-κB would be expected to generate phosphorylation. Alveolar macrophages have a significant protective role in mediating NF-κB activation in the lung and in initiation of neutrophilic inflammation [73, 88].

2. Inhalation of some agents cause activation of the NF-κB inflammatory pathway in the lung

Asbestos

Asbestos belongs to a group of physically occurring, hydrated mineral silicate fibers that are causally related to the progression of pulmonary diseases [88]. Iron, which exists in asbestos fibers, cause cellular redox changes by generation of intracellular reactive oxygen species, leading to activation of NF-κB. It has been shown that, after inhalation of crocidolite and chrysotile asbestos, nuclear translocation of RelA increases in rat airway epithelial cells (Table 1). The main reason is that macrophages phagocytize asbestos but cannot ‘‘digest’’ these fibers. Because the asbestos harms them, these macrophages secret TNF-α, and this cytokine mediates activation of NF-κB [73, 89-92].

inflammatory lung disease	The role of NF-κB
Asthma	Respiratory syncytial virus (RSV) and Rhinovirus cause induction of NF-κB activation
COPD	Cigarette smoke stimulates activation of redox-sensitive transcription factors such as NF-κB
CF	Activation of NF-κB may overproduct mucin during the increase of MUC2 mucin transcription
ARDS	NF-κB suggested to be a significant upstream regulator for cytokine gene expression
Inhalation of proinflammatory agents	Translocation of RelA increases in rat airway epithelial cells and activates the p38 and JNK MAPK pathways and cause the activation of NF-κB

Table 1. The implication of NF-κB in inflamatory lung disease.

2.1 Sulphur mustard Inhalation

Sulphur mustard (SM) is a chemical weapon used during the Iraq war against Iran of the late 1980s [93, 94]. It can produce damage in skin, eyes, and, , most importantly, in lung. 2-Chloroethyl ethyl sulphide (CEES) is a sulphur vesicating agent and an analogue of SM. Both of these agents are alkylating agents that affect cellular thiols and are highly toxic. CEES appears to decrease iNOS expression by associating with the LPS-induced stimulation of transcription factor NF-κB. CEES also alkylates the NF-κB consensus sequence, thus suppressing the binding of the NF-kB to the iNOS promoter. Even though the activation of NF-κB due to SM or CEES countering has been elucidated in different cell lines, the exact mechanism of this pathway is still poorly understood, and the question of whether activated NF-κB induces an inflammatory pathway remains to be elucidated [95].

2.2 Diesel exhaust

Diesel exhaust (DE) is a major pollutant;exposure increases a prominent inflammatory response in the airways, with induction of cytokines such as IL-8, IL-13 and activation of redox sensitive nuclear factors (NF-κB, AP-1) in the bronchial epithelium, including upregulation in the transcription of ICAM-1 and vascular endothelial adhesion molecules (VCAM-1). It has been established that DE activates the p38 and JNK MAPK pathways and causes the activation of NF-κB and AP-1 [96].

3. Strategies to block NF-κB activation

Several strategies have been proposed to block the activation of NF-κB. An extensive diversity of molecules (both natural and synthetic) has been highlighted as having an effect on activation of NF-κB and being able suppress it. These compounds suppress NF-κB

activation through various pathways by blocking NF-κB activation. Subsequent information has provided strategies for suppressing NF-κB activation in response to different type of stimuli. Both steroids and nonsteroidal anti-inflammatory agents are helpful (Table 2). Hence, it is important to get a better understanding of the activation of NF-κB and release of prostaglandins [64]. Glucocorticoids, including dexamethasone and prednisone, are commonly prescribed for their anti-inflammatory and immunosuppressive effects [97-99]. These components interact with the steroid receptor and cause reduction of the expression of particular genes that control the inflammatory procedure. NF-κB can be inhibited via glucocorticoids in different ways. Dexamethasone induces the expression of IκBα, which causes retention of NF-κB in the cytoplasm, especially of p65. Synthesis of IκBα by dexamethasone is likely to be dependent on p65 in pre-existing NF-κB complexes. These findings show that quick degradation of IκBα may be blocked by consequent expression of IκBα following dexamethasone treatment. Another pathway implicated in glucocorticoid-mediated repression of the NF-κB is that dexamethasone may inhibit the expression and p65-dependent transactivation in endothelial fibroblasts in murine models, but it does not have any effect on the IκB level. In the same way, dexamethasone alters NF-κB–mediated transcriptional activity in endothelial cells, but it does not alter IκB levels either [64].

type	Name
Steroids	Dexamethasone
	Prednisone
Nonsteroids (NSAIDs)	Aspirin
	Sodium salicylate
	Tepoxaline
	Defereoxamine
	Ibuprofen
	Mesalamine
	Sulindac
	MRS2481
	Parthenolide
	Azithromycin (AZM)

Table 2. Therapeutic agents and drugs which block NF-κB activation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively applied to improve the therapeutic status of chronic inflammatory states. The most widely hypothesis for the inhibitory property of these compounds on the inflammatory response supposes that NSAIDs inhibit COX activity to suppress prostaglandin synthesis [64].

