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P53 in kidney injury and repair: Mechanism and therapeutic potentials

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ABSTRACT

Acute kidney injury (AKI) is a major kidney disease with poor clinical outcome. Besides its acute consequence of high mortality, AKI may also contribute significantly to the occurrence and progression of chronic kidney diseases (CKD). Accumulating evidence has demonstrated that maladaptive and incomplete kidney repair after AKI leads to the development of renal fibrosis and, ultimately, CKD. p53, a well-known tumor suppressor, plays a critical role in AKI and subsequent kidney repair through the regulation of various cell biologic processes, including apoptosis, cell cycle arrest, and autophagy. Despite the notable progress in deciphering the involvement of p53 in kidney injury and repair, the underlying mechanisms of p53 in these pathological processes remain largely unknown. Further investigation in this area is essential for the application of p53 as therapeutic target to prevent and treat AKI or impede its progression to CKD. In this review, we summarize the recent advances in understanding p53 regulation of AKI and kidney repair, pinpoint the potential of p53 as a therapeutic target, and present future research interests and directions.

Contents

1. Introduction

Acute kidney injury (AKI), primarily caused by renal ischemia reperfusion (IR), nephrotoxins and sepsis, is a major kidney disease characterized by an abrupt loss of renal function (Chawla et al., 2017; Makris & Spanou, 2016). Pathologically, AKI is characterized by sublethal and lethal injury of kidney tubules, resulting in tubular dysfunction and cell death in the forms of necrosis and apoptosis (Agarwal et al., 2016; Bonventre & Yang, 2011; Linkermann et al., 2014). AKI has a poor clinical outcome. Besides its acute consequence of high mortality, AKI may also contribute significantly to the development and progression of chronic kidney diseases (CKD) (He et al., 2017; Heung et al., 2016; Hsu, 2012; Leung, Tonelli, & James, 2013). Following AKI, survival renal proximal tubular epithelial cells (RPTCs) undergo a robust proliferation to restore tubular integrity. Recent research has demonstrated that maladaptive and incomplete repair leads to the development of renal fibrosis and, ultimately, CKD (Basile et al., 2016; Ferenbach & Bonventre, 2015; Humphreys, 2018; Venkatachalam, Weinberg, Kriz, & Bidani, 2015). Accumulating evidence has also demonstrated that AKI development and subsequent kidney repair after AKI are complex and multifactorial, involving renal tubular, microvascular and inflammatory mechanisms that interplay with and amplify each other (Basile et al., 2012; Bonventre & Yang, 2011; Chawla et al., 2017; He

Abbreviations: AA, aristolochic acid; AKI, acute kidney injury; CKD, chronic kidney disease; IR, ischemia-reperfusion; IRI, ischemia-reperfusion injury; ROS, reactive oxygen species; RPTEC, renal proximal tubule epithelial cell; siRNA, short interfering RNA; TP53/p53, tumor protein p53.

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et al., 2017; Jang & Rabb, 2015; Kumar, 2018; Yang, Humphreys, & Bonventre, 2011).

p53, a well-known tumor suppressor protein, belongs to a family that includes another two structurally related members, p63 and p73. p53 is a key component of the cellular response to stress. The regulation of p53 includes its expression and stability in concert with a wide variety of reversible post-translational modifications (PTMs) (Kruiswijk, Labuschagne, & Vousden, 2015; Meek & Anderson, 2009; Saldana-Meyer & Recillas-Targa, 2011). In response to cellular stress, including DNA damage, oncogene expression, hypoxia, reactive oxygen species (ROS), and nutrient deprivation, p53 is induced and/or rapidly undergoes reversal PTMs allowing for its stabilization and activation (Kruiswijk et al., 2015). Subcellular localization also affects the function of p53. In the nucleus, p53 transcriptionally activates a wide range of genes involved in apoptosis, cell cycle, autophagy, and/or metabolism (Kruiswijk et al., 2015). On the other hand, cytoplasmic p53 functions in a transcription-independent manner by direct binding to cytoplasmic proteins, such as apoptotic and autophagy effectors (Green & Kroemer, 2009; Saldana-Meyer & Recillas-Targa, 2011; Tasdemir et al., 2008). Beside the well-known function as a tumor suppressor, p53 has a much broader role and its dysregulation contributes to the development a variety of human diseases (Kruiswijk et al., 2015).

Experimental studies in the past years have provided compelling evidence to support a pivotal role of p53 in the pathogenesis of AKI and post-AKI kidney repair. This review summarizes our current insights on the role and regulation of p53 in kidney injury and repair. The therapeutic potential of targeting p53 for preventing and treating AKI or impeding its progression to CKD is also discussed.

