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Review

Mitogen-Activated Protein Kinases and Hypoxic/Ischemic Nephropathy

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Key Words
Hypoxia • Ischemia • Nephropathy • Renal protection • Mitogen-activated protein kinases

Abstract
Tissue hypoxia/ischemia is a pathological feature of many human disorders including stroke, myocardial infarction, hypoxic/ischemic nephropathy, as well as cancer. In the kidney, the combination of limited oxygen supply to the tissues and high oxygen demand is considered the main reason for the susceptibility of the kidney to hypoxic/ischemic injury. In recent years, increasing evidence has indicated that a reduction in renal oxygen tension/blood supply plays an important role in acute kidney injury, chronic kidney disease, and renal tumorigenesis. However, the underlying signaling mechanisms, whereby hypoxia alters cellular behaviors, remain poorly understood. Mitogen-activated protein kinases (MAPKs) are key signal-transducing enzymes activated by a wide range of extracellular stimuli, including hypoxia/ischemia. There are four major family members of MAPKs: the extracellular signal-regulated kinases-1 and -2 (ERK1/2), the c-Jun N-terminal kinases (JNK), p38 MAPKs, and extracellular signal-regulated kinase-5 (ERK5/BMK1). Recent studies, including ours, suggest that these MAPKs are differentially involved in renal responses to hypoxic/ischemic stress. This review will discuss their changes in hypoxic/ischemic pathophysiology with acute kidney injury, chronic kidney diseases and renal carcinoma.

Introduction

Hypoxia/ischemia in the kidney is a widely encountered problem within vascular and urologic clinics because the kidney is sensitive to insufficient oxygen/blood delivery. This insufficiency leads to (or can be associated with) various pathological conditions, such as acute kidney injury, chronic kidney diseases, renal fibrosis, and renal cell carcinoma.

The kidneys are supplied with dense blood vessels, and high volumes of blood flow through them. Indeed, the blood flow to the kidney is second to the brain, and accounts for around 20% of cardiac output [1, 2]. Increasing renal blood flow increases glomerular

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filtration rate and the filtered reabsorptive load. This increases oxygen demand due to a linear relationship between tubular transport of filtered sodium and oxygen consumption [3]. High metabolic activity, primarily due to the activity of the basolateral Na/K-ATPase, further increases oxygen demand. Consequently, the kidneys are very vulnerable to changes in oxygen supply. Hypoxia resulting from an imbalance in oxygen supply vs. demand has long been considered an important factor in the pathogenesis of kidney disease [4-7]. In acute and chronic kidney diseases, as well as in renal cancers, tissue hypoxia does not only cause energy deficiency, but also induces regulatory mechanisms that have a profound influence on signaling pathways [8].

The responses of renal cells to hypoxia encompass a series of signaling pathways that enables them to adapt to hypoxic conditions. Among the large array of signaling pathways activated in the kidney, mitogen-activated protein kinase (MAPK) pathways have been intensively studied recently [9-13]. MAPKs are a group of parallel cascades of serine/threonine kinases that regulate cell proliferation, differentiation, and survival. The understanding of molecular mechanisms underlying hypoxia-MAPK signaling regulation and their relevance to kidney diseases is crucial for preventing renal damage and promoting renal recovery after hypoxic/ischemic injury. In this review, we will focus on the roles of MAPKs in response to hypoxic/ischemic conditions in the kidney.

Mitogen-activated protein kinases

MAPKs regulate diverse biological functions including proliferation, development, differentiation, apoptosis, inflammation and fibrosis [14-16].The dysregulation of MAPKs arises in a variety of human diseases, including neurodegenerative and metabolic diseases, developmental disorders, as well as cancers [17-20]. There are four different MAPKs: extracellular signal-regulated kinase-1 and -2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38 MAPK, and extracellular signal-regulated kinase-5 (ERK5/BMK1) [14, 21]. Each family of MAPKs is nonetheless activated through phosphorylation in a relatively specific fashion by a three-tiered cascade: MAPKKK, MAPKK and MAPK (Fig. 1). For example, ERK1/2 is activated by both MAPK/ERK kinase 1 and 2 (MEK1/2) whereas JNKs are activated primarily by MKK4 and MKK7 and p38 is activated by MKK3 and MKK6. Mammalian MAPK pathways can be

