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NF-κB in Renal Inflammation

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ABSTRACT

The NF-κB family of transcription factors regulates the induction and resolution of inflammation. Two main pathways, classical and alternative, control the nuclear translocation of NF-κB. Classical NF-κB activation is usually a rapid and transient response to a wide range of stimuli whose main effector is RelA/p50. The alternative NF-κB pathway is a more delayed response to a smaller range of stimuli resulting in DNA binding of RelB/p52 complexes. Additional complexity in this system involves the posttranslational modification of NF-κB proteins and an ever-increasing range of co-activators, co-repressors, and NF-κB complex proteins. Collectively, NF-κB regulates the expression of numerous genes that play a key role in the inflammatory response during human and experimental kidney injury. Multiple stimuli activate NF-κB through the classical pathway in somatic renal cells, and noncanonical pathway activation by TWEAK occurs in acute kidney injury. Under most test conditions, specific NF-κB inhibitors tend to reduce inflammation in experimental kidney injury but not always. Although many drugs in current use clinically influence NF-κB activation, there are no data regarding specific NF-κB inhibition in human kidney disease.

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NF-κB is a family of pleiotropic transcription factors that integrate an intricate network of extracellular perturbagens and signaling pathways, resulting in the transcriptional regulation of hundreds of genes related to inflammation, immunity, apoptosis, cell proliferation, and differentiation (for a list of genes, go to http://www.nf-kb.org).[1–4] NF-κB induces or represses genes by binding to discrete DNA sequences known as κB elements in promoter and enhancer elements of target genes.

In mammals, 15 potential NF-κB homo- or heterodimers are formed among the five members of the Rel protein family: NF-κB1 (p50, generated from p105), NF-κB2 (p52, generated from p100), RelA (p65), RelB, and c-Rel. Most of them bind DNA. In addition, non-Rel NF-κB subunits giving rise to trimeric NF-κB complexes.[5] The functional consequences of such variability are not fully understood. Rel proteins share a Rel-homology domain, which allows DNA binding and dimerization with other Rel proteins and contains a nuclear localization signal. The transcription activation domain necessary for target gene expression is present only in RelA, c-Rel, and RelB subunits.[1] The RelA/p50 dimer is the most abundant and best characterized member of this family. A wide range of stimuli relevant to kidney injury activate NF-κB, including cytokines and growth factors, pathogen-associated molecular pattern and damage-associated molecular pattern, Toll-like receptors and Nod-like receptors, metabolic (high glucose, advanced glycosylation end products) or genotoxic stress, immune mediators, proteinuria, and mechanical stretch.[6,7]

NF-κB ACTIVATION

Activation of NF-κB results in nuclear translocation and can proceed either through classical/canonical or alternative/noncanonical NF-κB and hybrid pathways[1,3,8] (Figure 1). Activating stimuli converge on phosphorylation and engagement of the inhibitor of the κB kinase (IKK) signalosome, which is composed of two catalytic subunits, IKKα (IKK1) and IKKβ (IKK2), and a regulatory subunit, IKKγ (NF-κB essential modulator). Inhibitors of κB (IκB) proteins, IκBα, IκBβ, p100 (IκBγ activity), p105 (IκBδ activity), and IκBε, regulate nuclear translocation and DNA binding of NF-κB[4,9] IκBs have ankyrin repeat–

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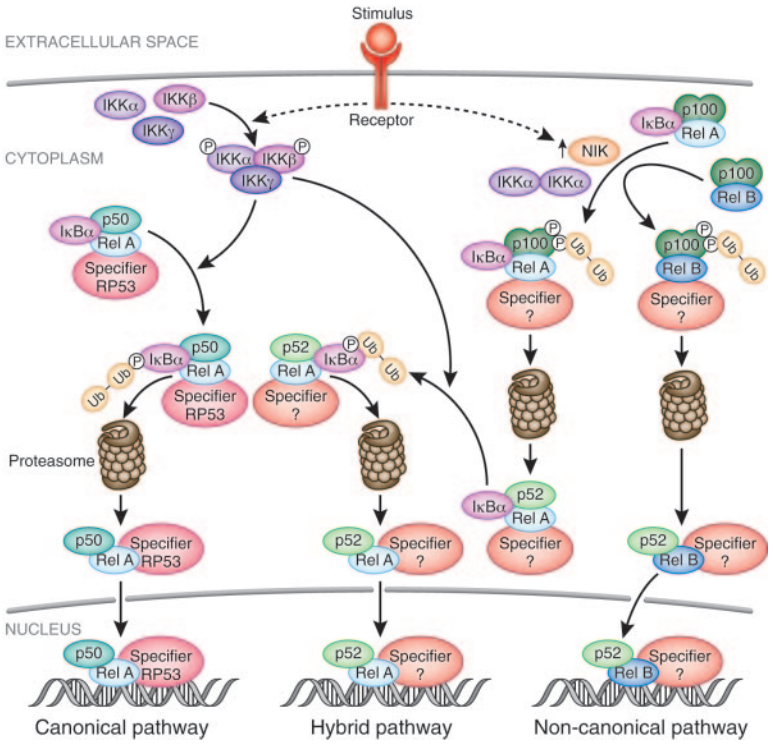