1.1. Role of p53 in the pathogenesis of AKI

Recent research offers compelling support for a key role of p53 in the pathogenesis of AKI (Table 1). The involvement of p53 in renal ischemic-reperfusion injury (IRI) was firstly described in a rat model by Dagher and colleagues in 2003 (Kelly, Plotkin, Vulgamott, & Dagher, 2003). They showed that renal IR induced p53 expression in renal medulla over 24 h postal IR, and importantly, chemical inhibition of p53 activity by pifithrin-α at the time of renal ischemia prevented tubular cell apoptosis and concurrently resulted in renal functional protection from IRI. Further studies by Molitoris et al. (Molitoris et al., 2009) demonstrated that inhibition of *p53* by short interfering RNA (siRNA), which was administrated by intravenous injection at 4 h after renal ischemia and primarily uptaken by RPTECs within the kidney, protected against apoptosis and renal functional impairment. We (Zhang et al., 2014) and Ying et al.(Ying, Kim, Westphal, Long, & Padanilam, 2014) demonstrated that specific ablation of *p53* gene from renal proximal tubules protected against IRI in kidney. Of note, ablation of *p53* from other renal tubular segments was not effective (Zhang et al., 2014). In vitro studies also provided evidence that chemical or genetic inhibition of p53 protects cultured RPTECs against ATP-depletion induced injury (Kelly et al., 2003). Together, these findings suggest a pathogenic role of renal tubular cell p53 in IRI.

p53 induction and activation also contributes critically to the pathogenesis of cisplatin -induced nephrotoxic AKI (Table 1) (Cummings & Schnellmann, 2002; Jiang & Dong, 2008; Jiang, Yi, Hsu, Wang, & Dong, 2004; Wei et al., 2007; Zhang et al., 2014). Cisplatin is a widely used cancer therapy drug, which is also notorious for its toxicity in normal organs and tissues, especially in kidneys (dos Santos, Carvalho Rodrigues, Martins, & dos Santos, 2012; Miller, Tadagavadi, Ramesh, & Reeves, 2010; Ozkok & Edelstein, 2014; Pabla & Dong, 2008; Zhu, Pabla, Tang, He, & Dong, 2015). Our studies showed that in cultured RPTECs, p53 was phosphorylated and upregulated early during cisplatin treatment, and inhibition of p53 by pifithrin-a or dominant-negative mutant p53 dramatically attenuated cisplatin-induced apoptosis (Jiang et al., 2004; Wei et al., 2007). Consistently, in vivo, administration of cisplatin resulted in p53 phosphorylation and accumulation in renal tubular cells in parallel with the development of kidney injury in mice (Wei et al., 2007). Importantly, co-administration of pifithrin-α at the time of cisplatin administration or global *p53* deficiency protected against cisplatin-induced nephrotoxicity (Wei et al., 2007). Our recent studies further demonstrated that targeted deletion of p53 in the proximal tubule (instead of other tubular segments) protected against cisplatin-induced kidney injury in mice (Zhang et al., 2014). Collectively, these findings demonstrate a pivotal role of proximal tubular cell p53 in the pathogenesis of cisplatin-induced AKI or nephrotoxicity.

In addition, p53 has also been associated with the pathogenesis of AKI induced by folic acid (Zhou et al., 2012), aristolochic acid (Zhou et al., 2010), glycerol injection(Homsi, Mota da Silva, et al., 2011), and vancomycin (Chen et al., 2016). However, the role of p53 in sepsis or contrast-induced AKI, two common forms of AKI in hospitalized patients, remains poorly understood.

Table 1
Summary of animal studies on the effect of p53 inhibition in kidney injury and repair.

AKI model	Approach for p53 inhibition	Time of p53 deletion or inhibition	Effects on AKI and renal fibrosis	References
IRI in rat	p53 siRNA	Single dose at 4 h post IR	Attenuate AKI	Molitoris et al. (2009)
IRI in mice	Targeted p53 deletion in RPTECs	Germline deletion by Pepck-cre	Attenuate AKI, reduce renal fibrosis	Ying et al. (2014)
IRI in mice	Targeted p53 deletion in RPTECs	Germline deletion by Pepck-cre	Attenuate AKI	Zhang et al. (2014)
IRI in mice	Global p53 deletion	Germline deletion	Aggravate AKI and renal fibrosis	Sutton et al. (2013)
IRI in mice	Pifithrin-α	At the time of renal surgery and then daily for 7 days	Aggravate AKI and renal fibrosis	Sutton et al. (2013)
IRI in mice	Chimeric mice lacking p53 in leukocytes		Aggravate AKI and renal fibrosis	Sutton et al. (2013)
IRI in rats	Pifithrin-α	At the time of surgery and then daily for 7 days	Aggravate renal fibrosis	Dagher et al. (2012)
UIRI in mice	Pifithrin-α	At day 14 after r surgery	Attenuate renal fibrosis	Yang, Besschetnova, Brooks, Shah, and Bonventre (2010)
IRI in rat	p53 siRNA	At 4 h before cisplatin and then daily for 2 days	Attenuate AKI	Molitoris et al. (2009)
Cisplatin-AKI in mice	Targeted p53 deletion in RPTECs	Germline deletion by Pepck-cre	Attenuate AKI	Zhang et al. (2014)
Cisplatin-AKI in mice	Pifithrin-α	A single dose at the same time of cisplatin treatment	Attenuate AKI	Wei et al. (2007)
Cisplatin-AKI in mice	Global p53 deletion	Germline deletion	Attenuate AKI	Wei et al. (2007)
AA-AKI in mice	Global p53 deletion	Germline deletion	Attenuate AKI	Zhou et al. (2010)
AA-AKI in mice	Pifithrin-α	At the time of AA injection and then daily for 3 days	Attenuate AKI	Zhou et al. (2010)
Glycerol-AKI in rats	Pifithrin-α	Before glycerol injection	Protection against AKI	Homsi et al. (2011)
VAN-AKI in mice	Global p53 deletion	Germline deletion	Protection against AKI	Chen et al. (2016))

IRI, Ischemia-reperfusion injury; AA, aristolochic acid; VAN, vancomycin; RPTEC, renal proximal tubule epithelial cell; PEPCK, Phosphoenolpyruvate carboxykinase.