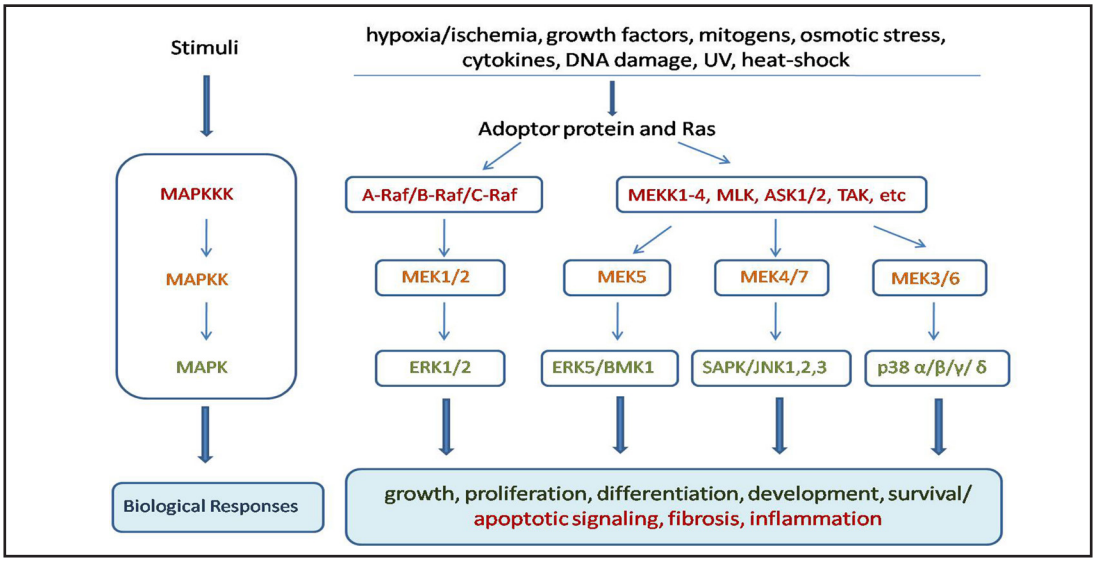

Fig. 1. The integral extracellular signal-regulated kinase/mitogen-activated protein kinase pathway. ERK: Extracellular signal-regulated kinase; SAPK/JNK, stress-activated protein kinase/c-Jun NH2-terminal kinase; MAPK: Mitogen-activated protein kinase; MEK, MAPK/ERK kinase; MEKK, MAPK/ERK kinase kinase; MKK, MAPK kinase; MKKK, MAPK kinase kinase.

activated in response to a wide range of stimuli such as growth factors, cytokines, reactive oxygen species, UV, DNA damage, mitogens, heat shock and osmotic stress [14, 15, 22, 23]. Activated MAPKs can phosphorylate several intracellular targets including transcription factors, nuclear pore proteins, membrane transporters, cytoskeletal elements, and other protein kinases [24].

MAPKs are commonly expressed in many cell types in most tissues, and the kidney is no exception. In general, there are relatively low levels of active kinases in most "normal" tissues under physiological conditions, as kinase activation is largely restricted to tissue stress or injury. The activation of MAPKs is differentially involved in the progression of a plethora of human diseases, ranging from Parkinson's disease [25] to tumorigenesis [20]. For example, our previous studies showed increased levels of phosphorylated p38 with a decrease in phosphorylated ERK1/2 levels in cortical neurons after prolonged exposure to severe hypoxia. This was prevented by a hypoxic preconditioning treatment [26]. MAPKs are expressed differently at different stages of kidney development; while ERK1/2 and p38 are strongly expressed in a developing kidney, JNK is predominantly detected in an adult kidney [27]. However, all of their phosphorylation levels are altered under certain conditions. For instance, the phosphorylation of p38, ERK1/2 and JNK is significantly increased during hypoxia-reoxygenation in the human kidney cells [28]. Our recent studies found that ERK1/2 and p38 were dramatically activated in rat kidney epithelial cells (NRK-52E) under hypoxic conditions (Fig. 2, unpublished data), despite the fact that their activation is comparatively low under normal conditions. This finding suggests that renal cells are very different from neuronal cells in terms of MAPK responses to hypoxic stress because we previously found that ERK and p38 show opposite responses to prolonged hypoxia in neuronal cells [26].

It is widely believed that MAPKs are differentially involved in the genesis and/or progression of many renal diseases, such as glomerulopathies, fibrosis, diabetic nephropathy, and renal carcinomas. MAPK pathways may regulate the pathogenesis of ischemia-reperfusion injury in a common pathway through activator protein 1 [29]. Also, a significant increase in cortical, and an even greater increase in glomerular ERK1/2 and JNK activity, was detected at 1, 3, and 7 days after induction of glomerulonephritis [30]. Gene expression patterns showed ERK1/2 activation in high-grade renal oncocytic carcinoma regions. ERK1/2's activation would further facilitate angiogenesis and invasiveness in those regions [31]. Moreover, recent *in vivo* and *in vitro* evidence suggests that the p38 pathway plays a very important role in the pathogenesis of diabetic nephropathy [32].