NSAIDs such as Aspirin and sodium salicylate correlate with NF-κB inhibition. At concentrations measured in the serum of patients treated with these drugs for chronic inflammatory situations, both aspirin and salicylate suppress NF-κB activation, and aspirin has been demonstrated to inhibit the activation of the IκB kinase complex [97, 100]. In particular, Aspirin and sodium salicylate prevent NF-κB nuclear translocation by blocking IkBα phosphorylation and degradation (Figure 1) [3, 100]. These drugs also inhibit TNF-α-induced mRNA transcription of adhesion molecules such as ICAM-1 in endothelial cells. Penetration of neutrophils from endothelial cells can be prevented following NF-κB inhibition in these cells. Recently, Yin *et al.* have reported that Aspirin can bind to and prevent the kinase activity of IKKβ by decreasing its capacity to bind ATP. Other NSADs, such as tepoxaline, defereoxamine, and ibuprofen, are also capable of suppressing NF-κB activity [100].

An aminosalicylate derivative with anti-inflammatory aspects, mesalamine, prevents IL-1–mediated activation of p65 phosphorylation without suppressing IκBα degradation [64]. Indomethacin, is another NSAID, is able to inhibit inflammatory responses via suppressing COX activity, but it does not prevent activation of the NF-κB pathway [64]. Sulindac is illustrated in Figure 1 as a NSAID that is structurally correlated with indomethacin and can inhibit activation of the NF-kB pathway by suppressing IKK activity [64, 97].

These findings suggest that inhibition of the NF-κB pathway might be implicated in the anti-inflammatory pathways as well as participation of NSAIDs in growth inhibitory properties.

4. Conclusion

NF-κB is one of the most important transcription factors and has an important role in inflammatory special lung disease [6]. The exact pathophysiological mechanism of NF-κB that leads to inflammation continues to be better understood. Pharmacologic therapy used for blocking this molecule can be useful for treatment of lung disease. The major recommendation for further research is to define the exact molecular mechanisms of each inflammatory lung disease that involves NF-κB. This is critical because the glucocorticoids which benefit patients with asthma do not work for COPD. Future research will to elucidate new methods of treatment for those patients [101].

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6. References

[1] Haddad, J.J.; Science review: Redox and oxygen-sensitive transcription factors in the regulation of oxidant-mediated lung injury: Role for nuclear factor-κB. Critical Care, 2002, 6, 481-490.

