The involvement of NF-κB Transcription factor in asthma

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NF-κB, nuclear factors, NF-κB and asthma, NF-κB signaling, NF-κB inhibitors, Mexico.

Abstract
PubMed search was performed using the key words: NF-κB, nuclear factors, asthma. Articles were selected based on their relevance to this review.
Objective: To review the literature regarding the involvement of the nuclear factor kappa-B (NF-κB) transcription factor in asthma.
Results: NF-κB is a critical transcription factor for the production of many inflammatory cytokines. NF-κB is associated with several diseases, including asthma, where there is an inflammation of the airways with cell infiltration. It is activated in bronchial asthmatic patient biopsies and active in the epithelium of the airways in mice after stimulation. It also participates in the maintenance of the chronic inflammatory response. NF-κB also acts synergistically with other transcription factors, to induce the maximal expression of genes involved with asthma. Activation of NF-κB by several stimuli induces the release and degradation of the inhibitory protein IκB from the dimeric complex followed by translocation of NF-κB to the nucleus.
Conclusions: The NF-κB pathway is central to the pathogenesis of asthma. NFκB is an important therapeutic target for the treatment of asthma, including intermediate products on the signaling pathway and protein related to Rel. Alterations in the NF-κB signaling pathway are associated with the disease.

PALABRAS CLAVE:
Factor nuclear NF-κB, NF-κB y asma, señalización de NF-κB, inhibidores NF-κB, México.

Participación del factor de transcripción NF-kB en el asma

Resumen
Se investigaron en PubMed las palabras clave: NF-κB, factores nucleares, NF-κB y asma, señalización de NF-κB, inhibidores de NF-κB. Los artículos se seleccionaron por su relevancia para esta revisión. Objetivo: Revisar la bibliografía existente acerca de la participación del factor de transcripción nuclear kappa-B (NF-κB) en el asma.
Resultados: NF-κB es un factor de transcripción crítico para la producción de muchas citocinas. NF-κB está asociado a varias enfermedades, entre ellas el asma, en donde encontramos una inflamación de las vías aéreas con infiltración de células. El NF-κB se encuentra...
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Introduction

The signaling pathways activated by the nuclear factor kappa-B (NF-κB) transcription factor are evolutionarily conserved and have an important role in activating and coordinating both innate and adaptive immune responses. NF-κB acts as a central pro-inflammatory factor in the induction of pro-inflammatory genes. Its activation leads to changes in gene expression, such as the synthesis of cytokines. NF-κB was first identified as a DNA-binding protein at the κB site, localized in the enhancer region of the immunoglobulin κ light chain B lymphocyte gene. It is a heterodimeric p65-p50 protein that belongs to a family of transcription factors, all of which have been found in all mammalian cells studied.

The NF-κB family has five members: Rel A (p65), c-Rel, Rel-B, NF-κB1 (p50) and NF-κB2 (p52). All have a conserved region of 300 amino acids, where the dimerization domain, DNA-binding region, and nuclear localization signal are all found. In addition, Rel A, Rel B and c-Rel (known as the Rel family) all have carboxy-terminal transcriptional domains that strongly activate transcription at the NF-κB-binding sites in target genes. The p50 and p52 proteins are generated by proteolysis from their precursors, p105 and p100, respectively. All members of NF-κB family can form homodimers (except Rel B) and heterodimers. In resting cells, the NF-κB dimers bind to proteins known as NF-κB inhibitors (IκBs), which retain the dimers in the cytoplasm. The binding of an IκB protein with a NF-κB protein masks the nuclear localization signal, thus inhibiting nuclear transport. The IκB gene family includes IκBα, IκBβ, IκBε, IκBγ, Bcl3; the precursors are p100 and p105. IκB proteins are characterized by the presence of multiple ankyrin domains, which mediate their protein-protein interactions with NF-κB. Both p100 and p105 proteins have repeated units of ankyrin that’s allow them to act as inhibitors. When cleaved, the ankyrin units are released as p50 and p52, (which can translocate to the nucleus).