Despite extensive research in the past, the precise roles of different MAPKs in renal pathology, especially in hypoxic/ischemic nephropathy, are still not well understood, and there are also major controversies in the literature. For example, some studies showed that the activation of ERK1/2 signaling pathway in the human kidney with glomerulopathies correlated with cell proliferation, histologic lesions, renal fibrosis and dysfunction [33], while other work suggests that apoptosis in diabetic rat kidneys is likely related to a decrease in phosphorylated ERK1/2 levels and an increase in phosphorylated JNK levels [34]. A better understanding of renal MAPK function under hypoxic/ischemic conditions may therefore

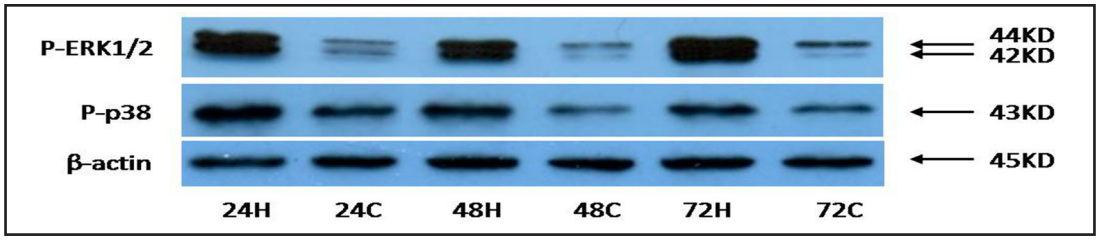

Fig. 2. ERK1/2 and p38 actiation by hypoxia in NRK-52E cells. NRK-52E cells were exposed to hypoxia at 1 % O_2 for 24-72 hours. 24H, 48H and 72H: 24, 48 and 72 hours in hypoxic control condition. 24C, 48C and 72C: 24, 48 and 72 hours in normoxic condition. Note that both phosphorylated ERK1/2 (P-ERK1/2) and p38 (P-p38) remarkably increased after hypoxic exposure.

provide a novel insight into new therapies by targeting MAPK pathways for the prevention and treatment of hypoxic/ischemic diseases.

Acute kidney injury

Acute kidney injury (AKI) is the leading cause of nephropathy and is associated with high mortality, morbidity and health care expenditure. AKI may be caused by an array of insults, e.g. ischemia-reperfusion (I/R) injury, cardiovascular surgery, radio-contrast administration, and sepsis. In particular, ischemia/reperfusion injury is one of the most common causes of AKI and occurs in many clinical settings including kidney transplantation and cardiac bypass surgeries [35-38]. I/R during kidney transplantation can lead to graft rejection, delayed graft function, renal cell death, and chronic graft dysfunction [39]. Ischemic-induced renal tissue hypoxia along with the generation of reactive oxygen species during reperfusion are believed to contribute to tissue injury in the development of acute renal failure [40, 41]. Since I/R injury plays an essential role in hypoxic/ischemic nephropathy, many research efforts have been devoted to elucidating its mechanism [42, 43]. However, the fundamental signaling pathways and the mechanisms of I/R injury are not yet fully understood.

The MAPKs participate in signal transduction pathways and the regulation of various cellular responses, such as cell proliferation, differentiation, and apoptosis [44, 45]. After hypoxic/ischemic injury, MAPK signaling pathways are activated in the kidney [46-49] as modulators of ischemia/reperfusion injury. In the past, many studies showed that p38 and JNK are pro-apoptotic, whereas ERKs are the modulators of cell survival under hypoxic/ischemic conditions [46, 50-53]. After comprehensively reviewing the literature, however, we believe that the precise changes and roles of MAPK expression and phosphorylation are not that simple. In fact, there were many controversies even in recent studies, especially regarding their roles in protective or detrimental effects on the kidneys. Table 1 lists major results from recent studies on the role of MAPKs in renal I/R conditions.

ERK1/2

ERK1/2 activation can increase cell survival during oxidative injury; this can be prevented by ERK1/2 inhibition in the kidney [46]. Moreover, inhibition of monoamine oxidase after I/R insult potentiates ERK1/2 activation and increases proliferation, and it decreases necrosis of renal tubular cells [50]. The phosphorylation of ERK1/2, induced by heme oxygenase-1, enhanced tubular recovery and subsequently prevented further renal injury in mouse kidneys [54]. Stable overexpression of sec10 in Madin-Darby canine kidney cells significantly increased phosphorylated ERK1/2, which led to cell protection against I/R-induced oxidative injury by decreasing the degree of H_2O_2 injury and increasing the rate of epithelial barrier recovery following injury [55]. Furthermore, it was indicated that sec10 overexpression increased ERK1/2 phosphorylation and that recovery from oxidative injury in renal tubular was epidermal growth factor receptor, ERK1/2, and endocytosis dependent [56]. In addition, there is evidence showing that activated ERK1/2 plays a key role in the restoration of damaged tubular epithelial cells following I/R injury in mouse kidneys [57]. Ischemic postconditioning in NRK-52E cells is effective in mitigating renal cell apoptosis and it potentially be mediated via an ERK1/2 signal [58]. Erythropoietin pretreatment can also attenuate renal I/R injury by promoting activation of ERK1/2 signaling in rat kidneys, which causes the inhibition of apoptosis [59]. Etanercept, a TNF inhibitor, has the ability to strengthen renal protection from I/R injury by stimulating the activation of ERK1/2 and increasing the Bcl-2/Bax ratio [60]. These results strongly suggest that renal cell survival under oxidative injury is dependent on ERK1/2 activity.