[2] Bernal-Mizrachi, L.; Lovly, C. M.; Ratner, L. The role of NF-κB-1 and NF-κB-2-mediated resistance to apoptosis in lymphomas. PNAS., 2006, 103,9220–9225.
[3] Sethi, G.; Sung, B.; Aggarwal, B.B. Nuclear Factor-κB activation: From bench to bedside. Exp. Biol., 2008, 233, 21–31.
[4] Miyamoto, S.; Seufzer, B. J.; Shumway, S. Novel IkBa proteolytic pathway in WEHI231 Immature B cells., Molecular and cellular biology, 1998, 18, 19–29.
[5] Tang, X.; Liu, D.; Shishodia, S.; Ozburn, N.; Behrens, C.; Lee, J. J.; Hong, W. K.; Aggarwal, B. B. ; Wistuba, I. I. Nuclear Factor-kB (NF-kB) is frequently expressed in lung cancer and preneoplastic lesions. Cancer, 2006, 107, 2637-2646.
[6] Choudhary, S.; Boldogh, S.; Garofalo, R.; Jamaluddin, M.; Brasier, A.R. Respiratory syncytial virus influences NF-κB-dependent gene expression through a novel pathway involving MAP3K14/NIK expression and nuclear complex formation with NF-κB2. Journal of virology, 2005, 79, 8948–8959.
[7] Aggarwal, B.B.; Takada, Y.; Shishodia, S.; Gutierrez, A.M.; Oommen, O.V.; Ichikawa, H.; Baba, Y.; Kumar, A.; Nuclear transcription factor NFkappa B: Role in biology and medicine. Indian J. Exp. Biol., 2004, 42(4), 341-353.
[8] Paul, A.G.; NF-kB: A novel therapeutic target for cancer. Eukaryon, 2005, 1, 4-5.
[9] Maggirwar, S. B.; Sarmiere, P.D.; Dewhurst, S.; Freeman, R. S. Nerve growth factor-dependent activation of NF-kB contributes to survival of sympathetic neurons. The Journal of Neuroscience, 1998, 18, 10356–10365.
[10] Weichert, W.; Boehm, M.; Gekeler, V.; Bahra, M.; Langrehr, J.; Neuhaus, P.; Denkert, C.; Imre, G.; Weller, C.; Hofmann, H.P.; Niesporek, S.; Jacob, J.; Dietel, M.; Scheidereit, C.; Kristiansen, G. High expression of RelA/p65 is associated with activation of nuclear factor-kB-dependent signaling in pancreatic cancer and marks a patient population with poor prognosis. British Journal of Cancer, 2007, 97, 523 – 530.
[11] Chabot-Fletcher, M.; A role for transcription factor NF-kB in inflammation. Inflamm. res., 1997, 46, 1–2.
[12] García-Román, R.; Pérez-Carreón, J.I.; Márquez-Quiñones A.; Salcido-Neyoy, M.E.; Villa-Treviño, S. Persistent activation of NF-kappaB related to IkappaB's degradation profiles during early chemical hepatocarcinogenesis. Journal of Carcinogenesis, 2007, 6:5, 1-11.
[13] Basak, S.; Shih, V. F-S.; Hoffmann, A. Generation and activation of multiple dimeric transcription factors within the NF-κB signaling system. Mol. Cell. Biol., 2008, 28, 3139–3150.
[14] Jacque, E.; Tchenio, T.; Piton, G.; Romeo, P-H.; Baud, V. RelA repression of RelB activity induces selective gene activation downstream of TNF receptors. PNAS., 2005, 102, 14635–14640.
[15] Ye, S.; Long, Y.M.; Rong, J.; Xie, W.R. Nuclear factor kappa B: A marker of chemotherapy for human stage Ⅳ gastric carcinoma. World J. Gastroenterol., 2008,14, 4739-4744.
[16] Meteoglu, I.; Erdogdu, I.H.; Meydan, N.; Erkus, M.; Barutca, S. NF-KappaB expression correlates with apoptosis and angiogenesis in clear cell renal cell carcinoma tissuesJournal of Experimental & Clinical Cancer Research, 2008, 27, 1-9.
[17] Woods, J. S.; Dieguez-Acuña, F. J.; Ellis, M. E.; Kushleika, J.; Simmonds, P. L. Attenuation of nuclear factor Kappa B (NF-κB) promotes apoptosis of kidney

