Nuclear Factor Kappa B as A Prognostic Factor in Nephrotic Syndrome and Acute Renal Failure

Thesis

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Introduction

NF-κB was first discovered in the lab of Nobel Prize laureate David Baltimore. (***Baltimore et al, 1986)***

NF-κB which is the nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls the transcription of DNA.

NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. ***(Brasier, 2006)***

NF-κB plays important roles in the immune system. NF-κB plays a key role in regulating the immune response to infection. Conversely, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases. ***(Beinke et al, 2004)***

Recent data have shown that NF-κB is activated in tubules and glomeruli in various experimental models of renal injury. In vitro studies also suggest that proteinuria could be an important NF-κB activator. ***(Mezzano et al, 2001)***

There is growing evidence that abnormal glomerular permeability to proteins causes proximal tubular cell

dysfunction, and that proteinuria elicits tubular activation associated with transcription factor activation and overexpression of chemokines and fibrogenic cytokines. ***(Mezzano et al, 2001)***

We therefore addressed the idea that NF-κB could be an indicator of renal damage progression in human proteinuric nephropathies and acute renal failure.

We studied the in situ expression of activated transcription factors NF-κB in renal biopsy sections of patients with nephrotic syndrome and acute renal failure.

We also approached the idea that NF-κB may be an indicator of renal damage progression in patients with acute renal failure.

Abstract

Nuclear Factor Kappa B as A Prognostic Factor in Nephrotic Syndrome and Acute Renal Failure

Background: Nephrotic syndromes and acute renal failure are very common diseases. NF-κB is a protein complex that controls the transcription of DNA. Recent data have shown that NF-κB is activated in tubules and glomeruli in various experimental models of renal injury. During the last few years, a number of articles have suggested that the detection of NF-κB in various tissues including the kidney may be a sign of injury. **Objectives:** We addressed the idea that NF-κB could be an indicator of renal damage progression in human proteinuric nephropathies. **Methods:** We studied the in situ expression of activated transcription factors NF-κB in renal biopsy sections of patients with nephrotic syndrome and acute renal failure. Kidney samples were obtained by percutaneous renal biopsy. The renal biopsies from 20 patients with nephrotic range proteinuria (10 with FSGS and 10 with any other glomerulonephritis) were studied and compared with those from 10 patients with acute renal failure. The diagnosis of GN and acute renal failure was made based on clinical and histological findings. Standard studies were done to exclude secondary causes. **Results:** The mean NF-κB level was higher in the ARF group (mean 1085, ±SD 463.4) compared to the nephrotic group (mean: 568.8, ±SD 283.4), and FSGS group, (mean 628.4 ±SD 183.1). NF-κB levels resulted in, that patients with MPGN had the highest levels, mean 795 SD ±643.5, followed by the MesPGN patients, mean 598.7, SD ± 166.5. The lowest levels were found in patients with membranous nephropathy, mean 387.5 and SD ± 101.1. There was a positive correlation with the serum creatinine level for all groups of patients before treatment (r=0.531, p=<0.01) and after three months follow up (r=0.568, p=<0.05). Yet we couldn't elicit a significant correlation with proteinuria except in the FSGS group. **Conclusion:** we couldn't prove NF-κB as a predictor for outcome yet further studies need to study the NF-κB subunits in different causes of nephrotic syndrome.

Keywords: nuclear factor-κB, nephrotic syndrome, acute renal failure

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Aim of Work

We addressed the idea that NF-κB could be an indicator of renal damage progression in human proteinuric nephropathies and patients with acute renal failure

The Nuclear Factor Kappa B

NF-κB was first discovered in the lab of Nobel Prize laureate David Baltimore. (***Baltimore et al, 1986)***

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NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. ***(Brasier, 2006)***

NF-κB plays important roles in the immune system; NF-κB plays a key role in regulating the immune response to infection. Conversely, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κB has also been implicated in processes of synaptic plasticity and memory. ***(Albensi & Mattson, 2000) (Beinke et al, 2004)***

NF-κB regulates the expression of cytokines, inducible nitric oxide synthase (iNOS), cyclo-oxgenase 2 (COX-2), growth factors, inhibitors of apoptosis and effectors enzymes in response to ligation of many receptors involved in immunity

including T-cell receptors (TCRs), B-cell receptors (BCRs) and members of the Toll-like receptor/IL-1 receptor super family.

NF-κB also plays a role in the development and the activity of a number of tissues including the central nervous system. Moreover, pathological dysregulation of NF-κB is linked to inflammatory and autoimmune diseases as well as cancer. ***(Memet 2006).***

The NF-κB family

In mammals, the NF-κB family is composed of five related transcription factors:

- p50,
- p52,
- RelA (p65),
- c-Rel
- RelB.