However, ERK1/2 expression and phosphorylation along with its renoprotective roles are called into question by some other studies. For example, Ka et al. [61] showed that 4,5,6,7-tetrabromobenzotriazole, an ATP/GTP competitive inhibitor of casein kinase-2 (CK2, a protein kinase), significantly protects against renal I/R injury in mice and is associated with

Table 1. Renal responses to MPAK changes in I/R conditions

Stimuli/Conditions	MAPK Changes	Outcome	References
ischemic postconditioning in NRK-52E cells or erythropoietin or etanercept pretreatment in rat kidneys	ERK1/2 ↑	cell survival	[58-60]
hemin preconditioning in mouse I/R kidneys	ERK1/2 ↑	renal protection	[54]
ERK inhibition with PD-098059 in murine kidney cells	ERK1/2 ↓	reduce cell survival	[46]
dexmedetomidine preconditioning in rat I/R kidneys	p38 ↑	cell survival	[69]
lentivirus-mediated ERK5 overexpression with I/R in human kidney cells	ERK5 ↑	renal protection	[72]
BML-111 treatment in rat I/R kidneys; SB203580 treatment in rat I/R kidneys	p38 ↑; p38 ↓	cell survival; cell injury	[71]
pretreatment with TBBt in mouse I/R kidneys	ERK1/2, p38 ↓	renal protection	[61]
low-molecular-weight fucoidan (LMWF) treatment in mouse I/R kidneys	p38, JNK ↓	renal protection	[28]
glycyrrhizin treatment in mouse I/R kidneys	p38 ↓	cell survival	[67]
treatment with U0126 in rat kidney I/R models	ERK1/2 ↓	renal protection	[62]
increased expression of ALDH-2 during I/R in rabbit kidneys	ERK1/2, p38, JNK ↓	renal protection	[66]
pargyline treatment in rat I/R kidneys	ERK1/2 ↑, JNK ↓	renal protection	[50]
preconditioning with low-dose cyclosporine A or FK506 in rat I/R kidneys	ERK1/2 ↑, p38, JNK ↓	renal protection	[51]

the suppression of NF-κB activation and concomitant inflammatory cytokine production through the inhibition of the ERK1/2 pathway. Another study showed that activation of the ERK1/2 pathway during I/R injury was linked to renal injury. When ERK1/2 inhibitor, U0126, was used to prevent ERK1/2 activation, there was a reduction in focal adhesion kinase, paxillin, and src phosphorylation. There was also increase in protection against focal adhesion restructuring and I/R-induced renal injury [62].

Taken together, most studies suggest ERK1/2 as a mediator of controlling cell survival in response to many stimuli including hypoxia/ischemia in the kidney. However, it is also reported that ERK1/2 is involved in injury and apoptosis rather than contributing to cell survival in kidney cells [61-63]. It is likely that ERK1/2 may have different effects on kidneys, which depends on experimental model, stress type, and many other factors. Therefore, ERK1/2 expression and phosphorylation, along with its renoprotective role need further clarification in future studies, especially among various models/species in different pathophysiological conditions.

Other MAPKs

Both p38 and JNK pathways are involved in pathological changes in human renal diseases, such as glomerulonephritis, diabetic nephropathy and acute renal failure. They can modulate the function of a variety of transcription factors through phosphorylation and thus induce a change in the pattern of gene transcription and results in inflammation and apoptosis [64]. In contrast, their inhibition might reduce I/R-induced apoptosis and inflammation and prevent cell death [53, 65].

Hypoxia in combination with noradrenaline enhances the vasoreactivity of renal arteries after hypoxia/reoxygenation by activating p38 MAPK in mouse model, which was suggested to be essential for the pathogenesis of AKI [12]. Recent studies on rabbits in New Zealand showed that increasing the expression of aldehyde dehydrogenase 2 can reduce renal cell apoptosis by inhibiting the p38 and JNK pathways in rabbits with I/R injury [66]. Similar data indicated that p38 inhibition can significantly protect against renal I/R injury in a mouse I/R model [61]. NPC 31145, a specific p38 MAPK inhibitor, blocked the p38 pathway and prevented a loss of renal function and substantially reduced acute renal inflammation in the diseased rat and human kidney [65]. The results of some other studies also demonstrated that suppression of p38 and JNK consequently causes a significant decrease of cytochrome c release from the mitochondria, a fall in the ratios of both Bax/Bcl-2 and cleaved caspase-3/caspase-3, and phosphorylation of p53. This ameliorated acute renal injury in both in mice model and in an *in vitro* culture model [28]. Glycyrrhizin also gives significant protection against I/R induced renal injury in mice by inhibiting inflammatory responses and renal cell apoptosis, associated with downregulation of p38 MAPK signaling [67]. Treatment of mouse proximal tubular epithelial cells with a p38 inhibitor, SB 203580, or a JNK inhibitor, SP600125, significantly suppressed LPS-induced chemokines CXCL2 and CCL2 mRNA expression [68]. Since CXCL2 expression in proximal renal tubular cells has been observed in ischemic renal injury, it suggests that p38 and JNK could be potential target molecules in the treatment of inflammatory injury.