epithelial cells: A potential mechanism of mercury-induced nephrotoxicity. Environmental Health Perspectives, 2002, 110, 819-822.
[18] Li, Q.; Withoff, S.; Verma, I.M. Inflammation-associated cancer: NF-kB is the lynchpin. Trends in Immunology, 2005, 26, 318-325.
[19] Azad, N.; Rojanasakul, Y.; Vallyathan, V. Inflammation and lung cancer: Roles of reactive oxygen/nitrogen species. Journal of Toxicology and Environmental Health, Part B, 2008, 11, 1–15.
[20] Brown, K.D.; Claudio, E.; Siebenlist, U. The roles of the classical and alternative nuclear factor-κB pathways: Potential implications for autoimmunity and rheumatoid arthritis. Arthritis Research & Therapy, 2008, 10, 212-225.
[21] Nunez, C.; Cansino, J. R.; Bethencourt, F.; Pe´rez-Utrilla, M.; Fraile, B.; Martı´nez-Onsurbe, P.; Olmedilla, G.; Paniagua, R.; Royuela, M. TNF/IL-1/NIK/NF-jB transduction pathway: A comparative study in normal and pathological human prostate (benign hyperplasia and carcinoma). Histopathology, 2008, 53, 166–176.
[22] Haeberle, H.A.; Nesti, F.; Dieterich, H.J.; Gatalica, Z.; Garofalo, R.P. Perflubron reduces lung inflammation in respiratory syncytial virus infection by inhibiting chemokine expression and Nuclear Factor–κB activation. Am J Respir Crit Care Med., 2002, 165, 1433–1438.
[23] Hayden, M. S.; Ghosh, S. Shared Principles in NF-κB signaling. Cell,2008, 132,344-362.
[24] Collins, T.; Cybulsky, M. I. NF-κB: Pivotal mediator or innocent bystander in atherogenesis?. The Journal of Clinical Investigation, 2001, 107, 255-264.
[25] Chen and, F.E.; Ghosh, G. Regulation of DNA binding by Rel/NF-kB transcription factors: Structural views. Oncogene, 1999, 18, 6845 - 6852.
[26] Jhaveri, K. A.; Ramkumar, V.; Trammell, R. A. ; Toth, L. A. Spontaneous, homeostatic, and inflammation-induced sleep in NF-κB p50 knockout mice. Am. J. Physiol. Regul. Integr. Comp. Physiol., 2006, 291, 1516–1526.
[27] Gao, Z.; Chiao, P.; Zhang, X.; Zhang, X.; Lazar, M.; Seto, E.; Young, H.A.; Ye, J. Coactivators and corepressors of NF-κB in IκB alpha gene promoter. J. Biol. Chem., 2005, 280(22), 21091–21098.
[28] Campbell, I.K.; Gerondakis, S.; O'Donnell, K.; Wicks, I.P. Distinct roles for the NF-kB1 (p50) and c-Rel transcription factors in inflammatory arthritis. The Journal of Clinical Investigation, 2000, 105, 1799-1806.
[29] Huxford, T.; Malek, S.; Ghosh, G. Preparation and crystallization of dynamic NF-kB/IkB complexes. The Journal of Biologocal Chemistry, 2000, 275, 32800–328
[30] Gilmore, T.D. The Rel/NF-kB signal transduction pathway: Introduction. Oncogene, 1999, 18, 6842 - 6844.
[31] Napolitano, M.; Zei, D.; Centonze, D.; Palermo, R.; Bernardi, G.; Vacca, A.; Calabresi, P.; Gulino, A. NF-kB/NOS cross-talk induced by mitochondrial complex II inhibition: Implications for Huntington's disease. Neuroscience Letters, 2008, 434, 241–246.
[32] Austin, R. L.; Rune, A.; Bouzakri, K.; Zierath, J. R.; Krook, A. siRNA-mediated reduction of inhibitor of Nuclear Factor-κB Kinase prevents Tumor Necrosis Factor-α–induced insulin resistance in human skeletal muscle. Diabetes, 2008, 57, 2066-2073.

[33] Basak, S.; Kim, H.; Kearns, J.D.; Tergaonkar, V.; O'Dea, E.; Werner, S. L.; Benedict, C. A.; Ware, C. F.; Ghosh, G.; Verma, I.M.; Hoffmann, A. A fourth IκB protein within the NF-κB signaling module. Cell, 2007, 128, 369–381.

[34] Dong, Q.G.; Sclabas, G. M, Fujioka, S.; Schmidt, C.; Peng, B.; Wu, T.; Tsao, M.S.; Evans, D. B.; Abbruzzese, J. L.; JMcDonnell, T.; Chiao, P.J. The function of multiple IkB: NF-kB complexes in the resistance of cancer cells to taxol-induced apoptosis. Oncogene, 2002, 21, 6510 – 6519.

[35] Haskill, S.; Beg, A.A.; Tompkins, S.M.; Morris, J.S.; Yurcochko, A.D.; Sampson-Johannes, A.; Mondal, K.; Ralph, P.; Baldwin, A.S. Characterization of an immediate-early gene induced in adherent monocytes that encodes IκBα-like activity. Cell, 1991, 65, 1281-1289.

[36] Thompson, J.E.; Philips, R.J.; Erdjument-Bromage, H.; Tempst, P.; Ghosh, S. IκBβ regulates the persistent response in a phasic activation of NF-κB. Cell, 1995, 80, 573-582.

[37] Whiteside, S.T.; Epinat, J.C.; Rice, N.R.; Israel, A. IκBe, a novel member of the IκB family, controls RelA and CRel NF-κB activity. EBMO. J., 1997, 16, 1413-1426.

[38] Ohno, H.; Takimoto, G.; MCKeithan, T.W. The candidate proto-oncogene bcl-3 is related to genes implicated in cell cycle control. Cell, 1990, 60, 991-997.

[39] Hay, R.T.; Vuillard, L.; Desterro J.M.P.; Rolriguez M.S. Control of NF-κB transcriptional activation by signal induced proteolysis of IκBα. Phil. Trans. R. Soc. Lond. B., 1999, 354, 1601-1609.