Figure 1. Different pathways for NF-κB activation. In the canonical pathway, IKK activation leads to IκB degradation, which allows RelA/p50 and other complexes to migrate to the nucleus and bind DNA. In the noncanonical pathway, NIK activation and IKKα recruitment lead to proteasomal processing of p100 to p52, generating RelB/p52 complexes that migrate to the nucleus and bind DNA; however, p100 also binds to and inhibits RelA, c-Rel, and p50, and, when processed, it generates p52/RelA, p52/c-Rel, or p52/p50 complexes. IκB molecules weakly sequester p52/RelB complexes, and they are free for nuclear translocation upon p100 processing. In the hybrid pathway, p52/RelA and p52/c-Rel complexes generated by noncanonical p100 processing are retained in the cytosol by IκB proteins and require classical pathway degradation of IκB proteins for activation. Ribosomal protein S3 (RPS3) has been recently identified as a non-Rel DNA-binding component of RelA/p50 NF-κB complexes, which promotes further DNA sequence specificity (specifier). The existence of such specifier molecules in other NF-κB complexes remains hypothetical. P, phosphorylation; Ub, ubiquitin.

containing inhibitory domains and bind to Rel subunits, sequestering them in the cytosol. IκBs also compete NF-κB complexes off their chromosomal locations and export them back into cytoplasm.[1] IKKs phosphorylate IκBs, marking them for ubiquitination and degradation (IκBα, IκBβ, and IκBε) or processing (p100) by proteasomes, thus releasing IκB-bound NF-κB. In addition, IKKs regulate transcriptional responses by phosphorylating nuclear NF-κB proteins and NF-κB–associated proteins.[3]

Classical NF-κB activation is usually a rapid and transient response to a wide range of stimuli. The NF-κB response to TNF has been characterized in detail; IKKs are recruited to activated receptor complexes whereby IKKβ is phosphorylated by either transautophosphorylation or TAK1 and MEKK3.[10] LUBAC-mediated nondegradative linear polyubiquitination of NF-κB essential modulator is required for IKKβ phosphorylation.[11,12] The activated IKK complex phosphorylates IκBα, tagging it for Lys 48–linked polyubiquitination and proteasomal degradation, thus releasing RelA/p50 and other dimers.[12] NF-κB–driven IκBα re-synthesis contributes to a fast turn-off response.

The alternative pathway involves slow activation of the RelB/p52 heterodimer leading to prolonged activation of NF-κB target genes.[13,14] The list of potential activators is smaller and includes TNF superfamily members such as TWEAK (Table 1).[15–17] This pathway requires activation of NF-κB–inducing kinase (NIK) and IKKα.[13,16] NIK activation modulates inhibition of constitutive proteasome-mediated degradation.[10] NIK phosphorylates p100, allowing IKKα recruitment. IKKα phosphorylates p100, promoting p100 polyubiquitination and subsequent proteasomal processing to p52, generating RelB/p52 dimers.[18] RelB/p52 and RelA/p50 induction of p100 and RelB mRNA facilitates full activation of the pathway.[19]

The hybrid pathway requires the contribution of both pathways: The alternative pathway generates the complex, and the classical pathway activates the complex (Figure 1).[18] Additional IκBα modification at specific residues, such as sumoylation, acetylation, and s-nitrosylation, can also trigger the degradation process.[1]

