Protein kinase signaling

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CHAPTER 2

Mitogen activated protein kinase signaling in the kidney: target for intervention?

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Abstract

Mitogen activated protein kinases (MAPKs) are intracellular signal transduction molecules, which connect cell-surface receptor signals to intracellular processes. MAPKs regulate a range of cellular activities including cell proliferation, gene expression, apoptosis, cell differentiation and cytokine production. The MAPK superfamily consists of at least four families: extracellular signal-regulated kinase (ERK), p38 MAPK, Jun-NH2-terminal kinase (JNK), and ERK5. Each of these families exerts particular downstream effects, although interactions have been described.

MAPK activity is present in the normal kidney. Moreover, in various types of renal disease, renal MAPK expression is increased. Interventions that provide renoprotection, such as ACE inhibition or statin therapy, may reduce renal MAPK expression, suggesting that increased renal MAPK expression is involved in the pathophysiology of renal damage. Studies using specific MAPK inhibitors have been used to further elucidate this role.

This review gives an overview of available in vitro data on MAPK activation (focussed on renal cell types), and describes MAPK localization and possible functions in the normal and diseased kidney in man, and in experimental renal disease. Studies reporting the effect of conventional renoprotective intervention on renal MAPK expression are reviewed, as well as the available data on specific MAPK inhibition, both in the clinical and experimental setting. The available data appear to support the potential of MAPK inhibition as a novel intervention strategy in renal disease, but future clinical studies are needed to substantiate this assumption, and to establish its safety.

Introduction

Mitogen activated protein kinases (MAPKs) are intracellular signal transduction molecules: enzymes that connect cell-surface receptor signals to intracellular effects such as gene modulation (1). They can covalently attach phosphate to the side chain of either serine or threonine amino acid of specific proteins inside cells. This process of phosphorylation results in changes in the enzymatic activity of the target protein, altering its interactions with other

proteins, its cellular location, or its degradability by proteases. Target proteins include other protein kinases, phospholipases, transcription factors, and cytoskeletal proteins (2). In this manner, MAPKs can regulate a range of cellular activities, including cell proliferation, gene expression, apoptosis, cell differentiation and cytokine production.

The MAPK superfamily consists of at least four broad families, namely extracellular signal-regulated kinase (ERK), p38 MAPK, Jun-NH2-terminal kinase (JNK), and ERK5 (or big MAPK 1, BMK-1) (3-8). MAPKs regulate many cellular processes, from gene expression to cell death (9). Thus, inappropriate MAPK activation could affect cellular function, and may result in cell death, and, ultimately, clinical disease. Whereas MAPK expression is altered in many types of disease, e.g. renal disease, it is not always clear whether MAPKs play a causal role in its initiation and progression.

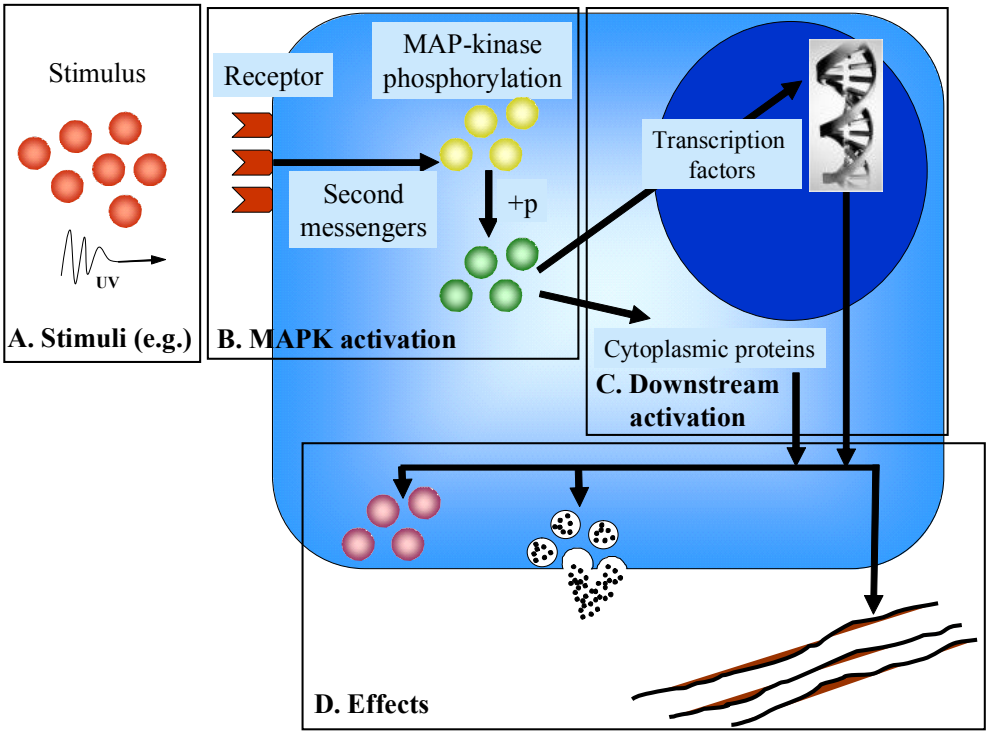

Figure 1. Overview of cellular MAPK activation

Schematic representation of how a stimulus can result in MAPK activation (phosphorylation). In turn, MAPK activation can activate transcription factors or other factors, for example in the cytoplasm. This results in cellular actions, e.g. cytokine release, proliferation or apoptosis. Details of this figure are shown in Tables (**1-4**). See page 181 for full color image.

We will summarize current knowledge on the main functions of MAPKs, and focus on the relevance of these molecules to renal physiology and pathophysiology in vitro, in animal models and in man. Moreover, we will address recent developments in MAPK inhibition, both in the experimental and in the clinical setting.

MAPK pathways: structure and functions

General principles of MAPK pathways

A schematic representation of the concept of MAPK signaling, including activation of downstream factors, and putative resulting cellular actions, is given in Figure 1. Figure 2 shows an overview of the main extracellular stimuli that lead to MAPK activation, and a number of currently known responses to MAPK activation. Currently available data on MAPK-activating stimuli relevant in renal cells are summarized in Table 1. As shown in this table, each of the MAPKs can be activated by a diverse and extensive number of stimuli, including growth factors, cytokines, and various aspecific stressors (irradiation, osmotic stress, oxidative stress etc).