[40] Massa, P.; Aleyasin, H.; Park, D.S.; Mao, X.; Barger, S.W.NFκB in neurons? The uncertainty principle in neurobiology. J. Neurochem., 2006, 97, 607–618.

[41] Newton, R.; Holden, N.S.; Catley, M.C.; Oyelusi, W.; Leigh, R.; Proud, D.; Barnes, P.J. Repression of inflammatory gene expression in human pulmonary epithelial cells by small-molecule IκB kinase inhibitors. JPET., 2007, 321, 734–742.

[42] Sachdev, S.; Hoffmann, A.; Hannink, M. Nuclear Localization of IkBa Is Mediated by the Second Ankyrin Repeat: the IkBa Ankyrin Repeats Define a Novel Class of cis-Acting Nuclear Import Sequences. Molecular and cellular biology, 1998, 18, 2524–2534.

[43] Karin, M.; The beginning of the end: IkB kinase (IKK) and NF-kB activation. The Journal of Biological Chemistry, 1999, 274, 27339–27342.

[44] Hiscott, J.; Kwon, H.; Génin, P. Hostile takeovers: Viral appropriation of the NF-κB pathway. The Journal of Clinical Investigation, 2001, 107,143-151.

[45] Sosne, G.; Qiua, P.; Christophersona, P. L.; Wheater, M.K. Thymosin beta 4 suppression of corneal NFκB: A potential anti-inflammatory pathway. Exp. Eye. Res., 2007, 84, 663–669.

[46] Malek, S.; Huang, D.B, Huxford, T.; Ghosh, S.; Ghosh, G. X-ray crystal structure of an IκBβ.NF-κB p65 homodimer complex. The Journal of Biological Chemistry, 2003, 278, 23094–23100.

[47] Hayakawa, M.; Miyashita, H.; Sakamoto, I.; Kitagawa, M.; Tanaka, H.; Yasuda, H.; Karin, M.; Kikugawa, K. Evidence that reactive oxygen species do not mediate NF-kB activation. The EMBO Journal, 2003, 22 , 3356-3366.

[48] Lentsch, A.B.; Czermak, B.J.; Bless, N.M.; Ward P.A. NF-KB Activation during IgG immune complex- induced lung injury.Am.J.Pathol., 1998, 152, 1327-1336.

[49] Desaki, M.; Okazaki, H.; Sunazuka, T.; Omura, S.; Yamamoto, K.; Takizawa, H. Molecular mechanisms of anti-inflammatory action of erythromycin in human bronchial epithelial cells: Possible role in the signaling pathway that regulates Nuclear Factor-κB activation. Antimicrobial agents and chemotherapy, 2004, 48, 1581–1585.

[50] Mukhopadhyay, A.; Manna, S.K.; Aggarwal, B.B. Pervanadate-induced Nuclear Factor-kB activation requires tyrosine phosphorylation and degradation of IkBa. The Journal of Biological Chemistry, 2000, 275, 8549–8555.

[51] Hideshima, T.; Chauhan, D.; Richardson, P.; Mitsiades, C.; Mitsiades, N.; Hayashi, T.; Munshi, N.; Dang, L.; Castro, A.; Palombella, V.; Adams, J.; Anderson K.C. NF-κB as a therapeutic target in multiple myeloma. The Journal of Biological Chemistry, 2002, 277, 16639–16647.

[52] LI, X.; MASSA, P.E.; Hanidu, A.; PEET, G. W.; ARO4, P.; Savitt, A.; Mische, S.; LI, J.; Marcu, K.B.. IKKα, IKKβ and NEMO/IKKγ are each required for the NF-κB mediated inflammatory response program. J. Biol. Chem., 2002, 277, 45129–45140.

[53] Wang, X.; Hussain, S.; Wang, E.J.; Wang, X.; Li, M. O.; García-Sastre. A.; Beg, A. A.Lack of essential role of NF-{kappa}B p50, RelA, and crel subunits in virus-induced Type 1 IFN expression. J. Immunol., 2007,178, 6770-6776.

[54] Livolsi, A.; Busuttil, V.; Imbert, V.; Abraham, R.T.; Peyron, J. Tyrosine phosphorylation-dependent activation of NF-kB requirement for p56 LCK and ZAP-70 protein tyrosine kinases. Eur. J. Biochem., 2001, 268, 1508-1515.

[55] Maniatis, T. A ubiquitin ligase complex essential for the NF-kB, Wnt/Wingless, and Hedgehog signaling pathways. Genes Dev., 1999, 13, 505-510.