REGULATION OF TRANSCRIPTION

The NF-κB system integrates information and allows for specificity in the induction or repression of individual genes, depending on context, stimulus, and cell system.[20] The κB site sequence affects dimer binding and which coactivators will form productive interactions with the bound NF-κB dimer; however, specificity of NF-κB family member for the κB site does not solely encode endogenous promoter sequences itself. Distinct NF-κB–mediated responses to different stimuli depend on signaling pathway–specific mechanisms that regulate the temporal profile of IKK activity.[21] Stimuli that activate NF-κB also activate other signaling pathways that modify the signal-processing characteristics of the signaling module (cross-talk) or coordinately regulate the activity of other transcription factors to effect stimulus-specific gene expression and cellular responses, even when the same NF-κB complexes are involved.[22] Fine-tuning of the system involves posttranslational modifications, particularly

Table 1. Canonical and noncanonical NF-κB activation

Parameter	Canonical	Noncanonical
Activator	Many	LTB, BAFF, CD40 ligand, CD70, TWEAK, and RANKL
Activator in renal injury	Many	TWEAK
Key IKK	IKKβ	IKKα
Key IκB protein	IκBα	p100
Key NF-κB complex	RelA/p50, other	RelB/p52
Target genes	Many	Many and, specifically, CCL19, CCL21, CXCL12, and CXCL13
Functional studies have defined role in kidney inflammation	Yes	Not yet
Renal disease where role suggested	Many	Experimental AKI[15] and experimental DN[59]

BAFF, B cell–activating factor; CCL19, EBI-1 ligand chemokine; CCL21, secondary lymphoid tissue chemokine; CXCL12, stromal cell–derived factor-1α; CXCL13, B lymphocyte chemoattractant; DN, diabetic nephropathy; LTB, lymphotoxin β; RANKL, receptor activator of NF-κB ligand.

phosphorylation or acetylation of Rel proteins; co-activators and co-repressors; and DNA acetylation that modulates DNA binding, interaction with co-repressors or co-activators, and the induction or repressive activity for transcription.[1,3,9,23] So far, nine phosphorylation sites have been identified in p65. NF-κB–responsive promoters contain consensus-binding sites for other transcription factors often clustered into enhancers. These factors include the constitutive transcription factor SP-1 and the inducible factors IRFs, STATs, ATFs, CEBPs, CREB, and AP-1, many of which interact directly with NF-κB.[22] Hormone-bound glucocorticoid receptor binds RelA-containing dimers and disrupts RelA's interaction with certain co-activators. Recently, the dimer-based model of NF-κB activity has been challenged. The ribosomal protein S3 is a non-Rel subunit of RelA homodimer and RelA-p50 heterodimer DNA-binding complexes that synergistically enhances DNA binding to selected RelA target genes, thus providing target specificity.[5] For this reason, ribosomal protein S3 has been labeled a specifier (Figure 1).[1]

Genetic data suggest, with some exceptions, that there is no clear dimer specificity in gene regulation.[22,24] On the basis of gene expression examined within a few hours of induction, most NF-κB target genes are regulated by RelA/p50; however, the RelB/p52 heterodimer might have an even broader range of activity on gene expression manifest at later time points.[25] RelB/p52 heterodimers bind and activate a unique class of genes present in the promoters of certain chemokines that contain κB sites that diverge significantly from classical κB sites (Table 1).[8] The newly described nuclear protein Akirin-2 binds to nuclear NF-κB complexes and is required for the transcription of a subset of NF-κB–dependent genes such as IL-6, CXCL10, and CCL5.[26]

The dynamics of classical NF-κB activation influence gene transcription.[27] Waves of NF-κB activity encode temporal molecular profiles with distinct functions.[28,29] NF-κB activation results in oscillations of nuclear NF-κB abundance. Stable behavior, when stimulated by LPS, is a consequence of the overlap of LPS and LPS-generated TNF activation of NF-κB.[30] There are a group of early genes whose transcription is guaranteed by short stimulations of NF-κB regardless of stimulus concentration. These include negative regulators of NF-κB activity (IκBα, IκBε, and A20) and inflammatory cytokines (IL-6, IL-8, monocyte chemoattractant protein 1, and IP10). Transcription of some of these genes, such as IκBs and A20, provides negative feedback for NF-κB activation and contributes to activation dynamics.