MAPK activation pathways consist of three basic components ("modules"), including MAPKs, MAPK kinases and MAPK kinase kinases, which are conserved from yeast to humans (Table 2). MAPKs are activated by MAPK kinases (MAPKKs, MKKs, or MEKs). The MAPKKs are dual-specificity kinases that recognize and phosphorylate a Thr-X-Tyr motif in the activation loop of MAPK (10). MAPKKs can, in turn, be activated by MAPK kinase kinases (MAPKKKs, MKKKs or MEKKs) (11,12). MAPKs can be inhibited by negative feedback loops (e.g. ERK -> Raf1), and by protein kinase phosphatases. The latter include MKP1-7, PAC1, M3/6, VHR, B23 (13-17). These phosphatases can reverse MAPK activation by dephosphorylation at the Thr(P)-Glu-Tyr(P) activation motif (18).

MAPK cascades can activate various other signaling pathways (Table 3) by activating transcription factors or effects on cytoplasmic proteins. Although function and relevance for the development of renal disease are yet unclear for many of the MAPK effectors, the downstream part of MAPK pathways are relevant in vivo, as demonstrated by MAPK inhibition in numerous animal models (addressed below).

Moreover, as shown in Table 4, MAPKs mediate multiple cellular actions, e.g. proliferation, apoptosis, and cell growth. Therefore, it is relevant to study mechanisms downstream of MAPK. Because of their specific properties, the various MAPK pathways will be separately addressed below. Cellular physiology of both yeast and mammalian MAPK pathways is extensively reviewed by Widmann et al in ref (19).

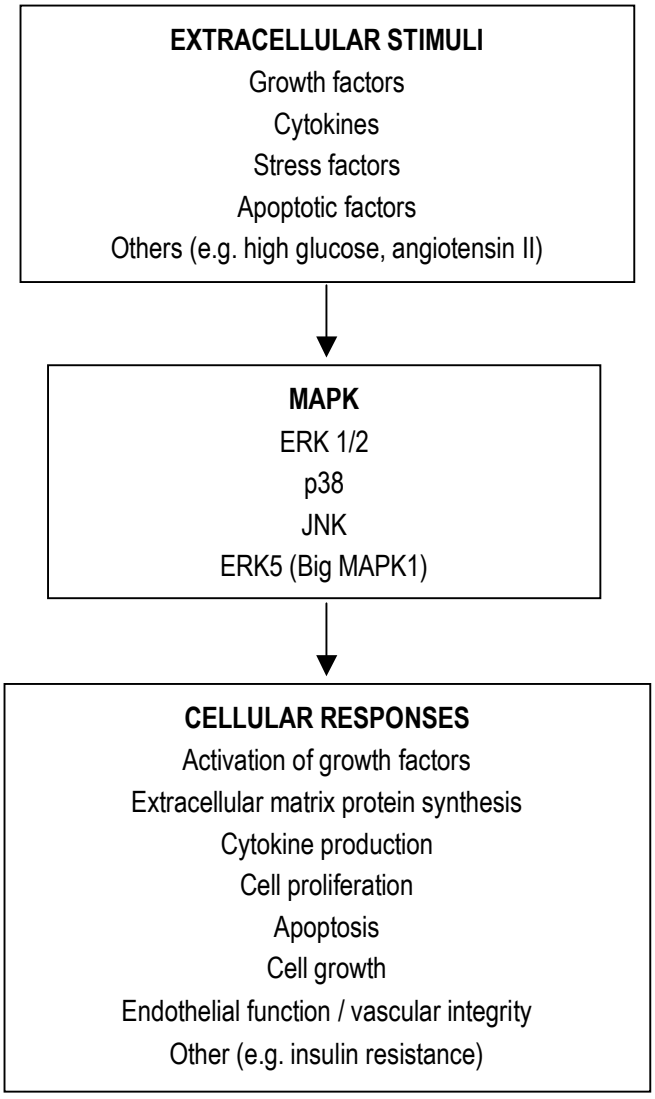

Figure 2. Overview of factors and processes that are up- and downstream of MAPK activation
Extracellular stress, including hyperglycaemia, oxidative stress and growth factors all contribute to MAPK activation. This in turn may lead to the activation of further growth factors and production of cytokines, increased extracellular matrix (ECM) accumulation, proliferation or apoptosis.

ERK		
Stimulus	Cell type	Ref
Growth factors		
Angiotensin II	E,M,T,V	[98,130-133]
PDGF	M,V	[138-140]
FGF	E,M,T,V	[143-146]
VEGF	E	[144]
TGF-beta	M,T,V	[150-152]
IGF	E,M,T,V	[158-161]
EGF	E,M,T,V	[144,165-169]
NGF	T,V	[172,173]
Cytokines		
TNF-alpha	E,M,T,V	[175,179-181]
IL-1beta	E,M,V	[186-188]
CD154	T,V	[174,185]
Stress factors		
LPS	E,M	[199,200]
Mechanical stress	E,M,T,V	[201,204-206]
Others		
Thrombin	E,V	[146,211]
High glucose	E,M,P,V	[163,214-216]
Endothelin	M,V	[212,221]
NO	E,V	[188,229]
Estradiol	E,M,V	[231-233]
Insulin	E,M,T	[236-238]
Bradykinin	E,M,V	[240-242]
Serotonin	M,V	[245,246]

JNK		
	Cell type	Ref
Growth factors		
Angiotensin II	E,M,V	[100,134-136]
PDGF	M,V	[140,141]
FGF	V	[142]
Cytokines		
TNF-alpha	E,M,V	[153,162,163]
IL-1beta	E,M	[170,171]
CD154	E,T	[170,174]
Stress factors		
LPS	E,T,V	[182-184]
Mechanical stress	E,M,V	[189-191]
UV irradiation	M	[193]
Oxidative stress	E,M,T,V	[170,174,194,195]
Osmotic stress	M,V	[193,196]
Others		
Thrombin	T	[208]
High glucose	E	[210]
Endothelin	M,V	[212,213]
NO	E,M,V	[217,218]
Estradiol	E,V	[222,223]

p38		
	Cell type	Ref
Growth factors		
Angiotensin II	E,M,T,V	[49,99,130,137]
FGF	V	[142]
PDGF	E,M,V	[140,141,147]
VEGF	E,V	[148,149]
TGF-beta	E,M,P,T,V	[153-157]
IGF	E	[164]
Cytokines		
TNF-alpha	E,M,T,V	[153,175,176]
IL-1beta	E,M,V	[148,177,178]
CD154	T,V	[174,185]
IL-17	E	[192]
Stress factors		
LPS	E,M,T,V	[183,197-199]
Mechanical stress	E,M,P,V	[190,201-203]
UV irradiation	V	[207]
Osmotic stress	T	[209]
Others		
Thrombin	E,V	[219,220]
High glucose	E,M,P,T,V	[224-228]
Endothelin	M,V	[212,230]
NO	M,V	[234,235]
Estradiol	E,V	[223,239]
Insulin	E,V	[243,244]