[56] Ziegelbauer, K.; Gantner, F.; Lukacs, N. W.; Berlin, A.; Fuchikami, K.; Niki, T.; Sakai, K.; Inbe, H.; Takeshita, K.; Ishimori, M.; Komura, H.; Murata, T.; Lowinger, T.; Bacon, K. B. A selective novel low-molecular-weight inhibitor of IjB kinase-b(IKK-b) prevents pulmonary inflammation and shows broad anti-inflammatory activity. British Journal of Pharmacology, 2005,145, 178–192.

[57] Garg, A.; Aggarwal, B.B. Nuclear transcription factor-_B as a target for cancer drug development. Leukemia, 2002, 16, 1053–1068.

[58] Zhang, G.; Ghosh, S. Toll-like receptor–mediated NF-kB activation: A phylogenetically conserved paradigm in innate immunity. The Journal of Clinical Investigation, 2001, 107, 13-19.

[59] Yao, H.; Yang, S.R.; Kode, A.; Rajendrasozhan, S.; Caito, S.; Adenuga, D.; Henry, R.; Edirisinghe, I.; Rahman, I. Redox regulation of lung inflammation: Role of NADPH oxidase and NF-κB signaling. Biochemical Society Transactions, 2007, 35, 1151-1155.

[60] Lucas, P. C.; McAllister-Lucas,L. M.; Nunez, G. NF-kB signaling in lymphocytes: A new cast of characters. Journal of Cell Science, 2004, 117, 31-39.

[61] Karin, M.; The IκB kinase – a bridge between inflammation and cancer. Cell Research, 2008,18, 334-342.

[62] Beinke, S.; Ley, S.C. Functions of NF-κB1 and NF-κB2 in immune cell biology. Biochem. J., 2004, 382, 393–409.

[63] Ward, C.; Walker, A.; Dransfield, I.; Haslett, C.; Rossi, A.G. Regulation of granulocyte apoptosis by NF-κB. Biochemical Society Transactions, 2004, 32,465-467.

[64] Yamamoto, Y.; Gaynor, R. B. Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. The Journal of Clinical Investigation, 2001, 107, 135-142.

[65] Tak P.P.; Firestein, G. S. NF-kB: A key role in inflammatory diseases. The Journal of Clinical Investigation, 2001, 107, 7-11.

[66] Corradi, M.; Zinelli, C.; Caffarelli, C. Exhaled breath biomarkers in asthmatic children. Inflamm Allergy Drug Targets, 2007, 6, 150-159.

[67] Bullens, D.M. Measuring T cell cytokines in allergic upper and lower airway inflammation: Can we move to the clinic?. Inflamm Allergy Drug Targets, 2007, 6, 81-90.

[68] Poynter, M.E.; Cloots, R.; Woerkom, T.V.; Butnor, K.J.; Vacek, P.; Taatjes, D. J.; Irvin, C.G.; Janssen-Heininger, Y. M.W. NF-κB Activation in airways modulates allergic inflammation but not hyperresponsiveness. The Journal of Immunology, 2004, 173, 7003–7009.

[69] Broide, D.H. Immunologic and inflammatory mechanisms that drive asthma progression to remodeling. J Allergy Clin. Immunol., 2008, 121, 560–572.

[70] Chetta, A.; Zanini, A.; Torre, O.; Olivieri D. Vascular remodelling and angiogenesis in asthma: Morphological aspects and pharmacological modulation. Inflamm Allergy Drug Targets, 2007, 6, 41-45.

[71] Fang, C.; Corrigan, C. J.; Ying, S. The treatment targets of asthma: From laboratory to clinic. Inflamm Allergy Drug Targets, 2008, 7, 119-28.

[72] Cousins, D. J.; McDonald, J.; Lee, T. H. Therapeutic approaches for control of transcription factors in allergic disease. J. Allergy. Clin. Immunol., 2008, 121, 803-9.

[73] Christman, J.W.; Sadikot R.T.; Blackwell, T.S. The role of nuclear Factor-k B in pulmonary diseases. Chest., 2000, 117, 1482-1487.

[74] Bracke, K. R.; Demedts, I. K.; Joos, G. F.; Brusselle, G. G. CC-chemokine receptors in chronic obstructive pulmonary disease. Inflamm Allergy Drug Targets, 2007, 6,75-79.