1.2. Involvement of p53 in kidney repair after AKI

Following AKI, the kidney has the capacity to restore injured tubules. Surviving tubular cells undergo dedifferentiation, proliferation, migration and redifferentiation into fully differentiated and polarized tubular cells to repair injured renal tubules. Normal repair restores tubular epithelial integrity and functions; however, incomplete or maladaptive repair after AKI, characterized by the atrophic and undifferentiated tubules, results in renal interstitial fibrosis and ultimate progression to CKD (Basile et al., 2016; Ferenbach & Bonventre, 2015). The repair process involves the activation of multiple signaling pathways in injured and regenerating tubular cells accompanied by the production and secretion of growth factors, cytokines, and inflammatory mediators (Basile et al., 2016; Ferenbach & Bonventre, 2015; He et al., 2017).

p53 has been implicated in maladaptive kidney repair. Higgins and colleagues provided comprehensive evidence that p53 activation and its assembly with SMAD family member 3 (SMAD3) are required for the transcription of profibrotic genes in renal tubular epithelial cells in the mouse model of unilateral ureteral obstruction and in cultured renal tubular cells exposed to transforming growth factor-β1, a principal driver of renal fibrosis (Higgins et al., 2018; Overstreet, Samarakoon, Meldrum, & Higgins, 2014; Samarakoon et al., 2013; Samarakoon et al., 2015). Moreover, genetic and pharmacological inhibition of P53 has been shown to modulate kidney repair after AKI (Table 1). Yang et al. showed that acute inhibition of p53 by a single dose of pifithrin-α on day 14 after renal ischemic injury ameliorated the development of renal fibrosis (Higgins et al., 2018; Yang et al., 2010). Furthermore, Ying et al. reported that target deletion of p53 in proximal tubule cells prevented interstitial fibrogenesis after acute renal ischemia injury in mice (Ying et al., 2014). On the contrary, Dagher et al. and Sutton TA et al. reported that p53 inhibition by pifithrin-a that was administered at the time of renal IR and lasted for 7 days ultimately increased renal fibrosis (Dagher et al., 2012; Sutton et al., 2013). Mechanistically, they revealed that p53 inhibition or deficiency in leucocytes sustained the survival and proinflammatory function of macrophages, thereby promoting renal fibrosis. These differing results suggest that the role of p53 in AKI repair is complicated and still incompletely understood.

1.3. How does p53 regulate AKI and kidney repair?

p53 regulates various cellular processes (Farnebo, Bykov, & Wiman, 2010; Kruiswijk et al., 2015). Recent research has provided substantial evidence supporting that p53 participates AKI development and subsequent kidney repair mainly through the regulation of apoptosis, cell cycle arrest, and autophagy (Fig. 1).

1.3.1. Cell death

p53 regulates different types of cell death, including apoptosis, necrosis and ferroptosis (Murphy, 2016; Vaseva et al., 2012; Xie et al., 2017). p53-dependent tubular cell death has been demonstrated as a major contributor to the pathogenesis of AKI (Linkermann et al., 2014). Mechanistically, transcription-dependent pro-cell death function of p53 contributes critically to its pathogenic role in AKI. The transcriptional activity of p53 was shown to be important for renal tubular apoptosis in cisplatin nephrotoxicity (Jiang et al., 2004). p53 transcriptionally up-regulates expression of components of both intrinsic and extrinsic apoptosis pathways. So far, it has been demonstrated that pro-apoptotic protein p53 upregulated modulator of apoptosis (PUMA), p53-induced protein with a death domain (PIDD), and executioner caspase-6 and -7 are primary mediators of p53-dependent tubular cell apoptosis in cisplatin nephrotoxicity (Jiang & Dong, 2008; Zhu et al., 2015). p53-depedent induction of PUMA, BCL2-associated X protein (BAX) and SIVA1 apoptosis inducing factor (SIVA1) has been demonstrated to be responsible for apoptosis following renal IR (Singaravelu & Padanilam, 2011; Zhang et al., 2014). p53 regulates extrinsic apoptotic pathway through inducing the expression of Fas receptor (FasR), death-receptor 4 and 5 (DR4 and DR45) (Olsson, Manzl, Strasser, & Villunger, 2007). Tumor necrosis factor alpha (TNF-α) and Fas-dependent extrinsic pathway of apoptosis has been indicated in tubular cell loss in ischemic and septic AKI (Cunningham et al., 2002; Ortiz, Lorz, & Egido, 1999), suggesting a possible role of p53-depedent extrinsic pathway of apoptosis in AKI. In addition to pro-apoptotic proteins, p53-dependent induction of noncoding RNAs also contribute to tubular cell apoptosis in AKI. For instance, Chen et al. revealed that microRNA (miR)-192-5p was induced via p53 to mediate vancomycin-induced AKI (Chen et al., 2016), and we recently