In order to become active, IκB proteins must be phosphorylated by IκB kinases (IKKs). IKKs form a complex of three subunits; the subunits IKKα (IKK1) and IKKβ (IKK2) are catalytic, while the third subunit, IKKγ (also known as NEMO for NF-κB essential modifier), play a regulatory role. Degradation of the IκB protein bound to an NFκB dimer exposes the nuclear localization signal and allows the dimer to translocate to the nucleus. Once in the nucleus, NF-κB dimers bind to DNA with the general consensus sequence 5’-GGGRN-NYYCC-3’ (R = purine, Y = pyrimidine, N = any nucleotide) to transcriptionally regulate numerous genes.

Mechanisms that regulate NF-κB-mediated responses include nuclear localization and nuclear export signals, proteolytic processing, phosphorylation, acetylases, methylases, the diversity of dimer combinations, and the presence of p50 and p52 homodimers. As p50 and p52 homodimers do not possess carboxy-terminal transcriptional activation domains, they compete with NF-κB dimers on DNA to modulate transcription.

Involvement of NF-κB in asthma

Alterations in NF-κB signaling are associated with various metabolic and inflammatory diseases and diverse types of cancer. Among these diseases are asthma, diabetes, gastritis Helicobacter pylori-associated, atherosclerosis, rheumatoid arthritis, systemic sclerosis and inflammatory bowel disease.
Asthma is of particular interest as the disease is characterized by airway inflammation and infiltration into the lungs by eosinophils, monocytes/macrophages, lymphocytes, and mast cells. It is also associated with the increased expression of several important inflammatory proteins, including cytokines and adhesion molecules, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). In particular, expression of these proteins positively correlates with NF-κB activation in bronchial biopsies from asthmatic patients. The increase in the all the aforementioned processes involves increased transcription of inflammatory genes that are known to be regulated by transcription factors. NF-κB regulates the expression of a large number of genes involved in the immune and inflammatory responses. NF-κB can be activated by various stimuli, including cytokines, reactive oxygen species and microorganisms that induce the degradation and release of IκB from p50 and p65 complex. Various lines of data suggest that NF-κB plays an important role in the maintenance of the chronic inflammatory response in asthma. Among these is the observed increase of cytokines in the airway epithelium, such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), IL-4 and IL-5; chemokines such as IL-8, monocyte chemotactic protein 1 (MCP-1), RANTES, eotaxin, macrophage inflammatory protein 1α (MIP-1α), granulocyte macrophage colony stimulating factor (GM-CSF); enzymes such as iNOS and COX-2, adhesion molecules including VCAM-1, ICAM, E-selectin and anti-apoptotic proteins. The genes of all these proteins are regulated by NF-κB. Additionally, the most effective treatment for asthma is glucocorticoids (GCs), which inhibit NF-κB. GCs have been shown to prevent interaction between NF-κB and DNA and the direct interaction between NF-κB and the glucocorticoid receptor (GR).

In this regard, several studies have shown that GC therapy reduces the activity of NF-κB in tissues ex vivo. Bronchial biopsies from patients with stable asthma show that treatment with budesonide increases GR-DNA binding and reduces the binding between NF-κB and DNA. The binding of GC with β2 agonists inhibits NF-κB more effectively. Further, administration of fluticasone and salmeterol diminishes phospho-IκB in T cells from asthma patients, which suggests that this molecule can be a target for the action of GCs.

Inducible and transcriptionally active forms of NF-κB have been demonstrated in samples from asthmatic patients, which reflect an increase in the expression of certain cytokines and enzymes observed in these patients. In asthma, NF-κB not only induces gene expression on its own, but it also acts synergistically with other transcription factors, including GR, activator protein-1 (AP-1) and nuclear factor of activated T cells (NF-AT) to induce the maximal expression of genes involved in asthma pathogenesis. NF-κB and AP-1 are increased in the majority of chronic inflammatory conditions (e.g., asthma, arthritis).

Inflammation in asthma is both a central pathological characteristic and the primary clinical manifestation. It is responsible for airway obstruction and hyper-reactivity. The histamine involved in this process promote inflammation by inducing NF-κB activation, which activates genes whose proteins promote inflammation and the maturation of T cells in asthma patients and animal models. Studies with transgenic mice show that inhibiting NF-κB in the airway epithelium diminishes inflammation, the expression of NF-κB-dependent inflammatory mediators and the production of the Th2-associated cytokines IL-4, IL-10 and IL-13; in addition, NF-κB inhibition also decreases the circulating levels of IgE.