The ERK pathway

Table 1 shows that in renal cells, a large number of stimuli can activate ERK. In most renal cell types, growth factors are important activators of ERK. However, also a broad number of other factors including high glucose, NO, LPS, and mechanical stress are ERK activators. ERK1/2 can be activated by different types of receptors, including receptor tyrosine kinases and G protein-coupled receptors (Table 2), see also ref (19-21). In the MAPK cascade, ERKs are activated by MAP/ERK Kinase 1 (MEK1) and MEK2, which are in turn activated by the Ras/Raf pathway. ERK1/2 can phosphorylate Raf1, inhibiting its activity (22). In this manner, the ERK pathway shows a classical negative feedback loop. Moreover, ERK can be inactivated by protein kinase phosphatases. MAPK phosphatase (MKP)-2, 3, and 4 are probably the protein kinase phosphatases most selective for ERK, although other phosphatases including MKP-1 and PAC1 also inactivate ERK, but in a less selective manner (16,17,23).

Effectors of activated ERK mainly include transcription factors (e.g. Elk-1, Ets 1, STATs), but also cytoplasmic proteins (see Table 3). As for MAPKKKs (see above), there is evidence of cross-reactivity in downstream MAPK pathways, for example Elk-1, which can be activated by ERK, p38, and JNK (24-26). ERK signaling has been implicated in mitogenesis and cell differentiation. ERK1/2 stimulates DNA synthesis through phosphorylation of carbamoyl phosphate synthase, a rate-limiting enzyme in pyrimidine nucleotide biosynthesis (27).

Moreover, the ERKs can promote cell-cycle progression by inactivating MYT1, a cell-cycle inhibitory kinase, but arrest meiotic cells at metaphase II by activating a cytostatic factor (28-30). Via activator protein-1 (AP-1) and cyclin D1 induction, ERKs can also stimulate cell proliferation indirectly (31). Furthermore, ERK activation results in eicosanoid production, and is therefore involved in the synthesis of prostaglandins and leukotrienes, in the presence of inducible cyclo-oxygenase-2 (32).

Table 1. Stimuli inducing MAPK activation in renal cells *in vitro* (previous page)

Detailed overview of a number of stimuli that can activate MAPKs. Activation of MAPKs is indicated per stimulus, the cell type in which activation has been described is also mentioned. Bold data represent stimuli that can activate more than one MAPK. Cell types: E = endothelial cells, M = mesangial cells, P = podocytes, T = tubular epithelial cells, V = vascular smooth muscle cells.

The JNK pathway

Cellular stress forms the most important activator of JNK, also known as stress-activated protein kinase (SAPK). The processes by which the various types of stress result in activation of JNK are unclear as the exact stress sensors and their regulation mechanisms remain merely unidentified. There is a diverse number of other factors that can activate JNK including

Receptors	Cytokine receptors (e.g. TCR, CD28, BCR), GPCRs, TKRs (e.g. EGF-R, PDGF-R, insulin-R), integrin clustering	TNF-R, GPCRs, TKR, cytokine receptors (e.g. TCR+CD28), IgE-R	TKRs, GPCRs, cytokine receptor	TKRs
MKKKs	Raf-1, A-Raf, **MEKK1-3,** B-Raf, Mos, **Tpl-2**	**MEKK1-3**, MEKK4, **TAK1**, **ASK1**, MUK, **Tpl-2**, **SPRK**, MST	**TAK1**, **ASK1**, **SPRK**, PAK	**MEKK2, MEKK3**
MKKs	**MEK1** **MEK2**	**MKK4** **MKK7**	**MKK3** **MKK6**	**MEK5**
MAPKs	**ERK1/2**	**JNK1/2/3**	**p38α/β/γ/δ**	**ERK5**

Table 2. MAPK activation cascades
Schematic representation of MAPK activation by its kinases and kinase kinases. Also, the respective receptors that lead to its activation are shown per MAPK pathway.
TCR = T cell receptor, BCR = B cell receptor, GPCRs = G-protein coupled receptors, TKRs = tyrosine kinase receptors, EGF-R = epithelial growth factor receptor, PDGF-R = platelet-derived growth factor receptor, MEKK = MKKK = MAPK kinase kinase, MEK = MKK = MAPK kinase, TNF-R = tumor necrosis factor-receptor, IgE-R = immunoglobulin E-receptor.

growth factors, cytokines and apoptotic factors (Table 1). JNKs undergo MKK-mediated dual phosphorylation on threonine and tyrosine of the Thr-X-Tyr activation motif. As shown in Table 2, MKK4 and MKK7 are the MKKs specific for JNK activation. JNK can be inactivated by various aspecific protein kinase dephosphatases, and selectively by M3/6 (16,33). Moreover, JNK activation can be inhibited by JIP-1 and NF-kappaB (34,35).

ERK	JNK	p38	ERK5
Transcription factors (directly)			
Elk-1	**Elk-1**	**Elk-1**	**MEFC2**
ATF-2	**ATF-2**	**ATF-2**	
SAP-1	**c-Jun**	**SAP-1**	
STATs	p53	**c-Jun**	
GATA4	DPC4	**MEF2C**	
Ets1	NFAT4	Chop	
c-Myc	NF-kappaB?	Max	
Tal			
P300/CBP			
Myb (inhibition)			
UBF			
Cytoplasmic proteins			
$p90^{rsk}$ S6 kinase	Unknown	**MSK 1/2**	c-Jun (via MEFC2)
c-Jun (via $p90^{rsk}$)		**CREB**	
c-Fos (via $p90^{rsk}$)		**NF-kappaB**	
AP-1 (via $p90^{rsk}$)		**ATF1**	
cytosolic phospholipase A_2		**Histone H3**	
MAP-1,-2,-4, Tau		**MNK**	
EGF receptor		**eIF4E**	
Sos		MAPKAPK-2/3	
Raf1 (inhibition)		HSP-27	
Mek1 (inhibition)		TTP	
		SRF	
		PRAK	

Table 3. Downstream activation of transcription factors and other proteins by MAPKs
Substrates of MAPKs are shown, including transcription factors and cytoplasmic proteins. Bold factors indicate factors that can be activated by more than one MAPK. For JNK, only transcription factors are known at this time. Indentation represents expression or activation by the previously mentioned factor, e.g. ERK can activate transcription factors c-Jun, c-Fos, and AP-1 via activation of the cytoplasmic $p90^{RSK}$ S6 kinase.