Although the previous data predominantly showed that the inhibition of p38 and JNK reduces cell apoptosis, there are still other opinions about their role in hypoxic/ischemic conditions. Recently, Lempiainen et al. [69] showed that dexmedetomidine, an α-2 adrenoceptor agonist, upregulates p38 signaling, which ameliorated renal I/R injury and inflammatory responses in rat kidneys. Moreover, endotoxin exposure protects isolated kidney cells against hypoxia-induced cell death, which appears to be mediated in part via the p38 and JNK pathways [70]. A lipoxin receptor agonist, BML-111, inhibits renal I/R injury via activation of the p38 pathway in NRK-52E cells [71].

There are few studies of the role of ERK5 in renal I/R injury. Kawakami et al. [72] reported that over-expression of full length ERK5 in the kidney serves a protective role against I/R injury.

Based on current information, we are inclined to agree with the opinion that the activation of ERKs，including ERK1/2 and ERK5, is critical for cell survival, while p38 and JNK contribute to cell apoptosis during I/R injury. However, the precise roles of MAPKs in renal I/R injury are not straightforward and are influenced by many factors and signaling pathways such as p53 [59], PI3K/Akt signaling pathways [49, 73], as well as NF-kappaB signaling pathways [61]. Thus, the further investigation for the function of MAPK in renal I/R injury is necessary before finding a correct direction toward clinical targets for the treatment of renal injury.

Chronic kidney diseases

The primary cause of chronic kidney diseases (CKD) is often related, directly or indirectly, to hypoxic/ischemic injury. This includes blood hypoperfusion, hypoxia, inflammatory damage in the case of glomerulonephritis and pyelonephritis, and toxic damage, which ultimately results in renal dysfunction [74]. The progression of renal fibrosis involves activation of intrinsic kidney cells as well as infiltrated cells, which leads to excessive accumulation and deposition of extracellular matrix, and the eventual loss of kidney function [75]. Prolonged hypoxia/ischemia is one of the most general mechanisms of CKD and is the leading cause and progression factor of end-stage renal diseases. Indeed, it has been considered to be a significant microenvironmental factor in promoting renal tubular atrophy and interstitial fibrosis, which are hallmarks of chronic kidney diseases [76, 77].

Fibrosis is a process whereby functional tissue is replaced by connective tissue and is the end result of a complex cascade of cellular and molecular responses initiated by organ damage [78]. Once this phenomenon exceeds the level of physiological repair, it will result in loss of organ architecture as well as loss of functional tissue. Fibrosis presents a number of characteristic features, including inflammatory cell infiltration, an increase in interstitial fibroblasts and matrix, and tubular atrophy, which is linked to epithelial cell apoptosis and epithelial to mesenchymal transition (EMT). Another characteristic feature of progressive renal disease is a loss of post-glomerular peritubular capillaries which leads to a reduction in oxygen supply. Therefore, it has been widely proposed that hypoxia is one of the common pathways of chronic renal disease progression [7, 79].

The majority of *in vitro* studies with tubular epithelial cells show that hypoxia can induce pathological changes that are consistent with a fibrogenic phenotype, such as promoting ECM accumulation with a switch to production of interstitial collagen type I and suppressing matrix turnover [80, 81]. Hypoxia can induce miR-155 as a pro-fibrotic cytokine to regulate TGF- β1 levels as well as the process of EMT; this promotes fibrosis of proximal tubule cells [82]. A transcription factor, Egr-1, is induced by hypoxia through the ERK1/2 pathway and can regulate the development of renal tubular EMT [83] In addition, hypoxia stimulates EMT of proximal tubular epithelial cells to a myofibroblastic phenotype [84, 85], a process that is increasingly implicated in fibrosis.

There is a range of organ-specific triggers during renal fibrosis; however, the fibrotic process and associated signaling pathways are highly conserved between different organs. MAPKs are involved in the pathology of a variety of kidney injuries, including renal fibrosis [14, 83]. *In vitro* hypoxia promotes a fibrogenic phenotype [86] with increased proliferation, enhanced myofibroblast differentiation, and altered ECM metabolism, which are all changes that are associated with sustained activation of MAPK signaling pathways. MAPKs can promote the fibrotic response through a number of different mechanisms, including: production and activation of transforming growth factor-β1 (TGF-β1), regulation of TGF-β1-Smad signaling; and TGF-β1 independent pro-fibrotic actions; see review [16].