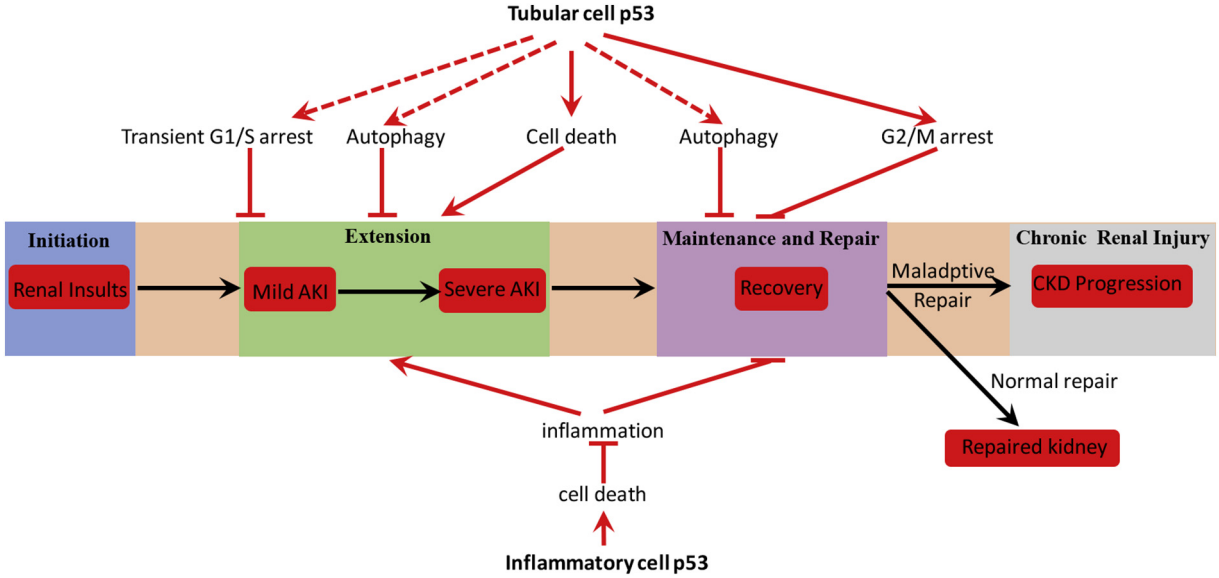

Fig. 1. Role of p53 in AKI development and progress to CKD. AKI can be generally divided into 4 phases: initiation, extension, maintenance and repair, and chronic renal injury. p53 in renal proximal tubular cells may induce transient G1/S cell cycle arrest and autophagy to protect against mild or early stage of injury. However, in prolonged or severe AKI, p53 induces tubular cell death to contribute to AKI. During kidney recovery or repair, tubular p53 may induce G2/M cell cycle arrest and persistent autophagy to prevent normal tubular repair, which consequently results in maladaptive kidney repair. In contrast, the activation of p53 in inflammatory cells may induce inflammatory cell death, resulting in the attenuation of inflammation to protect against AKI and promote kidney recovery/repair.

demonstrated that p53 and NF-κB collaboratively induced miR-375 for cisplatin-induced tubular cell apoptosis and nephrotoxicity (Hao et al., 2017). Besides transcription-dependent proapoptotic functions, p53 in mitochondria can directly induce apoptosis through direct binding to BCL-2 family members to initiate robust mitochondrial outer membrane permeabilization, leading to release of pro-apoptotic factors into the cytosol and consequent activation of the caspase cascade (Vaseva & Moll, 2009). In this regard, p53 translocation to mitochondrial during AKI has been reported (Kelly et al., 2003). In addition, we recently showed that mixed lineage kinase domain like pseudokinase (MLKL), a newly identified key regulator of necrosis downstream of the receptor interacting protein kinase 3 (RIPK3) is p53-dependently induced following renal IRI (Zhang et al., 2014), suggests that p53 may also be involved in tubular cell necrosis in AKI. Moreover, emerging evidence shows that ferroptosis, an iron-dependent form of regulated nonapoptotic cell death, contributes to damage in models of AKI (Martin-Sanchez et al., 2017; Martin-Sanchez et al., 2018), but the role of p53 in ferroptosis in the setting of AKI remains to be determined. Collectively, these findings suggest that the pro-cell death function is the major role of p53 in renal tubular damage in AKI.