Thus far, only transcription factors are known substrates of JNK activation (listed in Table 3). JNK binds to and phosphorylates the DNA binding protein c-Jun and increases its transcriptional activity, without affecting DNA binding (36). c-Jun is a component of the AP-1 transcription complex, which is an important regulator of gene expression. AP-1 contributes to the control of many cytokine genes and is activated in response to environmental stress, radiation, and growth factors - all stimuli that activate JNKs (2). JNK can induce apoptosis, probably by activation of transcription factors like c-Jun and DPC4, although the exact mechanisms are unclear (19,37). JNK activation may be relevant in maintaining the integrity of the cytoskeleton, as shown in intestinal epithelial cells (38).

ERK	**JNK**	**p38**	**ERK5**
Eicosanoid production	*Apoptosis*	*Cell growth*	*Endothelial function*
Arachidonic acid	*Microtubule assembly*	Alpha-skeletal actin	*Vascular integrity*
PGs, leukotrienes	*Insuline resistance*	Sarcomeric organisation	
ECM production	*Cytokine production*	*Cytokine production:*	
TGF-beta production	IL-12, RANTES	IL-1, IL-2, IL-6,	
Cell proliferation	*Cell proliferation*	TNF-alpha	
CPS		*Apoptosis*	
MYT1 (inhibition)		Fas-induced apoptosis	
Cyclin D1		*Cell proliferation*	
		IL-7	
		Others	
		COX-2	
		iNOS	
		VCAM-1	
		ANP/BNP gene induction	

Table 4. Processes mediated by MAPK activation

This table provides an overview of MAPK-specific downstream cellular effects.

ECM = extracellular matrix, CPS = carbamoyl phosphate synthase, RANTES = Regulated on Activation Normal T-cells Expressed and Secreted, COX-2 = cyclo-oxygenase-2, iNOS = inducible NO synthase, VCAM-1 = vascular cell adhesion molecule-1, ANP = atrial natriuretic peptide, BNP = brain natriuretic peptide.

The p38 pathway

Table 1 shows a number of stimuli that are able to activate p38, however, many more studies have been done to identify p38-stimulating factors, almost all in vitro; as reviewed recently (also in non-renal cells) by Ono et al(39). Stress factors have been demonstrated to be important p38 stimuli in vitro, but inflammatory cytokines and growth factors are also important p38 MAPK activators (Table 1) (40,41). Apparently, p38 plays a role in inflammation and cell growth and development. Indeed, p38 is abundantly expressed during rat kidney growth and nephrogenesis(42). All four p38 MAPK isoforms are activated by MKK3, whereas MKK6 preferentially activates p38α, γ, and δ isoforms (Table 2). Activation of p38 MAPK is preferentially inhibited by MKP-1, MKP-5, MKP-7 and M3/6, where the MKPs only inactivate p38α and p38β (13,16,33,42).

Effectors of p38 include both transcription factors (ATF-2, Elk-1, Chop, Max, MEF2C) and enzymes (e.g. MAPKAP kinase-2 and -3) (43). Moreover, p38 activation stabilizes certain mRNA strains (for example COX-2) (44,45). By selective inhibition, it has been elucidated that p38 regulates many different genes expressing cytokines, transcription factors, and cell surface receptors. Downstream effects of p38 include inflammation: production of proinflammatory cytokines (e.g. IL-1β, TNF-α and IL-6), modulation of extracellular matrix, expression of intracellular enzymes such as iNOS, and the production of adhesion molecules such as VCAM-1 (46-48). The role of p38 in apoptosis is not clear; it is dependent on cell type and stimulus. In tubular epithelial cells, angiotensin II induces apoptosis via p38 (49). MKK3 and MKK6 knockouts resulted in reduced p38 activation and increased tumorigenesis, suggesting an important role in cellular proliferation (50). Indeed, through cyclin D1 expression, p38 is involved cell cycle progression and proliferation (51). Cells arrested in M phase demonstrate p38 activation (52). Finally, p38 MAPK plays a role in hypertrophy and cell differentiation in a number of cell types (53,54).

The ERK5 pathway

The ERK5 (also known as big MAPK1, BMK1) pathway is by far the least known mammalian MAPK pathway. ERK5 and MEK5 (its upstream kinase) are activated by MEKK2 or MEKK3,

as shown in Table 2 (55-57). A recent review on ERK5 supplies an overview of its activators; these include mainly stress signals, and a number of growth factors (EGF, NGF, VEGF) (58). Moreover, it has been demonstrated that in renal glomerular mesangium, high glucose activates ERK5 both in vivo and in vitro (59). The activation of ERK5 induces its translocation to the nucleus, where it can activate transcription factors including MEF2C, inducing c-Jun expression (60). Genetic ablation of ERK5 in mice leads to embryonic lethality, however Hayashi et al created a ERK5 conditional mutation in mice in which disruption of the ERK5 gene was under the control of the inducible Mx1-Cre transgene. The authors concluded that ERK5 is essential for endothelial function and for maintaining blood vessel integrity (61).

MAPK activation in the rat kidney

MAPKs in the healthy rat kidney

In the normal adult rat kidney, ERK is expressed in the distal tubules, collecting ducts, and podocytes. Phosphorylated ERK has been demonstrated in occasional distal tubules and collecting ducts of normal rats (62). In healthy adult rats, JNK is abundantly present and located in tubular cells and podocytes (42). Stambe et al describe phosphorylated JNK in the glomerulus of normal rats, specifically in podocytes and epithelial cells of Bowman's capsule; moreover, most of the cortical tubuli contain pJNK-positive epithelial cells (63). Stambe et al describe that pp38-positive cells can be found at the same locations as pJNK, however, two other papers report that in the normal rat kidney, there is neither unphosphorylated nor active p38 present in the normal adult rat kidney (62-64). Interestingly, p38 activation is involved in COX-2 production in the renal macula densa in response to changes in tubular sodium concentration (65). These findings underline the relevance of MAPK signaling in renal physiology.

As mentioned, MAP kinases play an important role in numerous pivotal biological processes such as proliferation, differentiation, extracellular matrix production, and apoptosis. Recent studies reported that during rat renal development, when cell turnover is high, p38 and ERK

are over-expressed and highly activated, whereas pJNK is slightly detectable in embryos (64). Oppositely, in the adult kidney, where cell turnover is only 0.01%, expression of p38 and ERK is low, while JNK is abundantly present and activated (66). Exposure of rat metanephroi cultured from 15-day-old embryos to the ERK 1/2 and p38 inhibitors PD98059 and SB203580, respectively, demonstrates that growth and nephrogenesis require p38, while ERK is important in tubulo-nephrogenesis (67).