Shen et al. reported that pretreatment with metformin prevents renal fibrosis by preventing angiotensin II-induced ERK1/2 activation and ECM overproduction in angiotensin II-treated renal fibroblast NRK-49F cells [87]. Fluorofenidone treatment inhibits the progression of renal interstitial fibrosis by suppressing oxidative stress and ERK1/2 signaling pathways in rat proximal tubular epithelial cells [88]. Similarly, paclitaxel in low nontoxic doses also relieves the effects of renal fibrosis, by blocking many steps in the TGF-β1-induced signaling pathway, such as the ERK1/2 pathway in inner medullary collecting duct cells [89]. A newly developed angiotensin II receptor blocker, fimasartan, has beneficial effects in reducing renal oxidative stress, inflammation, and fibrosis by inhibition of the ERK1/2 and JNK pathways and upregulation of nuclear factor erythroid 2-related factor 2 signaling in mice with unilateral ureteral obstruction (UUO) and HK-2 cells [90]. Moreover, Kruppel-like factor 15 is a major factor in renal interstitial fibrosis, and can potentially prove to be an antifibrotic factor by regulating the ERK1/2 and JNK signaling pathways [91].

There is a study showing that p38 inhibition attenuates H_2O_2-induced apoptosis and alleviated renal tubulointerstitial fibrosis pathogenesis in tubular epithelial cells in rat and human kidneys [92]. NPC 31169, a specific p38 MAPK inhibitor, blocked the p38 pathway and inhibited renal fibrosis in rat unilateral ureteric obstruction model [93]. Wang et al. indicated that blocking p38 activity partially reduced interstitial fibrosis, tubular atrophy and interstitial inflammation in the stenotic kidney [94]. Reduction of tubulointerstitial fibrosis in unilateral ureteral obstruction mouse kidney and NRK-49F cells by spleen tyrosine kinase inhibition is associated with down-regulation of p38 MAPK, which can reduce deposition of ECM protein and the expression of smooth muscle proteins such as α-smooth muscle actin, type I collagen, and fibronectin [95]. On the other hand, p38 activation of proximal tubular epithelial cells by astrocyte elevated gene-1 plays an important role in TGF-β1-induced epithelial to mesenchymal transition, which is an important cellular event in organogenesis, cancer and renal tubulointerstitial fibrosis [96]. A member of the MAPKKK family, apoptosis

Table 2. MAPKs versus renal fibrosis

Stimuli/Conditions	MAPK Changes	Outcome	References
peroxiredoxin 1 treatment in NRK-52E cells	p38 ↓	inhibit renal fibrosis	[92]
overexpression of astrocyte elevated gene-1 in HK-2 cells; p38 inhibition in HK-2 cells	p38 ↑; p38 ↓	promote EMT; inhibit EMT	[96]
SB203580 treatment in mouse renal artery stenosis models and SB202190 treatment in rat MC cells	p38 ↓	reduce intertital fibrosis	[94]
apoptosis signal-regulating kinase 1 deficient in mouse kidneys	p38, JNK ↓	inhibit renal fibrosis	[97]
metformin pretreatment in mice and NRK-49F cells	ERK1/2 ↓	prevent renal fibrosis	[87]
astragaloside IV treatment in HK-2 cells; SB203580 treatment in HK-2 cells; TGF-beta1 treatment in HK-2 cells	p38, JNK ↓; p38 ↓; p38, JNK ↑	inhibit fibrosis; inhibit fibrosis; promote fibrosis	[98]
fimasartan treatment in mouse kidney and HK-2 cells	ERK1/2, JNK ↓	inhibit renal fibrosis	[90]
spleen tyrosine kinase inhibition in UUO mouse kidneys and NRK-49F cells	p38 ↓	inhibit renal fibrosis	[95]
NPC 31169 treatment in rat UUO model	p38 ↓	inhibit renal fibrosis	[93]
paclitaxel treatment in IMCD cells; TGF-beta1 treatment in IMCD cells	ERK1/2, JNK ↓; ERK1/2, JNK ↑	ameliorate fibrosis; promote fibrosis	[89]
fluorofenidone treatment in NRK-52E cells	ERK1/2 ↓	inhibit renal fibrosis	[88]
kruppel-like factor 15 in NRK-49F cells; TGF-beta1 treatment in NRK-49F cells	ERK1/2, JNK ↓; ERK1/2, JNK ↑	inhibit fibrosis; promote fibrosis	[91]

signal-regulating kinase 1, can induce activation of p38 and JNK to promote renal fibrosis in an obstructed mouse kidney [97]. Xu et al. showed that increasing the activation of the JNK and p38 pathways plays a prominent role in renal tubular cell apoptosis, which subsequently accelerates the progression of renal tubulointerstitial fibrosis. As such, the inhibitory effect of astragaloside IV on cell apoptosis may be related to the inhibition of these two MAPK signaling pathways [98]. Moreover, Baicalein protects against inflammatory responses in the unilateral ureteral obstruction mouse model to ameliorate tubulointerstitial fibrosis via inactivation of NF-κB and MAPK signal pathways [99].