In turn, there are late genes that are transcribed only when NF-κB activation lasts for at least 1 hour, such as cell surface receptors, adhesion molecules and signal adapters, and some chemokines such as RANTES/CCL5 (Figure 2). Impaired DNA accessibility is thought to play a role in late gene activation.[31] Specific chromatin modifications and configurations are required for NF-κB proteins to access chromosomally embedded cognate κB motifs.[24] A later wave of gene transcription may depend on noncanonical NF-κB activation by certain stimuli, which, in turn, is facilitated by canonical activation (Figure 2). Another level of complexity is added by Rel-associating proteins, a group of tissue or cell context–specific negative regulators of NF-κB beyond the IκB.[1]

NF-κB may also function as a repressor of gene expression through various mechanisms: Inactive complexes, competitions of the RelA subunit with co-activators of transcription, posttranslational modifications of RelA that regulate its function as either an activator or a repressor of gene expression, and post-translational modification of histones surrounding the NF-κB target genes.[32–36] Homo- or heterodimers of p50 and p52 repress κB site–dependent transcription possibly as a result of competition for DNA binding with other transcriptionally active dimers, such as p50/RelA.[37] Suppressors of cytokine signaling 1 forms part of a nuclear protein complex that promotes the ubiquitylation and proteasomal degradation of RelA-containing dimers, thus quenching NF-κB responses.[38] Recently, suppressors of cytokine signaling 1 overexpression was shown to decrease inflammation in experimental diabetic nephropathy.[39] Anti-inflammatory cytokines, such as IL-10, may induce the synthesis of nuclear-located atypical IκB proteins, including B cell lymphoma 3, IκBζ, and IκBNS, which bind to DNA-bound NF-κB dimers and repress transcription of inflammatory genes.[38] Repression by NF-κB is implicated in sepsis-induced downregulation of kidney aquaporin/V2 receptor and may have a role in resolution of inflammation.[40,41]

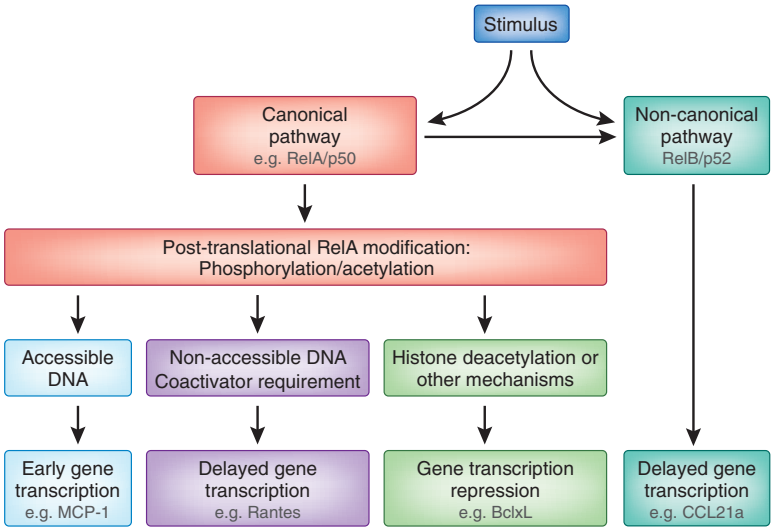

Figure 2. Different roles and timing of NF-κB–activating pathways on gene transcription. Classical NF-κB activation leads to early or delayed transcription. Noncanonical NF-κB activation leads to delayed gene transcription. NF-κB mediates both gene repression and transcription. Of the many potential molecular determinants of repression, only one involving RelA/p50 complexes is illustrated. Gene repression by noncanonical RelB/p50 is less well characterized. RelA/p50 promotes transcription of RelB and p100 and may facilitate noncanonical pathway activation.

NF-κB ACTIVATION IN RENAL CELLS

NF-κB activation regulates neutrophil, macrophage, lymphocyte, and dendritic cell biology. In addition, NF-κB activation has been documented *in vivo* and *in vitro* in intrinsic glomerular cells such as podocytes and mesangial, tubular, and endothelial cells in renal injury or after exposure to inflammatory stimuli. Many stimuli activate canonical NF-κB in cultured renal cells to regulate the transcription of multiple proinflammatory molecules.[7] TNF superfamily cytokines and angiotensin II (AngII) are key activators of NF-κB in renal disease.[42,43] The TNF superfamily cytokines TWEAK and TNF induce different patterns of inflammatory gene activation in tubular cells.[44] TNF leads to transient activation of the canonical NF-κB pathway mainly characterized by RelA-containing DNA-binding complexes.