Activated MAPK	Time of increased expression	Effect of specific blockade	Ref
Glomerulonephritis			
p38	Early (2 hrs post-induction)	Reduced UP, glomerular neutrophil accumulation, MCP-1	[63,89]
ERK	Later (> 6 days)	Reduced # of mitotic figures, total # of glomerular cells	[74]
JNK	Later	75% reduced UP, 70% reduced glomerular cell proliferation	[92]
Diabetic nephropathy			
p38	Early, decline after 4 months	Unknown	[76,225,247]
ERK	Unknown	Unknown	[75,214]
Hypertensive renal damage			
p38	Unknown	Reduced glomerular desmin, interstitial SMA expression, MME	[102]
ERK	>7 wks in dTGR rats	Reduced glomerular desmin, interstitial SMA expression	[80,102]
JNK	>10 wk high sodium diet	Unknown	[79,80]
Unilateral ureteral obstruction			
p38	6 hrs - >7 days post-ligation	Reduced interstitial fibrosis and collagen IV	[88]
ERK	peaks at <30 min, 4 and 7 d	Unknown	[248]
Remnant kidney			
p38	9 wks	Increased UP, tubular dilation, infiltration of ED-1+ cells, proliferation, tubulointerstitial fibrosis	[93]

Table 5. Overview of *in vivo* data on MAPK activation and effects of pharmacological inhibition in experimental renal disease

Overview of currently available data on MAPK activation in experimental renal disease and the reported effect of specific pharmacological MAPK blockade. UP = proteinuria, SMA = smooth muscle actin, MME = mesangial matrix expansion.

Together, these findings support the concept that ERK and p38 are involved in cell growth, proliferation, and differentiation. It is likely that JNK, known to play a role in apoptosis and responses to extracellular stress, plays a role in maintaining cellular homeostasis in the (adult) physiological situation.

Many of the stimuli that are able to activate the MAPK pathways have been implicated in renal disease (reviewed in (68-71)). Moreover, many of the MAPK substrates are associated with renal disease. However, little is known about the exact functions and the relevance of these pathways in vivo. Nevertheless, a number of studies in experimental renal disease support a role for MAPK in renal disease.

MAPKs in experimental renal disease

MAPK activation has been demonstrated in numerous models of experimental renal disease. Moreover, specific MAPK inhibitors have been administered to animals in order to specifically study their effect in a given model. An overview of recent findings is presented in Table 5; renal expression and activation of MAPKs in a number of models of renal damage as well as effects of pharmacological intervention will be addressed in this paragraph.

Renal expression and activation

Glomerulonephritis. In anti-glomerular basement membrane (GBM) glomerulonephritis and anti-Thy 1.1 experimental model of mesangioproliferative glomerulonephritis, ERK 1/2 and JNK are activated during the later proliferative stage of the disease, whereas p38 is activated early (2 hours post anti-Thy 1.1. antibody injection) in the disease (72-74). More recent studies have shown that in inflammatory renal diseases, such as crescentic glomerulonephritis, a marked increase in p38 activation is observed in glomerular endothelial cells and neutrophils as early as 3 hours after the induction of the disease (63). In progressive anti-GBM disease, p38 and JNK are activated within podocytes, glomerular endothelial cells and infiltrating macrophages, highlighting the importance of these signaling molecules in inflammation (63).

Diabetic nephropathy. In the glomeruli of streptozocin-induced diabetic rats, a model of type I diabetes, ERK 1/2 activation is increased (75). This increase in ERK 1/2 activation is thought to regulate cellular growth. Hyperosmolarity and oxidative stress are features of diabetic nephropathy; this has led investigators to postulate that p38 mediates some of the complications of diabetic nephropathy. Indeed, activation of p38 has been observed in the glomeruli of early diabetic rats (76). One and two months post-streptozotocin, p38 activity is increased in the glomeruli of diabetic rats compared to controls, however, this decreased to control levels following four months of diabetes. The same pattern of activity was observed for the upstream kinase activators of p38, MKK3/6 (76). Although it was observed that during the same time course there was an increase in extracellular matrix and hypercellularity, the investigators were not able to conclude that there was a clear association between p38 activation and features of diabetic nephropathy. Studies have also been conducted in models of Type II diabetes, including the db/db mouse and the Otsuka Long Evans Tokushima Fatty (OLETF) rats (59,77). An upregulation in ERK 1/2 and ERK5 has been observed in the glomeruli of the diabetic rats, suggesting a role in mesangial cell proliferation (59,77).
In diabetic nephropathy, early tubulointerstitial disease is a predictor of renal function (78). Although all MAPK family members are present in distal and collecting tubules of control rats, an increase in activation of p38 is observed in streptozotocin induced diabetic rats (62). Fujita and colleagues demonstrated that in streptozotocin diabetic rats, ERK 1/2 and p38 were activated in the tubules and that p38 co-localized with TGF-ß (62), however, it can not be concluded that there was a relationship between the two, as the investigators did not inhibit MAPK activation.

Hypertension. An increase in dietary salt intake as well as hypertension leads to the activation of MAPK family members within the glomerulus (79-81). Moreover, immunohistochemical analysis of ERK 1/2 in the hypertensive Ren2 rat has confirmed its presence in the glomerulus (82), demonstrating that a number of hypertension-associated external stimuli activate the MAPK family in vivo.

Although the studies mentioned so far have shown an increase in MAPK activation, the implication of this increase is not clearly known. Furthermore, the exact stimuli for MAPK

activation may vary between the different diseases. For example, in vitro studies have reported p38 activation in mouse mesangial cells stimulated with TGF-ß (83), while mesangial cells treated with high glucose concentrations activate ERK 1/2 which in turn leads to increased TGF-ß stimulation (84). Thus, in mesangial cells MAPK may be involved in a vicious cycle resulting in accumulation of extracellular matrix proteins such as collagen and fibronectin, contributing to renal fibrosis (85). Inhibition of growth factors, such as EGF, normalizes MAPK activation in the renal cortex and in turn reduces collagen I expression (86). Together, the available studies demonstrate an increase in MAPK activation in various renal diseases, suggesting that MAPKs may play a pivotal role in transducing information from the extracellular region to the intracellular compartment, resulting in the activation of further growth factors and molecules that contribute to renal pathology.

MAPK inhibition. To establish a pathological role for a given factor, one must demonstrate, according to the modified Koch's Postulates, that blockade of the factor would attenuate the manifestations of the disease (87). The advantage of using experimental animal models is the ability to test inhibitors of the MAPK family and to examine their role in renal disease.