All these studies suggest that MAPKs play important roles in the transformation process of the renal fibrosis. Activation of one or multiple MAPKs can have a potential effect on the signaling pathways in the development and progression of renal fibrosis. Suppressing ERK1/2 individually or with p38/JNK signaling can inhibit the progress of renal fibrosis. Therefore, a blockage of MAPKs may have therapeutic potential for the treatment of chronic renal fibrosis.

Renal tumorigenesis

Hypoxia is commonly associated with the pathological changes of many types of solid tumors, including renal tumors [100]. Tumor hypoxia and the critical molecular mediators of hypoxia, hypoxia-inducible factors (HIFs), regulate multiple steps of renal tumorigenesis including tumor formation, progression, and response to therapy [100, 101]. To date,

three HIFs (HIF-1, -2, and -3) have been identified that regulate transcriptional programs in response to low oxygen levels. Consistent with tumor hypoxia as a mechanism of HIF activation, HIF proteins are commonly detected in perinecrotic regions of sporadic tumors and overlaps with staining for known hypoxic markers. A recent survey of malignant and normal tissues found that the expression of both HIF-1 and HIF-2 is commonly increased in a variety of human tumors, including bladder, breast, colon, glial, hepatocellular, ovarian, pancreatic, prostate, and renal tumors [102]. A variety of clinical and mechanistic data supports that HIF-1α has an important role in promoting tumorigenesis in a clinically important and large subset of human renal carcinoma (see review [103] by Gudas et al.).

Renal tumors account for approximately 3% of all neoplasias, with renal cell carcinoma (RCC) being the most widespread malignant tumor in the adult kidney. The most common RCC is the clear cell carcinoma (ccRCC), which represents about 70% of all RCCs. The ccRCC is associated with von Hippel-Lindau (VHL) disease, which is characterized by its relatively poor prognosis due to late presentation and resistance to various therapeutical manipulations [104, 105]. In response to hypoxic stress, several survival pathways are activated in renal tumor cells to perform their essential biological processes in different ways in comparison to normal cells. In ccRCC, hypoxic stress causes reactive oxygen species (ROS) production, which can lead to enhanced MAPK cascade stimulation [106]. The understanding of the signaling pathways involved in renal tumorigenesis will hopefully provide insight leading to the optimization of specific therapies for renal tumors.

An *in vitro* study [107] showed that the suppression of MAPK pathways impaired human ccRCC cells' proliferation, clonogenicity, anoikis resistance, migration, and invasion capabilities. Phosphorylated ERK1/2 expression is significantly upregulated in renal clear cell carcinoma when compared to normal cells, in relation to the pathological grade and clinical stage of ccRCC [108]. Oka et al. described that constitutive activation of MAPKs may be associated with the carcinogenesis of human renal cell carcinoma [109]. Huang et al. *in vivo* studies showed that the expression of MAPK kinase 1 and ERK2 in human clear cell RCC were significantly higher than normal controls, and the suppression of one or more MAPK signaling pathways using Anthrax lethal toxin inhibited RCC growth by disrupting tumor vasculature [110].

MAPKs appear to be critical in the activation of the HIF-1. It was reported that either ERK1/2 or p38 can phosphorylate HIF-1 [111-113], while inhibition of these two MAPKs was capable of blocking the expression of reporter genes of the HIF-1 activity [114]. More recently, the use of p38 as a potential biomarker of ccRCC, which correlates well with Fuhrman grade, has been proposed [115]. In short, there is noticeable evidence suggesting that MAPK signaling pathways may be critical in the biological effects of the HIF in ccRCC and that the activation of MAPK signaling pathways plays a crucial role in tumorigenesis, metastasis, and angiogenesis of RCC. All this data suggests that MAPKs are linked to the progression of renal cell carcinomas.

ERK1/2

ERK1/2 has been thought as an important factor contributing to renal tumor proliferation since most studies show that ERK1/2 is critical for cell survival against stress. Suzuki et al. indicated that inhibiting the ERK1/2 pathway using bisebromoamide in ccRCC cell lines can induce apoptosis to combat tumor cell proliferation [116]. Also, stimulating alkaline phosphatase in renal tumor cell lines can deactivate ERK1/2; so, alkaline phosphatase may be used as a potential therapeutic target of RCC [117]. Docetaxel may suppress proliferation of RCC cells under *in vitro* and *in vivo* settings by suppressing cell growth, by inducing of both apoptosis and G2/M cell cycle arrest, which is related to reduced phosphorylation of ERK1/2 [118]. *In vivo* growth of a resistant to sunitinib human RCC cell line in nude mice is significantly inhibited after treatment with axitinib (compared to after treatment with sunitinib); accompanying the marked inhibition of angiogenesis, which proves that the antitumor activity of axitinib in RCC cells, at least in part, is involved in the inactivation of ERK1/2 [119]. RCC cell proliferation and invasion, as well as the inhibition of RCC cell apoptosis