TWEAK promotes both an early canonical pathway nuclear translocation of RelA and a prolonged, noncanonical pathway activation with p52/RelB NF-κB DNA-binding activity (Figure 3). Both cytokines induce parthenolide-sensitive expression of early (monocyte chemoattractant protein 1/CCL2) and more delayed (RANTES/CCL5) chemokines, but only TWEAK induces the late NIK-sensitive, parthenolide-insensitive expression of CCL21 and CCL19. TWEAK also induces noncanonical NF-κB activation *in vivo*.[15] The relevance of this pathway to kidney disease remains to be established. For unknown reasons, p52/RelB and p52/p52 homodimers do not produce strongly shifted complexes in electrophoretic mobility shift assays, and this may have hindered these studies.[15,25] Interestingly, RelB has anti-inflammatory actions in fibroblasts that have not been explored in kidney injury, and RelB null mice display a multifocal inflammatory disease.[45,46]

NF-κB may also influence the inflammatory response in renal injury by actions beyond regulation of the expression of inflammatory mediators. Although there is little information in renal cells, NF-κB promotes the transcription of the miR-146a gene, which targets TRAF6 and IRAK1, thus activating a negative feedback loop.[47] NF-κB activation may also promote cell proliferation and regulate cell survival.[48–50] In most situations NF-κB has antiapoptotic properties. RelA null mice display massive TNF-mediated liver apoptosis.[51] TNF or TNF-related apoptosis-induced ligand activates simultaneous death and NF-κB–dependent survival signals in renal cells.[52] Inhibition of NF-κB in these circumstances promotes cell death; however, NF-κB/RelA activation is involved in the apoptosis of podocytes in HIV-transgenic mice mediated by NF-κB–dependent Fas and Fas ligand expression in nephrotoxin and ischemia-induced tubular cell apoptosis.[42,49,53,54]

NF-κB ACTIVATION IN EXPERIMENTAL AND HUMAN RENAL DISEASE

Descriptive data link NF-κB activation to human and experimental kidney disease; however, many of the techniques used in these reports do not offer a comprehensive description of NF-κB activation or its function. Thus, to be active, NF-κB must localize to nuclei (immunohistochemistry) also bound to DNA (electrophoretic mobility shift assay), where it may promote or repress transcription. The later point has not been satisfactorily addressed in the kidney *in vivo* in most reports. Moreover, many reports regarding NF-κB *in vivo* are restricted to the localization of RelA/p50 and not other NF-κB subunits or do not address post-translational modifications of Rel proteins.

In experimental renal disease, NF-κB activates in podocytes and mesangial cells during glomerular injury as well as in tubular cells during the course of proteinuria or primary tubulointerstitial diseases, including ischemia reperfusion, obstruction, and septic or toxic acute kidney injury (AKI).[7,15,44,55–57] Most studies describe the presence of RelA and p50 in the complexes, although c-rel is also localized to NF-κB DNA-binding complexes in some studies.[58] There is less information on noncanonical pathway components. NIK phosphorylation in podocytes and tubular cells is increased during human and experimental ischemia reperfusion, although additional events in the noncanonical NF-κB pathway are not explored, and, furthermore, NIK activates other signaling pathways.[59] In experimental diabetic nephrop-