In the non-inflammatory model of unilateral ureteric obstruction, Stambe et al reported that p38 activity is increased as early as 6 hours post-ligation and continues for at least 7 days (88). Using the specific p38 inhibitor NPC31169, which inhibits phosphorylated p38 from phosphorylating down stream targets such as activated transcription factor 2 (ATF2), there was a reduction in interstitial fibrosis and collagen IV protein and mRNA. However, there was no effect on TGF-ß, suggesting that the activation of extracellular matrix in this experimental model of renal disease is not mediated by TGF-ß (88), although in vitro studies provided evidence that the activation of TGF-ß and its effects on extracellular matrix proteins is through ERK (84,85).

In the anti-GBM glomerulonephritis model of experimental crescentric glomerulonephritis, blockade of p38 with NPC31145 or FR167653 reduced proteinuria, glomerular neutrophil accumulation (89) and monocyte chemoattractant protein-1 (90), suggesting that p38 is important in inflammatory renal diseases, and that its blockade may be a useful target for therapy. In addition, in the hypertensive stroke prone rats on a high salt and fat diet, glomerular hypertrophy, tubulointerstitial changes and urinary albumin excretion were

attenuated with the p38 inhibitor SB239063 (91). In a recent study by Ikezumi et al, utilising an acute model of macrophage-mediated renal injury, JNK inhibition with SP600125 was associated with a reduction in proteinuria and macrophage proliferation, suggesting that macrophage accumulation may be mediated by JNK (92).

However, a recent study in the remnant kidney model (93), using the p38 inhibitor NPC31169 for 9 weeks at 100 mg/kd/day, shows that MAPK inhibition was associated with increased proteinuria, tubular dilation, infiltration of ED-1 positive cells, proliferation and tubulointerstitial fibrosis. Furthermore, ERK1/2 expression was increased with p38 blockade, suggesting that there is cross-talk between the intracellular pathways in renal disease (93). The authors suggested that the lack of renoprotection, as opposed to the renoprotective effects in anti-GBM nephritis, may indicate that inhibition of p38 is beneficial mainly in inflammatory diseases where the level of pro-inflammatory cytokines is high, while the remnant model is characterized by a low level of pro-inflammatory cytokines. Yet, the beneficial effects in other non-inflammatory models such as unilateral ureteric obstruction (88) and stroke-prone rats (91) indicate that a prominent inflammatory component is not a prerequisite for a therapeutic effect of MAPK inhibition.

Taken together, the available data indicate that p38 and ERK1/2 blockade can provide renoprotection in various renal conditions. Apparently, however, MAPK inhibition is not uniformly renoprotective but can also aggravate renal damage. This argues against a too straightforward application of MAPK inhibition in renal damage, but rather emphasizes the need for better understanding of the complex role of MAPK in renal damage in order to delineate the therapeutic potential of MAPK modulation.

Renin-Angiotensin-Aldosterone System and Renal MAPK Expression

Angiotensin II (AngII) has a key role in the pathophysiology of a number or renal diseases. The most successful approach to treating progressive renal diseases includes angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) as reported in numerous in vitro, animal and clinical studies(94-96), although more specific intervention may be appropriate (97). The beneficial effects relate to their efficacy in not only reducing blood

pressure and proteinuria, but also inhibiting the non-hemodynamic functions of AngII. AngII binding to its G-protein coupled receptor activates a number of intracellular signaling molecules, including MAPK family members.

As shown in Figure (3), AngII activates ERK, JNK and p38 in rat mesangial cells, resulting in hypertrophy (ERK), proliferation (JNK), and TGF-beta production (p38) (98-100). In tubular epithelial cells, AngII can activate the same MAPKs, however, p38 activation results in apoptosis in these cells (49). This indicates that effects of MAPK activation by AngII may be cell type-specific. Together, these data implicate that MAPK activation by AngII may be relevant in the pathophysiology of renal damage. Furthermore, p38 is able to stimulate angiotensin II gene expression, in turn leading to the increase in pro-fibrotic growth factors and cellular hypertrophy (101), suggesting that the interaction between MAPK and angiotensin II has the potential to elicit a vicious cycle relevant to renal damage.

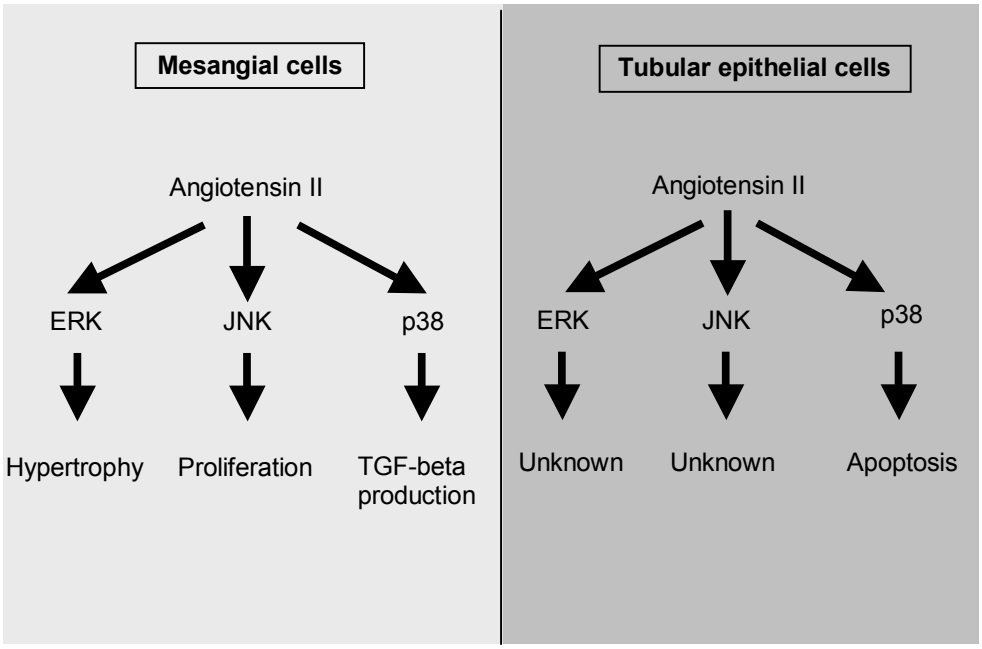

Figure 3. MAPK-mediated effects of angiotensin II in renal mesangial and tubular epithelial cells
Schematic representation of MAPK activation by angiotensin II in mesangial cells and tubular epithelial cells. This illustrates that cellular responses of MAPK activation may be cell type-specific.

Importantly, inhibition of either p38 or ERK ameliorated angiotensin II-mediated renal damage in homozygous Ren2 rats (102). This provides proof of principle that MAPK inhibition has the potential to ameliorate angiotensin II-induced renal damage in vivo, which may turn out highly relevant, considering the important role of angiotensin II in progressive renal disease.