1.3.2. Cell cycle arrest

Recent research has provided substantial evidence that cell-cycle arrest plays an important role in AKI pathogenesis and subsequent kidney repair. p53 is a key player in the regulation of cell cycle arrest at both G1 and G2 phases by transcriptional induction of p21, 14–3-3 phosphoserine/phospho-threonine binding protein (14–3-3δ), and growth arrest and DNA damage inducible alpha (Gadd45) (Hermeking & Benzinger, 2006; Jin et al., 2002). p21 is the primary mediator of p53-dependent cell cycle arrest at G1 phase, whose induction inhibits G1 cyclin-dependent kinases (CKD) that are essential for the G1/S transition (Harper, Adami, Wei, Keyomarsi, & Elledge, 1993). On the other hand, induction of 14–3-3δ and Gadd45 inhibits the activity of CDC2/cyclin B complexes that is essential for the G2/M transition, thereby leading to cell cycle arrest at G2 phase (Hermeking & Benzinger, 2006; Jin et al., 2002). Renal tubular cell arrest at G1 phase was implicated in septic AKI rat model induced by cecal ligation and puncture as indicated by the association of the induction of p53 and p21 with tubular cell G1 arrest (Yang et al., 2009). In human, two inducers of G1 cell cycle arrest, tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor binding protein-7 (IGFBP-7), were specifically increased in the urea of early AKI (Aregger et al., 2014; Kashani et al., 2013). Among them, IGFBP7 is a p53-responsive gene (Chen et al., 2011). These findings suggest an association of p53 induction with tubular cell G1/S arrest in AKI. Functionally, pharmacological and genetic studies have suggested that transient tubular cell G1/S arrest before the onset of AKI is renoprotective (DiRocco et al., 2014; Nishioka et al., 2014; Pabla et al., 2015), which is possibly mediated through favoring subsequent tubular cell proliferation after kidney injury. In contrast, persistent tubular cell cycle arrest at G2/M phase results in maladaptive repair and consequently the progression to CKD after AKI. Mechanistically, G2/M-arrested proximal tubular cells show increased production and secretion of profibrotic factors (Yang et al., 2010), which may drive fibrosis and the progression to CKD via autocrine and paracrine functions. Importantly, inhibition of p53 by pifithrin-α or targeted deletion of p53 in the proximal tubule attenuated cell cycle arrest at the G2/M phase and consequently post AKI renal fibrosis (Yang et al., 2010; Ying et al., 2014), suggesting a key role of p53 in tubular cell G2/M arrest during AKI. Together these findings suggest that p53-mediated tubular cell cycle arrest plays a pivotal role in AKI pathogenesis and subsequent kidney repair, and thus modulation of tubular cell cycle arrest provides a novel therapeutic strategy for AKI.

1.3.3. Autophagy

Autophagy is a cellular process where autophagosomes deliver cytoplasmic constituents to lysosomes for degradation (He & Klionsky, 2009). p53 may participate in the regulation of autophagy and has been implicated in autophagy regulation in AKI. In cultured renal tubular cells, cisplatin-induced autophagy was partially suppressed by chemical inhibition of p53 (Periyasamy-Thandavan et al., 2008), suggesting a pro-autophagic role of p53 in this experimental condition. The pro-autophagic role of p53 depends on its nuclear localization. It has been demonstrated that nuclear p53 transactivates a large set of target genes that are involved in the autophagic program, including AMP-activated protein kinase (AMPK) β1 and β2 subunits, sestrin 1 and 2, tuberous sclerosis protein 2, pro-apoptotic BCL-2 proteins (e.g. BAX, BNIP3, and PUMA), and more (Kenzelmann Broz et al., 2013; Maiuri et al., 2010). Among these proteins, AMPK, sestrin 2 and BNIP3 have been shown to participate in autophagy activation in renal tubular cells in AKI (Ishihara et al., 2013; Li et al., 2016). In contrast to the pro-autophagic role of nuclear p53, cytosolic p53 may have anti-autophagic function. Hoshino and colleagues (Hoshino et al., 2013) showed that cytosolic p53 impairs mitophagy, a specific form of autophagy that degrades damaged or unwanted mitochondria, which has been implicated in AKI (Tang et al., 2018; Zhao et al., 2017). Notably, a very recent study by Goiran et al. demonstrated that the transcriptional activity of p53 also represses autophagy by down-regulating the transcription of *PINK1* which encodes a key protein involved in mitophagy (Goiran et al., 2018). Collectively, these findings suggest that p53 may have a key role in regulating autophagy in kidney.

Functionally, evidence has accumulated supporting a kidney protective role of autophagy in AKI (Kaushal & Shah, 2016; Livingston & Dong, 2014). In 2008, we reported the first evidence of autophagy induction in AKI by using the model of cisplatin nephrotoxicity (Periyasamy-Thandavan et al., 2008). Then after, we (Jiang et al., 2012) and others have further demonstrated that blockade of autophagy worsens AKI by using inhibitors and autophagy-deficient mice. More recently, we provided evidence that activation of PINK1-PARK2 pathway of mitophagy protected against renal IRI (Tang et al., 2018). Unlike the accepted view that autophagy is renoprotective in AKI, the role of autophagy in kidney repair remains unclear and controversial. We and others showed that persistent autophagy in proximal tubules promoted tubular atrophy, inflammation, and renal fibrosis (Livingston et al., 2016; Yan et al., 2018). In sharp contrast, several studies presented the evidence for an anti-fibrosis role of autophagy in unilateral urinary obstruction (Ding et al., 2014; Li et al., 2016; Shi et al., 2016). Currently, very limited is known about autophagy in renal fibrosis post-AKI. Taken together, the role of p53 in autophagy regulation in kidney diseases awaits further investigation.

1.4. How is p53 induced during AKI and subsequent kidney repair

A variety of cellular stress stimuli, including DNA damage, oncogene expression, hypoxia, reactive oxygen species (ROS) and nutrient fluctuation, have been demonstrated to induce p53 activation via distinct signaling pathways (Horn & Vousden, 2007). Among them, DNA damage, ROS and hypoxia act as major factors of p53 induction in proximal tubular cells during AKI development and kidney repair (Fig. 2).