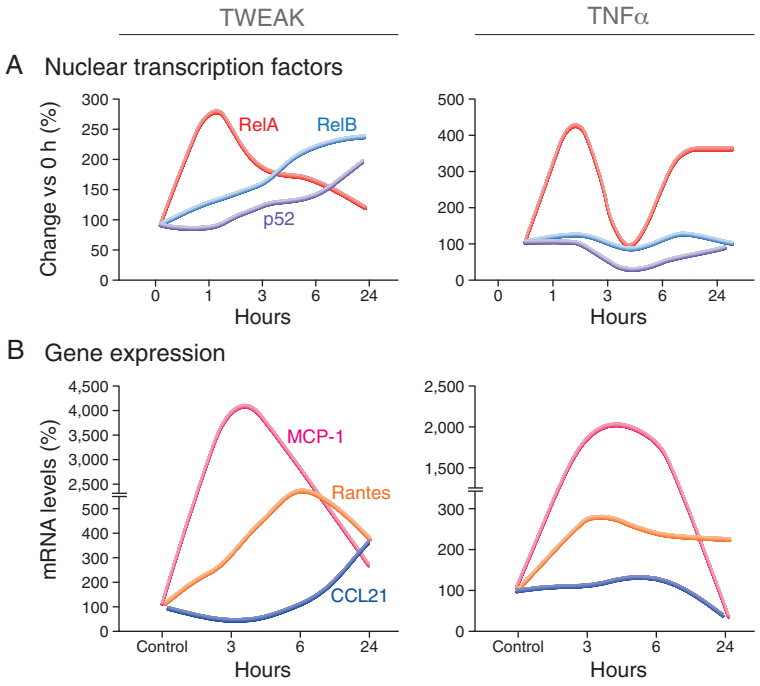

Figure 3. Time course of NF-κB activation by TNF and TWEAK in cultured renal tubular cells. (A) Nuclear NF-κB complex proteins, as assessed by ELISA in cultured proximal tubular cells. (B) Expression of mRNA in cultured proximal tubular cells. TWEAK activates both the canonical and noncanonical NF-κB activation pathways. The latter results in induction of CCL21 mRNA expression. Adapted from data in reference 13.

athy, tubular NIK and RelB DNA binding increases.[60] TWEAK-dependent nuclear RelB and p52 and the renal expression of the RelB/p52 gene targets increase in tubular cells during toxic AKI.[15] During resolution of experimental glomerulonephritis and endotoxemic AKI, the main NF-κB dimers switch from RelA/p50 to p50/p50.[41]

In human renal disease, there is histologic evidence of NF-κB activation in diabetic nephropathy, glomerular disease, and AKI (Table 2). In general, NF-κB activates in macrophages and glomerular (including podocytes in proteinuric diseases) and tubular parenchymal cells and correlates with parameters of severity of disease such as proteinuria or inflammation.[59,61–65] These data have been interpreted as supportive for the role of NF-κB in promoting inflammation; however, inflammation itself will promote NF-κB activation, and because these data are descriptive, the precise role of the various NF-κB complexes in human kidney injury remains uncertain. Functional evidence of NF-κB activation has been obtained by transcriptomics-based pathway mapping[66]; in progressive diabetic nephropathy, there is upregulation of 54 of 138 known NF-κB targets with special enrichment in NF-κB/IRFF module target genes.

NF-κB MODULATION IN EXPERIMENTAL RENAL DISEASE

More than 800 synthetic and naturally occurring compounds partly mediate their effects through the modulation of NF-κB activation.[67] Beneficial effects in experimental kidney injury have been reported for agents that inhibit or antagonize NF-κB–activating stimuli, such as AngII or TNF. Benefit is also seen with pleiotropic drugs in clinical use for treatment of renal disease, such as steroids, statins, and vitamin D receptor activators, and preclinical Rho kinase inhibitors, among other actions, inhibit NF-κB activation.[44,56,68–74] Other drugs in clinical use, such as the proteasome inhibitor bortezomib, also inhibit NF-κB activation and have beneficial effects in animal models of nonrenal inflammation[75]; however, bortezomib aggravates renal ischemia-reperfusion injury and cell death despite decreasing local inflammation.[76] These are not further discussed here.

NF-κB is involved in both the onset and the resolution of acute inflammation.[77,78] During resolution, NF-κB downregulates inflammatory genes, upregulates anti-inflammatory genes, and induces the apoptosis of leukocytes; however, most studies in kidney disease address the potential anti-inflammatory role of NF-κB, frequently using nonspecific prophylactic anti–NF-κB for short timeframes (Table 3). For many small-molecule NF-κB inhibitors, the specific-

Table 2. Evidence for NF-κB activation in human kidney disease

Human Disease	Method	Protein	Localization	Correlation
Diabetic nephropathy[63]	SW	p65, p50	Tubular epithelial cells	Proteinuria, interstitial cell infiltration
IgA nephropathy[64]	SW	p65, p50	Tubular and interstitial	Progression of renal tissue injury
Membranous nephropathy[61]	SW	p65, p50	Tubules	Proteinuria
Minimal change disease[61]	EMSA	p65, p50		Course of the disease
Crescentic glomerulonephritis[62]	IH		Necrotizing and crescentic lesions, tubular epithelial cells and interstitium	Inflammatory cells and chemokines
Delayed graft function[58]	IF	NIK	Tubular cells	
Lupus nephritis[60]	SW	p65, p50	Glomerular endothelial, mesangial cells, podocytes	Proteinuria

EMSA, electrophoretic mobility shift assay; IF, immunofluorescence; SW, Souhtwestern.