Mutations that inactivate NF-κB are generally lethal due to the essential role that NF-κB plays in protecting cells from apoptosis. The improper functioning of NF-κB in apoptosis has an important role in the chronicity of many inflammatory diseases, including asthma, where recruitment of immune cells can have adverse effects. NF-κB is crucial in the perpetuation of the inflammatory reaction in asthma and its levels of expression increase with the severity of the disease. Increased expression of the anti-apoptotic Bcl-2 protein coupled with decreased expression of the pro-apoptotic Bax protein has been observed in peripheral blood lymphocytes taken from patients during asthmatic episodes.

Some studies show that NF-κB stimulates the expression and activity of Bcl-2, while inhibiting Bax. Abdulamir and cols. found a significant increase in NF-κB in patients with severe asthma. The increased levels of NF-κB expression in these patients may explain the increase in the Bcl-2/Bax ratio. This suggests a progressive decrease in apoptosis and an increase in the survival
of lymphocytes that infiltrate the lung of patients with severe asthma, these observations indicate an important role of these proteins in the pathophysiology of asthma. In addition to the physical injury observed in the airway epithelium of asthmatic patients, there are also signs of stress with the expression of heat shock proteins, and the activation of transcription factors such as NF-κB.

A better understanding of the mechanisms of NF-κB activation will provide an excellent platform for the development of new therapies to combat inflammatory diseases.

NF-κB represents an attractive and important therapeutic target for the treatment of inflammatory diseases, including asthma. In the last decade, several compounds that interfere with this pathway have been studied. Plant-derived compounds including, lignans polyphenols, resveratrol, epigallocatechins and quercitins have been evaluated as possible NF-κB inhibitors. One example is andrographolide, the principal active compound from the medicinal plant Andrographis paniculata. It has been shown to reduce airway inflammation and decrease cellular infiltration into the lung; further, andrographolide has been shown to inhibit ovalbumin-induced airway inflammation in a dose-dependent manner. Treatment with andrographolide resulted in decreased total numbers of lymphocytes, macrophages, neutrophils and eosinophils and reduced concentrations of the cytokines IL-4, IL-5, and IL-13 in broncho-alveolar lavage fluid. It also blocks the nuclear translocation of p65 and DNA binding activity in nuclear extracts from lung tissues of mice treated with ovalbumin (OVA). These studies illustrate a therapeutic value for andrographolide in the treatment of asthma, as it inhibits NF-κB signaling by blocking κB kinase-beta activation. Other authors have suggested that the anti-inflammatory mechanisms of andrographolide are associated with the expression of NF-κB in the lung and the suppression of the translocation of NF-κB from the cytoplasm to the nucleus in airway epithelial cells, where inflammation and cellular infiltration is reduced. The above mentioned is founded in the observation that inflammation in asthma, independent of stimulus, is mediated, at least in part, by NF-κB in various cell types.

Regulation of gene transcription.

Pernis and Rothman suggest the possible participation of the JAK and STAT pathway in asthma. TNF-α and IL-4, cytokines relevant to asthma, stimulate the expression of the eotaxin gene by activation of NF-κB and STAT 6. IL-4-induced STAT 6 signaling is essential for the increase in the production of IgE in asthma, and a polymorphism in this gene could explain the genetic predisposition of high levels of IgE in asthma patients.

In bronchial asthma, STATs 5 and 6 are responsible for cellular responses to IL-4 and IL-5. These STATs migrate into the nucleus and dimerize, attaching themselves to regulatory sequences and nuclear transcription factors. In T lymphocytes, STAT dimmers interact with NF-κB and NF-AT, while in Th2 lymphocytes, STAT dimmers interaction with the transcription factors c-maf, GATA 3 and STAT 6. In Th1 lymphocytes, the transcription factors T- bet and STAT 4 interact with STAT dimers. All are under the control of positive and negative regulatory sequences. In STAT 6 -/- mouse models, a significantly diminished response of airways has been observed, along with a lower number of infiltrating eosinophils and a change of cytokines from Th1 to Th2.

A detailed characterization of the molecules involved in NF-κB activation is required in order to develop specific pharmacological inhibitors of this protein, which could have potent anti-inflammatory effects.

References

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