[75] Ning, W.; Li, C.J.; Kaminski, N.; Feghali-Bostwick, C. A.; Alber, S.M.; Di, Y.P.; Otterbein, S.L.; Song, R.; Hayashi, S.; Zhou, Z.; Pinsky, D.J.; Watkins, S.C.; Pilewski, J.M.; Sciurba, F.C. ; Peters, D.G.; Hogg, J.C.; Choi, A.M. K. Comprehensive gene expression profiles reveal pathways related to the pathogenesis of chronic obstructive pulmonary disease. PNAS.; 2004, 10, 14895–14900.

[76] Szulakowski, P.; Crowther, A. J. L.; Jime´nez, L.A.; Donaldson, K.; Mayer, R.;. Leonard, T.B.; MacNee, W.; Drost. E.M. The effect of smoking on the transcriptional regulation of lung inflammation in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care, 2006, 174, 41–50.

[77] Preciado, D.; Lin, J.; Wuertz, B.; Rose, M. Cigarette smoke activates NFκB and induces Muc5b expression in mouse middle ear cells. Laryngoscope, 2008, 118, 464–471.

[78] Liu, X.; Togo, S.; Al-Mugotir, M.; Kim, H.; Fang, Q.; Kobayashi, T.; Wang, X.; Mao, L.; Bitterman, P.; Rennard, S. NF-kappaB mediates the survival of human bronchial epithelial cells exposed to cigarette smoke extract. Respiratory Research, 2008, 9, 1-11.

[79] Brown, V.; Elborn, J. S.; Bradley, J.; Ennis, M. Dysregulated apoptosis and NFκB expression in COPD subjects. Respiratory Research, 2009, 10, 1-12.

[80] Caramori, G.; Romagnoli, M.; Casolari, P.; Bellettato, C.; Casoni, G.; Boschetto, P.; Chung, K. F.; Barnes, P.J.; Adcock, I .M.; Ciaccia, A.; M Fabbri, L.; Papi, A. Nuclear localisation of p65 in sputum macrophages but not in sputum neutrophils during COPD exacerbations. Thorax, 2003, 58, 348–351.

[81] Di Stefano, A.; Caramoriw, G.; Ricciardoloz, F. L. M., Capelli, A.; Adcock , I. M.; Donner, C. F. Cellular and molecular mechanisms in chronic obstructive pulmonary disease: An overview. Clin. Exp. Allergy, 2004. 34, 1156–1167.

[82] Muselet-Charlier, C.; Roque, T.; Boncoeur, E.; Chadelat, K.; Clement, A.; Jacquot, J.; Tabary, O.Enhanced IL-1beta-induced IL-8 production in cystic fibrosis lung epithelial cells is dependent of both mitogen-activated protein kinases and NF-kappaB signaling. Biochem. Biophys. Res. Commun., 2007, 357, 402-407.

[83] Reiniger, N.; Ichikawa, J.K.; Pier, G.B. Influence of cystic fibrosis transmembrane conductance regulator on gene expression in response to *Pseudomonas aeruginosa* infection of human bronchial epithelial cells. Infect. Immun., 2005, 73, 6822-6830.

[84] Joseph, T.; Look, D.; Ferkol, T. NF-kappaB activation and sustained IL-8 gene expression in primary cultures of cystic fibrosis airway epithelial cells stimulated with *Pseudomonas aeruginosa*. Am. J. Physiol. Lung. Cell Mol. Physiol., 2005, 288, 471-479.

[85] Tchilibon, S.; Zhang, J.; Yang, Q.; Eidelman, O.; Kim, H.; Caohuy, H.; Jacobson, K.A.; Pollard, B.S.; Pollard, H.B. Amphiphilic pyridinium salts block TNF alpha/NF kappa B signaling and constitutive hypersecretion of interleukin-8 (IL-8) from cystic fibrosis lung epithelial cells. Biochem. Pharmacol., 2005, 70, 381-393.

[86] Saadane, A.; Masters, S.; DiDonato, J.; Li, J.; Berger, M. Parthenolide inhibits IkappaB kinase, NF-kappaB activation, and inflammatory response in cystic fibrosis cells and mice. Am. J. Respir. Cell. Mol. Biol., 2007, 36, 728-36.

[87] Nicolis, E.; Pasetto, M.; Cigana, C.; Pradal, U.; Assael, B.M.; Melotti, P. The GCC repeat length in the 5'UTR of MRP1 gene is polymorphic: a functional characterization of its relevance for cystic fibrosis, BMC Med Genet. 2006 7;7:7.