1.4.1. DNA damage

DNA damage induces p53 activation mainly through ataxia-telangiectasia mutated (ATM) and ATR (ATM and Rad3-related) protein kinases-dependent pathways (Smith, Tho, Xu, & Gillespie, 2010). ATM and ATR are activated in response to DNA damage, which in turn phosphorylates p53 and results in p53 uncoupling from ubiquitin E3 ligase MDM2 proto-oncogene (MDM2) and negative regulator MDM4, leading to p53 stability and activation. Meanwhile, activated ATR further activates checkpoint kinase 2 (CHK2) to induce p53 phosphorylation and activation (Smith et al., 2010). We and others have recently demonstrated that DNA damage is a major trigger for p53 activation during AKI (Bartz et al., 2014; Jiang & Dong, 2008; Ma, Wei, Dong, Huo, & Dong, 2014; Pabla & Dong, 2008; Pabla, Huang, Mi, Daniel, & Dong, 2008; Yan, Tang, Ma, Huang, & Dong, 2016). For instance, we revealed

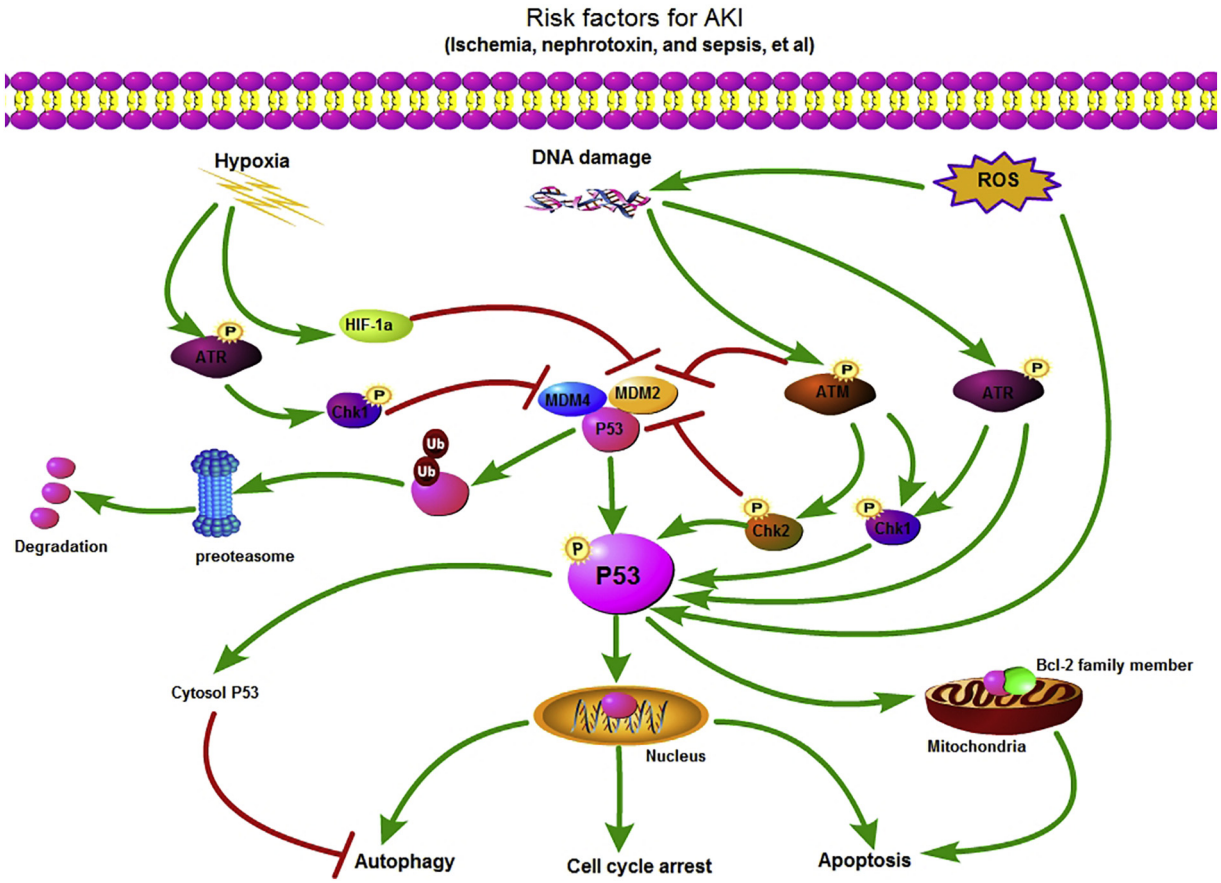

Fig. 2. Regulation of p53 in AKI development and progress to CKD. Renal insults leads to hypoxia, DNA damage, and/or ROS production in kidney cells, which subsequently activate p53 by post-translational modification (e.g. phosphorylation) through distinct signaling pathways. DNA damage induces p53 activation mainly through ATM and ATR-dependent pathways. ROS regulate p53 activity by inducing signaling pathways response (e.g. DNA damage response pathway) for p53 activation, or through a direct redox modification called s-glutathionylation on p53 to inhibit its DNA binding activity. Hypoxia induces p53 activation mainly through HIF-1a and ATR. Upon activation, nuclear p53 transactives a wide range of genes involved in apoptosis, cell cycle arrest, and autophagy. Cytoplasmic p53 functions in a transcription-independent manner by its direct interactions with cytoplasmic proteins, such as apoptotic effectors.