Table 3. Some examples of *in vivo* NF-κB modulation in experimental renal disease

Approach	Experimental Model	Result
Nonspecific approaches		
PDTC	Glomerulonephritis, Heymann[78]	Decreased proteinuria
	Nephrosis,[57] adriamycin[79]	Decreased proteinuria
	Diabetic nephropathy[80]	Decreased inflammation
	AKI, sepsis[39]	Decreased inflammation
	AKI; zymosan[81]	Decreased inflammation
	5/6 renal ablation model[82]	Decreased inflammation
	AngII-infused renal injury[54,83]	Decreased inflammation
Parthenolide	Glomerulonephritis[56]	Decreased inflammation, proteinuria
	AKI; cisplatin[87]	Decreased inflammation, proteinuria
	AngII-induced kidney injury[67]	Decreased inflammation
gliotoxin	Glomerulonephritis[56]	Decreased inflammation, proteinuria
DHMEQ	Glomerulonephritis[88]	Decreased inflammation, proteinuria
Specific approaches		
decoy κB ODN	Glomerulonephritis, crescentic[90]	Decreased inflammation
	Allogenic renal transplant[92]	Decreased inflammation
	AKI, ischemia-reperfusion[89]	Decreased inflammation
	UUO[91]	Decreased inflammation
p50 siRNA	AKI, sepsis[39]	Improved renal function, decreased inflammation
p50 knockout	AKI, endotoxemia[40]	Prolonged inflammation, increased mortality
IκBα super-repressor	Protein overload proteinuria[93]	Decreased inflammation

DHMEQ, dehydroxymethyl-epoxyquinomicin; ODN, oligodeoxynucleotides; PDTC, pyrrolidinedithiocarbamate; siRNA, small interfering RNA; UUO, unilateral ureteral obstruction.

ity is unproved. Thus, if beneficial in experimental models, although they serve to template structurally similar molecules, they do not provide conclusive evidence for the involvement of NF-κB. Ammonium pyrrolidinedithiocarbamate is an antioxidant and nonspecific inhibitor of NF-κB that has been widely and successfully used in animal models.[40,55,58,79–84] Parthenolide and gliotoxin inhibit IKK activity, enhance the stability of IκBα, and block DNA binding of NF-κB[85,86]; however, they may have additional actions, because gliotoxin disorganizes F-actin stress fibers.[87] Parthenolide and gliotoxin also have beneficial effects in experimental mesangial proliferative glomerulonephritis.[57] Parthenolide also decreases interstitial monocyte accumulation in AngII-mediated and cisplatin-induced renal injury.[88] Dehydroxymethyl-epoxyquinomicin is an inhibitor of RelA nuclear translocation that does not modify IκB.[89]

There is more specific evidence linking NF-κB with renal disease. Prophylactic decoy DNA oligodeoxynucleotides containing the NF-κB target sequence inhibit renal injury, leukocytic infiltration, and inflammatory mediators in ischemia-reperfusion AKI, glomerulonephritis, ureteral obstruction, and allogenic renal transplantation.[90–93] An adenoviral vector encoding a truncated, super-repressor form of IκBα attenuates proteinuria-induced tubulointerstitial injury.[94] Targeting p50/p105 by small interfering RNAs or null mice protect from renal inflammation within the first 24 hours of sepsis-induced AKI[40]; however, the lack of p50 increases early mortality and prolongs renal inflammation at 48 hours.[41]

The experience is scarce with specific NF-κB inhibition in humans. There are preliminary reports using decoy oligodeoxynucleotides to prevent re-stenosis after percutaneous coronary interventions.[95] A search for NF-κB on ClinicalTrials.gov (http://clinicaltrials.gov/ct2/results?term = nf-kappab, accessed January 1, 2010) identified a completed, not-yet-published phase 1/2 randomized, placebo-controlled trial of topical NF-κB decoy in atopic dermatitis.

CONCLUSIONS

There is experimental evidence supporting the critical role of NF-κB activation in the pathogenesis of renal inflammation. Indeed, conventional therapies in clinical use modulate NF-κB activation, including renin-angiotensin inhibitors, AT1 receptor antagonists, glucocorticoids, and hepatic hydroxymethyl glutaryl–CoA reductase inhibitors; however, the system is more complex than previously recognized, and data on specific modulation in human renal disease is lacking. The increasing awareness of NF-κB diversity in terms of regulatory components and actions calls for more detailed preclinical studies to pinpoint the timeframe and optimal target for potential clinical therapy.

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