[88] Moine, P.; Mclntyre, R.; Schwartz, M.D.; Kaneko, D.; Shenkar, R.; Tulzo, Y.L.; Moore, E.E.; Abraham, E. NF-KB Regulatiory mechanism in alveolar macrophages from patients with acute respiratory distress syndrome. Shock, 2000,13, 85-91.

[89] Yang, H.; Bocchetta, M.; Kroczynska, B.;. Elmishad, A.G.; Chen, Y.; Liu, Z.; Bubici, C.; Mossman, B. T.; Pass, H.I.; Testa, J.R.; Franzoso, G.; Carbone, M. TNF-α inhibits asbestos-induced cytotoxicity via a NF-κB-dependent pathway; A possible mechanism for asbestos-induced oncogenesis, PNAS., 2006, 103, 10397–10402.

[90] Janssen, Y.M.; Driscoll, K.E.; Howard, B. Asbestos causes translocation of p65 protein and increases NF-kB DNA binding activity in rat lung epithelial and pleural mesothelial cells. Am. J. Pathol., 1997, 151, 389–401.

[91] Gius, D.; Botero, A.; Shah, S. Intracellular oxidation/ reduction status in the regulation of transcription factors NF-kB and AP-1. Toxicol. Lett., 1999, 106, 93–106.

[92] Janssen, Y.M.; Barchowsky, A.; Treadwell, M. Asbestos induces nuclear factor kappa B (NF-kB) DNA-binding activity and NF-kB-dependent gene expression in tracheal epithelial cells. Proc. Natl. Acad. Sci.; 1995, 92, 8458–8462.

[93] Ebrahimi M, Roudkenar MH, Imani Fooladi AA, Halabian R, Ghanei M, Kondo H, Nourani MR. Discrepancy between mRNA and protein expression of neutrophil gelatinase-associated lipocalin in bronchial epithelium induced by sulfur mustard. J Biomed Biotechnol. 2010;2010:823131. Epub 2010 May 20.

[94] Beheshtia, J.; Marka, E. J.; Akbaeib, H. M. H.; Aslanib, J.; Ghanei, M.; Mustard lung secrets: Long term clinicopathological study following mustard gas exposure, Pathology – Research and Practice, 2006, 202, 739–744.

[95] Qui, M.; Paromov, V.M.; Yang, H.; Smith, M.; Stone, W. L: Inhibition of inducible nitric oxide synthase by a mustard gas analog in murine macrophages. BMC Cell Biology, 2006, 7, 1-9.

[96] Pourazar, J.; Blomberg, A.; Kelly, F.J., Davies, D.E.; Wilson, S.J.; Holgate, S.T.; Sandström, T. Diesel exhaust increases EGFR and phosphorylated C-terminal Tyr 1173 in the bronchial epithelium. Particle and Fibre Toxicology, 2008, 5, 1-9.

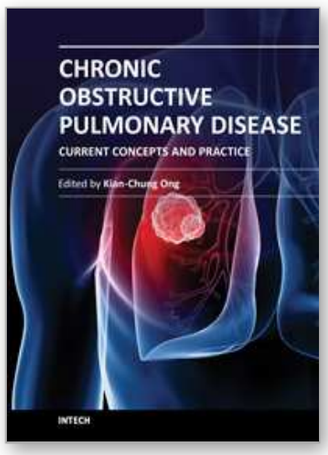
[97] Baldwin, A.S. The transcription factor NF-kB and human disease. The Journal of Clinical Investigation, 2001, 107, 3-6.

[98] Baldwin, A.S. Control of oncogenesis and cancer therapy resistance by the transcription factor NF-κB. The Journal of Clinical Investigation, 2001, 107, 241-246.

[99] Feng, B.; Cheng, S.; Pear W.S.; Liou, H.C. NF-kB inhibitor blocks B cell development at two checkpoints. Medical Immunology, 2004, 3, 1-16.

[100] Epinat, J.C.; Gilmore, T.D. Diverse agents act at multiple levels to inhibit the Rel/NF-kB signal transduction pathway. Oncogene, 1999, 18, 6896 - 6909.

[101] Ghanei, M.; Hosseini Khalili, A.R.; Arab, M.J.; Mojtahedzadeh, M.; Aslani, J.; Lessan-Pezeshki, M.; Panahi Y.; Alaeddini, F. Diagnostic and therapeutic value of short-termcorticosteroid therapy in exacerbation of mustard gas-induced chronic bronchitis. Basic & Clinical Pharmacology & Toxicology, 2005, 97, 302–305.



Chronic Obstructive Pulmonary Disease - Current Concepts and Practice

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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