that ATR/CHK2-dependent DNA damage signaling pathway was responsible for cisplatin-induced p53 activation (Pabla et al., 2008). ATR was activated early during cisplatin treatment in renal tubular cells, and then accumulated in cell nuclei, where it colocalized with histone H2AX to form nuclear foci at the site of DNA damage (Pabla et al., 2008). ATR then phosphorylated and activated CHK2. Importantly, inhibition of ATR or CHK2 either by dominant-negative mutants or by gene deletion attenuated cisplatin-induced p53 activation and cell apoptosis (Pabla et al., 2008). Consistently, activation of ATR and CHK2 was also detected in renal tissues after cisplatin treatment (Pabla et al., 2008). DNA damage was also detected in proximal tubular cells following renal IR in mice and in cultured tubular cells subjected to ATP-depletion injury as indicated by the increased phosphorylation of ATM, H2A histone family member X (H2AX), CHK2, and p53 (Ma et al., 2014). Moreover, DNA damage in kidney cells occurred in response to sepsis (Bartz et al., 2014). Notably, in contrast to the compelling evidence for DNA damage in AKI, little is known about DNA damage during kidney repair post-AKI at the moment.

1.4.2. Reactive oxygen species

ROS play a critical role in the development of AKI and consequent renal fibrosis as indicated by the excessive ROS generation during the acute phase and the recovery phase of AKI in experimental AKI models, and the protective effect of ROS scavengers on AKI development and repair (Basile, Anderson, & Sutton, 2012; Chouchani et al., 2014; Doi, Suzuki, Nakao, Fujita, & Noiri, 2004; Himmelfarb et al., 2004; Kim, Seok, Jung, & Park, 2009; Winterberg et al., 2013). ROS is an important inducer of p53 activation. Research from others and us has demonstrated that ROS active p53 during AKI (Jiang et al., 2007; Ju et al., 2014). We showed that in response to cisplatin treatment, hydroxyl radicals accumulated rapidly in renal tubular cells, correlating with early p53 phosphorylation and preceding p53 protein stabilization and induction. Importantly, amelioration of hydroxyl radical accumulation by antioxidants dimethylthiourea and *N*-acetyl-cysteine (NAC) attenuated p53 activation, and consequently alleviated tubular cell apoptosis, renal tissue damage, and decline of renal function (Jiang et al., 2007). NAC was also shown to suppress ATP depletion-induced p53 phosphorylation in renal tubular cells (Ma et al., 2014). Mechanistically, ROS can indirectly regulate p53 activity through inducing signaling pathways response for p53 activation. For example, ROS-induced DNA damage response contributed to the increased phosphorylation of p53 in ATP-depletion renal tubular cell (Ma et al., 2014). ROS may also regulate p53 activity through a direct redox modification called *S*-glutathionylation on p53 (Maillet & Pervaiz, 2012; Velu, Niture, Doneanu, Pattabiraman, & Srivenugopal, 2007). The glutathionylation was shown to locate at the cysteine sites of DNA binding domain in p53 and inhibited its DNA binding activity, leading to p53 inactivation (Velu et al., 2007). However, the possible redox modifications of p53 and its effects on AKI remain unknown. In terms of kidney repair, emerging evidence suggests ROS contribute critically to progression of kidney fibrosis following renal IRI in mice (Kim et al., 2009), but its involvement in the regulation of p53 in this condition remains unclear.

1.4.3. Hypoxia

Hypoxia is the deprivation of oxygen, which elicits a range of adaptive responses in cells and tissues, a process regulated by proteins

known as hypoxia-inducible factors (HIF). Experiment studies provided compelling evidence that hypoxia contributes critically to AKI and its progression to CKD (Andringa & Agarwal, 2014; Kapitsinou et al., 2012; Liu et al., 2017; Singh, Ricksten, Bragadottir, Redfors, & Nordquist, 2013; Tanaka, Tanaka, & Nangaku, 2014). Hypoxia and p53 are reciprocally regulated (Sermeus & Michiels, 2011). Sustained hypoxia increases cellular p53 level and usually promotes cell death, while p53 negatively regulates hypoxic pathways (Sermeus & Michiels, 2011). In kidney, p53 was induced in RPTECs after hypoxia during in vitro or in vivo renal IRI; on the other hand, p53 reduction or depletion blocked hypoxia-induced cellular response in tubular cells (Hao et al., 2017) Moreover, Liu et al. have recently demonstrated that p53 upregulation contributed critically to hypoxia-induced renal tubular cell G2/M arrest and consequent renal fibrosis in cultured RPTECs and a mouse UUO model (Liu et al., 2018). Mechanistically, hypoxia-induced p53 activation seems to involve HIF-1a and ATR. Under the condition of hypoxia, HIF-1α may directly bind MDM2, which suppresses MDM2-mediated p53 ubiquitination, nuclear export and degradation, resulting in p53 stabilization (Chen, Li, Luo, & Gu, 2003). Hypoxia can also induce ATR-CHK1 dependent MDM4 phosphorylation, thereby suppressing MDM4 activity and consequently inducing p53 activation (Lee et al., 2012). Collectively, these studies suggest that hypoxia may be a major trigger of p53 activation during kidney injury and repair, although the detailed underlying mechanism remains elusive.