The effect of renin-angiotensin-aldosterone-system(RAAS)-blockade on MAPK activation in renal disease has only recently been investigated. In the streptozotocin-induced model of diabetes, the effect of ACEi on ERK 1/2 has been investigated in the glomerulus, and it was reported that ACEi reduced ERK 1/2 phosphorylation (103). Studies by Hamaguchi et al provided in vivo evidence that angiotensin II infusion led to the activation of ERK 1/2 and JNK (79). Furthermore, ARB or inhibition of ERK 1/2 blocked the angiotensin II induced stimulation of collagen 1 α gene in renal cortical slices (104). In a recent study, Nishiyama and colleagues examined the effect of ARB on the activities of ERK 1/2, JNK and ERK5 in Dahl salt-sensitive rats fed a high salt diet (105). ARB treatment reduced urinary protein excretion and collagen accumulation, without affecting blood pressure, highlighting the non-hemodynamic role of angiotensin II. In the salt sensitive rats fed a high salt diet, ERK 1/2, JNK and ERK5 were activated in the kidney cortex. The activation of these MAPK molecules were normalized with ARB (105). The results of this study suggest that effects on MAPK pathways may partly mediate the renoprotective effects of ARB.

It is important to note that, in spite of their proven efficacy, ACEi or ARB only partially reduce the progression of chronic renal damage. In fact, in many patients renal function loss continues despite apparently adequate RAAS-blockade, which prompts for the development of new therapies. A recent prospective study into the renal mechanisms of resistance to renoprotective therapy in adriamycin-induced renal damage in rats revealed that the extent of pre-fibrotic renal damage and its associated macrophage infiltration present at onset of therapy were negative predictors of the antiproteinuric benefit of RAAS-blockade (106). This suggests that specific interference in pathways involved in macrophage influx and fibrogenesis may have the potential to overcome resistance to the renoprotective effects of RAAS-blockade. Considering the involvement of MAPK in these processes, in this respect, MAPK modulation would be a relevant strategy to investigate.

MAPK activation in man

MAPK activation in the normal human kidney

In the healthy adult human kidney, immunostaining revealed pp38 (activated p38) in some glomerular visceral (podocytes) and parietal epithelial cells, in a minority of tubular epithelial cells, and occasionally in peritubular interstitial cells (107,108). In human embryonic kidneys (gestational ages 19-34 wks) however, the activated isoform pp38 cannot be detected (109).

	p38			ERK			JNK			
Disease	glom	tub	interst	glom	tub	interst	glom	tub	interst	Ref
TMD	=	=	=	=	=					[108,110]
MCD	+	+++	=	=	=					[108,110]
ATN								++	++	[111]
GN	++	=	=							[108]
Cresc GN	++									[113]
PIGN	+++	+++	=							[108]
IgA	+++	+++	=							[108]
Vasculitis	+++	+++	+++	+	=					[108,110]
SLE	+++	+++	+++	=	=					[108,110]
FGS	++	=	=	=	=					[108,110]
DN	+	++	+++	+						[107,114]

Table 6. MAPK activation in human renal disease
Overview of available data on MAPK activation in human renal disease. All indicated changes are relative to controls. Legend: = no change, + 2-4 times increased, ++ 4-6 times increased, +++ >6 times increased. TMD = thin membrane disease, MCD = minimal change disease, ATN = acute tubular necrosis, MGN = membraneous glomerulonephritis, cresc GN = crescentic glomerulonephritis, PIGN = postinfectious glomerulonephritis, SLE = systemic lupus erythematosis, FGS = focal glomerulosclerosis, DN = diabetic nephropathy. All indicated differences are significant ($p<0.05$). Blank fields indicate unavailable data.

This is in contrast with findings in the rat that show abundant p38 activation in renal development (64). pERK, in the normal human kidney, is almost completely restricted to some collecting duct cells (110). In the embryonic stage, pERK can be detected in epithelial cells in distal tubules and in collecting duct cells (109). The localisation of activated JNK in the healthy human kidney has only been described in one recent study showing pJNK expression in the tubulointerstitium (111). Embryonic kidneys (19-34 wks) reveal faintly positive staining for pJNK in distal tubulus and collecting ducts (109). The differences in MAPK activation between humans and rats may suggest separate functions of MAPKs in both species, although the amount of data on MAPK activation in human kidney development is only minimal to date.

MAPK activation in human renal disease

Multiple studies report increased MAPK activation in various renal diseases, suggesting a role for MAPKs in the pathophysiology of human renal disease (Table (6)). Limited data is available on the relationship between altered renal MAPK expression and the severity of renal function impairment or proteinuria.

Glomerulonephritis (GN). Human GN is characterized by infiltration of inflammatory cells, including T-cells and macrophages. Influx of inflammatory cells correlates with renal function and histopathologic lesions (78,112). In GN, activation of p38 MAPK in intrinsic renal cells and in infiltrating leukocytes correlates with renal dysfunction and histopathology (108). An increased number of pp38 positive glomerular cells has been observed in both nonproliferative (minimal change disease (MCD), membranous glomerulonephritis (MGN)) and proliferative (IgA, systemic lupus erythematosis (SLE), vasculitis) GN, although there is greater activation of p38 in proliferative than in non-proliferative GN (108). Furthermore, in proliferative GN, there is increased p38 activation in all tubular segments, as opposed to non-proliferative GN (108,113). Unlike p38, controversy exists as to whether ERK or JNK activation occurs in human glomerulonephritis. Makaki et al report that ERK activation does not occur in thin membrane disease (TMD), MCD, or SLE, while in patients with vasculitis, there is increased glomerular ERK activation in the glomerular tuft and in crescents (110).

Diabetic nephropathy (DN). In human DN, increased glomerular activation of both ERK and p38 has been described (107,114). Interestingly, Toyoda et al described an inverse relationship between glomerular (mainly mesangial and epithelial) ERK activation and mesangial matrix expansion in DN, indicating that ERK activation mainly plays a role in the early stage of tissue damage in DN (114). This may be of interest for prevention strategies. For p38 activation, such a correlation has never been studied in man, but studies in diabetic animals indicate increasing activation up to 8 months after streptozotocin injection(107). Moreover, activated p38 has been found in accumulating interstitial macrophages and fibroblasts in kidneys of patients with type 2 diabetes, suggesting involvement of p38 activation in inflammation in DN. However, the authors could not correlate p38 activation to proteinuria or renal function, probably due to a small number of biopsies (107).