These transcription factors are related through an N-terminal, 300 amino acid, DNA binding/dimerization domain, called the Rel homology domain (RHD), through which they can form homodimers and heterodimers that bind to 9-10 base pair DNA sites, known as κB sites, in the promoters and enhancer regions of genes, thereby modulating gene expression. RelA, c-Rel and RelB contain C-terminal transcriptional activation domains (TADs), which enable them to activate target gene expression. In contrast, p50 and p52 do not contain C-terminal TADs; therefore, p50 and p52 homodimers repress transcription unless they are bound to a protein containing a TAD, such as RelA, c-Rel or RelB or Bcl-3 (a related transcriptional co-activator). Unlike the other NF-κB family members p50 and p52

are derived from larger precursors, p105 and p100, respectively. ***(Moynagh 2005)***

NF-κB is not synthesized de novo; therefore its transcriptional activity is silenced by interactions with inhibitory IκB proteins present in the cytoplasm. There are currently seven identified IκB family members - IκBa, IκBb, Bcl-3, IκBe, IκBg and the precursor proteins p100 and p105 - which are characterized by the presence of ankyrin repeats. ***(Hoffmann et al., 2006).***

NF-κB is a critical regulator of many cellular processes including cell survival and inflammation. NF-κB functions as a hetero- or homo-dimer which can be formed from five NF-κB subunits, NF-κB1 (p50 and its precursor p105), NF-κB2 (p52 and its precursor p100), RelA (p65), RelB and c-Rel. The most studied dimer is p50:p65, which is activated by the classical pathway and usually promotes gene expression. Activation of p50:p65 is linked with cell survival and promoting inflammation. ***(Pereira & Oakley, 2008)***

The NF-κB signaling pathways

There are two signaling pathways leading to the activation of NF-κB known as the canonical pathway (or classical) and the non-canonical pathway (or alternative pathway).

The common regulatory step in both of these cascades is activation of an IκB kinase (IKK) complex consisting of catalytic kinase subunits (IKKa and/or IKKB) and the regulatory non-enzymatic scaffold protein NEMO (NF-κB essential modulator also known as IKKg).

Activation of NF-κB dimers is due to IKK-mediated phosphorylation-induced proteasomal degradation of the IκB inhibitor enabling the active NF-κB transcription factor subunits to translocate to the nucleus and induce target gene expression. NF-κB activation leads to the expression of the IκBa gene, which consequently sequesters NF-κB subunits and terminates transcriptional activity unless a persistent activation signal is present. ***(Gilmore 2006)***

In the canonical signaling pathway, binding of ligand to a cell surface receptor such as a member of the Toll-like receptor super family leads to the recruitment of adaptors to the cytoplasmic domain of the receptor (Figure 1). These adaptors in turn recruit the IKK complex which leads to phosphorylation and degradation of the IκB inhibitor. The canonical pathway activates NF-κB dimers comprising of RelA, c-Rel, RelB and p50.

The non-canonical pathway is responsible for the activation of p100/RelB complexes and occurs during the development of lymphoid organs responsible for the generation of B and T lymphocytes (Figure 2). Only a small number of stimuli are known to activate NF-κB via this pathway and these factors include lymphotoxin B and B cell activating factor (BAFF).

This pathway utilizes an IKK complex that comprises two IKKa subunits, but not NEMO. In the non-canonical pathway, ligand induced activation results in the activation of NF-κB-inducing kinase (NIK), which phosphorylates and activates the IKKa complex, which in turn phosphorylates p100 leading to the processing and liberation of the p52/RelB active heterodimer. In contrast to p100, p105 undergoes constitutive cleavage to produce p50, whether p105 can undergo inducible processing remains a contentious issue ***(Hayden and Ghosh 2004)***

The dimers bind at kappa-B sites in the DNA of their target genes and the individual dimers have distinct preferences for different κB sites that they can bind with distinguishable affinity and specificity. Different dimer combinations act as transcriptional activators or repressors, respectively.

NF-κB is controlled by various mechanisms of post-translational modification and subcellular compartmentalization as well as by interactions with other cofactors or co-repressors. NF-κB complexes are held in the cytoplasm in an inactive state

complexed with members of the NF-κB inhibitor (I-kappa-B) family. ***(Beinke et al, 2004)***

In a conventional activation pathway, I-kappa-B is phosphorylated by I-kappa-B kinases (IKKs) in response to different activators, subsequently degraded thus liberating the active NF-κB complex which translocates to the nucleus.

NF-κB heterodimeric p65-p50 and RelB-p50 complexes are transcriptional activators. The NF-κB p50-p50 homodimer is a transcriptional repressor, but can act as a transcriptional activator when associated with BCL3.

NF-κB1 appears to have dual functions such as cytoplasmic retention of attached NF-κB proteins by p105 and generation of p50 by a cotranslational processing. ***(Beinke et al, 2004)***

The proteasome-mediated process ensures the production of both p50 and p105 and preserves their independent function, although processing of NF-κB1/p105 also appears to occur post-translationally. p50 binds to the kappa-B consensus sequence 5'-GGRNNYYCC-3', located in the enhancer region of genes involved in immune response and acute phase reactions. In a complex with MAP3K8, NF-κB1/p105 represses MAP3K8-induced MAPK signaling; active MAP3K8 is released by proteasome-dependent degradation of NF-κB 1/p105. ***(Beinke et al, 2004)***