1.5. p53 as a therapeutic target for AKI and its progression to CKD

Given the compelling evidence that p53 activation in tubular cells plays a critical role in AKI pathogenesis and maladaptive kidney repair after AKI, inhibition of p53 could be a novel and potential strategy for the treatment of this disorder. Currently, a small interfering RNA (siRNA) targeting p53 (QPI-1002) is under a phase 2 study to evaluate the efficacy and safety for the prevention of AKI in subjects at high risk for AKI following cardiac surgery (https://clinicaltrials.gov/ct2/show/NCT02610283). There are, however, challenges that must be addressed before this strategy can be considered tenable and feasible for AKI treatment. First, cell-specific roles of p53 in kidney injury and repair remain largely unknown. Kidney is a heterogeneous organ that is composed of more than 20 types of cells. Both parenchymal kidney cells and circulating pro-inflammatory leukocytes have been implicated in the pathogenesis of AKI (Liu et al., 2014; Reidy, Kang, Hostetter, & Susztak, 2014). Thus, inhibition of p53 in different cell types may result in different, even opposing, effects on AKI. For instance, specific inhibition of *p53* in proximal tubular cells by siRNA or gene knockout protected against AKI by reducing tubular cell death (Molitoris et al., 2009; Zhang et al., 2014), however, inhibition of leukocyte *p53* may worsen ischemic AKI by sustaining the survival and proinflammatory function of macrophages (Sutton et al., 2013). Thus, a comprehensive understanding of the cell-specific roles of p53 and being able to selectively target specific-cell types are critical for optimizing the opportunity of *p53* inhibition as a therapeutic strategy for AKI and its progression to CKD. The second challenge is the question of what precise role p53 plays in difference phases of AKI. The pathogenesis of AKI can be divided into four distinct clinical and cellular phases: initiation, extension, maintenance, and recovery (Basile, Leonard, Beal, Schleuter, & Friedrich, 2012). Each of these phases encompasses distinct cell types and cellular events. Thus, inhibition of p53 at different phases may have different effects on AKI pathogenesis and repair. For instance, acute inhibition of p53 by pifithrin-α at the time of renal IR was shown to protective, while a long-term inhibition from the time of renal IR to day 7 after IR induced kidney fibrosis (Dagher et al., 2012). Moreover, a single dose of pifithrin-α on days 3 and 14 after renal ischemia injury was shown to ameliorate post-AKI renal fibrosis (Yang et al., 2010). Thus, it would be very important to determine an optimal condition and therapeutic window in which inhibition of p53 may yield protective effects. The third challenge is whether p53 inhibition in proximal tubular cells is protective for all forms of AKI. The primary clinical causes of AKI include IR, sepsis, and nephrotoxins. So far, most of studies suggesting a renoprotective role of p53 inhibition were conducted in experimental models of ischemic and cisplatin nephrotoxic AKI, whether p53 inhibition has similar protective effects on AKI resulted from sepsis and contrast media remain largely unclear. In addition, despite the compelling experimental evidence for the beneficial effects of p53 inhibition, large clinical trials are needed to provide more definitive information on its efficacy in AKI.

2. Conclusions and perspectives

Despite compelling evidence supporting a critical role of p53 in AKI, several major questions remain open. First, roles of p53 in specific kidney cell-types and distinct phases of AKI remain largely unclear. Second, the key signaling pathways that regulate p53 activation, and the key downstream targets of p53 during AKI remain unknown. Third, the past studies have mainly focused on renal IRI and cisplatin nephrotoxic AKI, and the role of p53 in other forms of AKI like those associated with sepsis- and contrast medium exposure remain elusive. In terms of kidney repair, emerging evidence suggests the involvement of p53 in maladaptive kidney repair after AKI, but its role and underlying mechanisms in these conditions remain largely undetermined. In addition, p63 and p73, two p53 family members, are also activated in response to various stress stimuli, and transcriptionally upregulates genes involved in apoptosis and cell cycle arrest (Berkers, Maddocks, Cheung, Mor, & Vousden, 2013; El Husseini & Hales, 2018; Levrero et al., 2000). Moreover, there is evidence that p53 and its family members may regulate each other's activity. Emerging evidence has further suggested that p63 and p73 may also contribute to cell injury and fibrotic process (Chilosi et al., 2002; Murata et al., 2007), although their precise roles in kidney injury and repair await for investigation. Thus, further studies should focus on these areas to elucidate the role and regulation of p53 in kidney resident and circulating cells during AKI and post-AKI kidney repair, and define the precise roles played by p53 in the pathological processes, which will facilitate the discovery of pharmacological modulators for the prevention and treatment of AKI or impeding its progression to CKD.

Conflict of interest statement

All authors declare that they have no commercial or other conflicting interests.

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