Renal dysplasia. In dysplastic epithelia of the human kidney (both pre- and postnatal), pp38 is strongly expressed, in contrast to normal prenatal kidneys, where p38 is not activated at all (109). Moreover, dysplastic epithelia stained exclusively positive for ERK and pERK. Surprisingly, pJNK, which was present in tubular epithelia of normal kidneys, could hardly be detected in dysplastic renal epithelia (109), suggesting that proliferation is the key mediator of this disease. Indeed, the authors propose that the activation of p38 and ERK may mediate hyperproliferation of dysplastic tubules resulting in cyst formation, whereas the concomitant down-regulation of JNK expression may be the cause or the result of an undifferentiated state of dysplastic epithelia (109).

Acute tubular necrosis (ATN). To our knowledge, there is only one paper on JNK activation in human renal disease, showing that there is indeed increased JNK activation in the tubulointerstitium of patients with acute tubular necrosis (ATN), where it might induce apoptosis (111). There are no data on the role of other MAPK in human ATN.

MAPK inhibition in human subjects

There is limited experience with MAPK inhibition in human disease. Recently, a review paper addressed current standings in pharmacological intervention in MAPK signaling (115). To our knowledge, no studies on MAPK inhibition in human renal disease have yet been done.

However, studies on MAPK inhibition in other human disorders, such as endotoxemia, may give an indication of the therapeutic potential of MAPK inhibition. Fijen et al were the first to give an oral p38 inhibitor, RWJ 67657, to human subjects and demonstrated strong (>90%) dose-dependent inhibition of plasma TNF-α, IL-6, and IL-8 responses, and neutrophil and endothelial cell activation in human endotoxemia (116). Branger et al also demonstrated strong inhibition of TNF-α, IL-6, IL-10, and IL-1RA using the p38 inhibitor BIRB 796 BS in human endotoxemia (117). This p38 inhibitor dose-dependently ameliorated coagulation, fibrinolysis, and endothelial cell activation in human endotoxemia (118). Regan et al selected BIRB 796 as a clinical candidate for the treatment of inflammatory diseases for its significant improvements in binding affinity, cellular activity, and in vivo reduction of TNF-α production and arthritis severity (117,119,120). This provides further evidence that MAPK is important in diseases characterized by inflammation and hypercellularity.

At the moment, BIRB 796 (doramapimod) is in clinical trials for the treatment of psoriasis (phase III), rheumatoid arthritis and Crohn's disease (both phase IIb) (121). The p38 inhibitor VX-702 is currently in clinical trials for treatment of acute coronary syndromes (phase IIa) (121). To our knowledge, there are no publications describing the use of specific ERK- or JNK-inhibitors in human subjects. Moreover, there is yet no data on MAPK inhibition in human renal disease, there is a new field of powerful pharmacological intervention to be explored.

Possible side effects of MAPK inhibitors

Little is known about potential side effects of MAPK inhibition in patients. At least one group of p38 inhibitors, the pyridinylimidazoles (SK&F 86002 and SB 203580), not only efficiently inhibit proinflammatory cytokine synthesis, they also potently inhibit human liver P450 isozymes (122-124). Inhibition of human cytochrome P450 can potentially cause drug-drug interactions or lead to other hepatic changes such as P450 enzyme induction. In 10- and 14-day dose-ranging toxicological studies in rats using SK&F 86002 and SB203580, liver weight increased, and significant elevations of hepatic P450 enzymes were demonstrated (122,125). However, the newer second generation p38 MAPK inhibitors – the pyrimidine analogs of the

pyridinylimidazole class of p38 inhibitors – have reduced effects on cytochrome P450, as well as an increased oral activity (122). In the studies using RWJ-7457, there was no apparent drug toxicity, based on clinical findings and standard hematological and biochemical tests (116,126). Moreover, this inhibitor has been shown to have acceptable safety and pharmacokinetics in a single oral dose study in healthy men (127).

It can be considered remarkable that p38 inhibitors apparently are relatively well tolerated in spite of the broad spectrum of physiological functions of MAPKs. Possibly, due to redundant MAPK pathways, inhibition of one MAPK elicits activation of other MAPKs, resulting in alternative activation cascades. Activation of other MAPK pathways upon specific MAPK blockade has indeed been described experimentally, both in vitro and in animals, however is it not clear whether the net effect is always beneficial (93,128,129). Another explanation may be that in a diseased organ, MAPKs become “overactivated”, so that inhibition has relatively more effect at the target tissue or organ than elsewhere in the body. The latter can be expected to result in a more favorable profile in terms of therapeutic window. It is also possible that both phenomena occur; but obviously, much more data on the safety of MAPK inhibition in human renal diseases are needed.

Conclusions and future directions

MAPKs play an important role in various crucial cell processes like proliferation, inflammation, and apoptosis. Whereas current insight in the complex MAPK interrelations is still limited, particularly considering the apparent aspecificity in some parts of their signaling cascades as opposed to specificity in other parts, nevertheless intervention in MAPK pathways afforded increasing insight in the role of MAPK in renal disease. Studies by MAPK intervention support a pathogenetic role of MAPKs in various experimental renal conditions characterized by inflammation, fibrosis and apoptosis, and moreover, demonstrated the renoprotective potential of MAPK inhibition in these conditions. Importantly, the deleterious effect of MAPK inhibition in remnant kidney, a model characterized by hypertrophy, indicates that the specific type of renal damage is relevant to the eventual effect of MAPK inhibition. Data from renal biopsies in man have shown upregulation of MAPKs in a variety of renal conditions,

suggesting involvement in human renal disease as well, and may provide a new target for intervention.

Several important issues should be addressed in order to explore the potential of MAPKs as a novel intervention strategy in renal disease. It would be important to establish the renal conditions that can specifically benefit from MAPK inhibition, and to delineate the role of specifically modulating the different MAPK families in the various renal conditions. Safety would be particularly important to consider, in view of the ubiquitous expression of MAPKs throughout organs and cell-types, and the interaction between the different MAPK pathways.

So far, no studies on MAPK inhibition in renal disease in man have been conducted. Yet, clinical data on the use of MAPK inhibitors in other human conditions show that the use of MAPK inhibition is feasible in man. Animal data suggest that MAPK inhibition may be of use in acute inflammatory renal disorders, and in chronic conditions characterized by fibrosis. Considering the current role of RAAS-blockade as first line of therapy in chronic progressive renal function loss disease – and the interactions between angiotensin II and MAPK signaling, it might be useful to study the possible role of MAPK inhibition as an adjunct to RAAS blockade.

Finally, although most studies on MAPK inhibition in renal disease are promising, it is obvious that there is still much to be learned about the complex regulation of MAPK pathways. Combining information from different lines of research in pharmacology, physiology, cellular biology, and clinical medicine is pivotal to obtain a more complete and balanced concept of MAPK function, and to delineate the opportunities for its role as a target for therapy.

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