by activating the smad and ERK1/2 pathways can be mediated by nodal overexpression [120]. In RCC cells, simvastatin stimulates apoptosis, anti-metastasis, and the inhibition of the ERK1/2 pathway [121]. In addition, the effects of the multi-target drug, sorafenib, on ccRCC necrosis by regulating cyclophilin D expression are related to the inhibition of phosphorylated-ERK1/2 [122]. This data suggests that the ERK1/2 signaling pathway plays a vital role in renal carcinoma proliferation, with very few reports expressing an opposite opinion. Fang et al. suggested that the ERK1/2 signaling pathway mediates the regulation of cell cycle-related proteins, effectively inhibits cell proliferation, and also causes G1 phase arrest in RCC cell lines [123]. Protein kinase C epsilon (PKCε) plays as an important mediator in cancer stem cell pathogenesis of renal cell cancer by regulating the phosphorylation of ERK1/2 in RCC 769P side population cell line [124]. Xu et al. suggested that the anti-tumor activities of acyldepsipeptides are dependent on the down-regulated expressions of cyclin D1, CDK4, and PCNA, along with the decreased expression of phosphorylated ERK1/2 in renal 786-O and 769-P cells [125]. Restraining the activation of ERK1/2 suppressed cellular proliferation and migration in an RCC cell line (786-0), this suggested that ERK1/2 may play important roles as a positive regulator to RCC [126].

In short, ERK1/2 activation may contribute to renal tumor cell proliferation and metastasis.

p38 / JNK

The p38 and JNK pathways act as pro-apoptotic factors. It was reported that overproduction of ROS due to cisplatin administration in cancer patients can trigger inflammatory responses and apoptosis in rat kidneys by increasing the expression of pro-inflammatory cytokine, tumor necrosis factor-α and apoptotic marker p38 [127]. Kim et al. indicated that p38 mediates interleukin 4-induced growth inhibition and cellular senescence in certain human RCC cell lines [128]. Inhibition of the p38 MAPK and JNK signaling pathways attenuated mifepristone-induced apoptotic cell death and anti-tumor activity via regulating the expression of CCAAT/enhancer-binding protein homologous protein in renal carcinoma cells [129]. These studies showed above suggest that p38 MAPK and JNK signaling pathways may act as anti-tumor factors in renal carcinomas. Although, it is also showed that JNK activity affects pVHL-deficient RCCs in *in vitro* and *in vivo* growth, JNK stimulates c-Jun phosphorylation, activation, and dimerization with c-Fos. This forms a transcriptionally competent activator protein-1 complex, which drives the transcription of the Twist gene and induces EMT, which is essential for renal tumor metastasis [130]

ERK5

The specific knockdown of ERK5 in pVHL-negative cell lines promotes a decrease in proliferation and migration, thus supporting the role of this MAPK in cellular transformation. Furthermore, high levels of ERK5 correlated with more aggressive and metastatic stages of human ccRCC, based off a short series of fresh samples of the disease [131]. Therefore ERK5, similar to ERK1/2, very likely promotes renal tumor proliferation and migration.

Altogether, the activation of ERKs (including ERK1/2 and ERK5) has been associated with renal cancer proliferation and migration, while p38 and JNK may contribute to growth inhibition and cellular senescence in renal tumors. Chaves Neto et al have more evidence to help the argument. They demonstrated that downregulation of the ERK1/2 pathway and activation of the p38 and JNK pathways have antitumor effects. This is done through the inhibition of matrix metalloproteinase-2 activity and reducing the expression of renal cancer aggressiveness markers caveolin-1, low molecular weight phosphotyrosine protein phosphatase, as well as vascular endothelial growth factor receptor 2 [132]. Since there is substantial data on the role of MAPK-mediated signaling in controlling renal tumorigenesis, MAPK pathways may have great therapeutic value against ccRCC. However, it may be a complex issue to enhance or inhibit one or more MAPKs specifically, in renal cancer treatment since many factors affect the outcome.

Conclusions

Renal hypoxia/ischemia is a common condition in clinical settings and is associated with many disorders. Among the complex mechanisms underlying hypoxic/ischemic pathophysiology in the kidney, MAPK signaling is critically involved in the genesis and progression of both acute and chronic kidney diseases as well as renal carcinoma. Activation of ERK1/2 or deactivation of p38/JNK may promote renal survival against I/R stress, while the same treatment may contribute to tumor cell proliferation and metastasis. It is therefore possible to prevent/treat hypoxic/ischemic kidney injury and other kidney diseases by targeting MAPK signals. However, more investigations are needed to further verify the clinical and laboratory results and elucidate the molecular mechanisms in detail. It is our belief that future studies will provide novel treatments of hypoxic/ischemic kidney disease by targeting MAPK pathways.

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Disclosure Statement

The authors declare no conflict of interest.

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