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Review

The regulatory role of HIF-1 in tubular epithelial cells in response to kidney injury

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Summary. The high sensitivity to changes in oxygen tension makes kidney vulnerable to hypoxia. Both acute kidney injury and chronic kidney disease are almost always accompanied by hypoxia. Tubular epithelial cells (TECs), the dominant intrinsic cells in kidney tissue, are believed to be not only a victim in the pathological process of various kidney diseases, but also a major contributor to kidney damage. Hypoxia inducible factor-1 (HIF-1) is the main regulator of adaptive response of cells to hypoxia. Under various clinical and experimental kidney disease conditions, HIF-1 plays a pivotal role in modulating multiple cellular processes in TECs, including apoptosis, autophagy, inflammation, metabolic pattern alteration, and cell cycle arrest. A comprehensive understanding of the mechanisms by which HIF-1 regulates these cellular processes in TECs may help identify potential therapeutic targets to improve the outcome of acute kidney injury and delay the progression of chronic kidney disease.

Key words: Hypoxia inducible factor-1, Kidney, Tubular epithelial cell, Apoptosis, Autophagy, Inflammation, Metabolic pattern alteration, Cell cycle arrest

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Introduction

Hypoxia inducible factor-1 (HIF-1), the master regulator of cellular response to hypoxia, is a heterodimeric protein composed of an oxygen-regulated α subunit and a constitutively expressed β subunit. Under normoxia, cytosolic HIF-1α is hydroxylated by prolyl hydroxylase domains (PHDs) enzyme, and then is degraded through a proteasome-dependent pathway. The inhibition of PHDs induced by hypoxia leads to the stabilization of HIF-1α, which allows HIF-1α to translocate into the nuclei, wherein it combines with HIF-1β to form heterodimer HIF-1. Then HIF-1 binds to hypoxia response element (HRE) to stimulate the transcription of its downstream target genes (Conde et al., 2012; Gonzalez et al., 2018).

HIF-1 is expressed in most cell types in kidney, containing tubular epithelial cells (TECs). Hypoxia occurs in both acute kidney injury (AKI) (including all phases of AKI, from onset to recovery) and chronic kidney disease (CKD) under multifarious clinical and experimental conditions (Basile et al., 2003; Rosenberger et al., 2007; Kimura et al., 2008; Fu et al., 2016; Hirakawa et al., 2017). The high sensitivity to hypoxia makes TECs involved in the pathogenesis of various kidney diseases. HIF-1 dominates the adaptive response to hypoxia in TECs by regulating multiple cellular processes, including apoptosis, autophagy, inflammation, metabolic pattern alteration, cell cycle arrest and so on, which may participate in renal protection or progressive renal failure (Fernandez-Martínez et al., 2014; Pastor-Soler et al., 2015). This review focuses on the regulatory role of HIF-1 in these

cellular processes of TECs during kidney injury.

HIF-1 and apoptosis

Apoptosis is a major mode of TECs death in AKI and prevention of apoptosis is believed to be an effective way to protect renal function (Havasi and Borkan, 2011). It is well-known that mitochondria play a key role in regulating apoptotic cell death (Cory and Adams, 2002; Nie et al., 2008, 2014; Hu et al., 2012). During AKI, massive reactive oxygen species (ROS) directly lead mitochondria to release apoptosis signaling molecules that are classified into caspase-dependent and caspase-independent apoptosis pathways (Ravagnan et al., 2002; Sinha et al., 2013).

Apoptotic stimulus such as ROS or nutrient deprivation induces the caspase-dependent apoptosis pathway via upregulation of pro-apoptotic BH3-only "activators" proteins, e.g. Bcl-2-interacting mediator of cell death (Bim) and p53-upregulated modulator of apoptosis (Puma), or via cleavage of BH3-interacting domain death agonist (Bid) to active, truncated form (tBid). These "activators" are bound and sequestered by pro-survival proteins such as Bcl-2, B-cell lymphoma-extra large (Bcl-xL), and myeloid cell leukaemia 1 (Mcl-1), but they can activate Bcl-2-associated X protein (Bax) and/or Bcl-2 antagonist/killer (Bak) once pro-survival proteins are saturated or absent. The activated Bax and Bak are oligomerized, causing mitochondrial outer membrane permeabilization (MOMP), which in turn results in the release of apoptogenic molecules including second mitochondria-derived activator of caspases (SMAC), serine protease OMI and cytochrome c from mitochondrial intermembrane space. Cytochrome c binds apoptotic protease-activating factor 1 (APAF1) in cytosol to form apoptosome, which serves as a platform for caspase activation. These events promote the activation of initiator caspase (caspase-9) and executioner caspases (caspases-3, -6 and -7) for dismantling of the cell via preparation of apoptotic cell for phagocytosis. Upstream damage or stress signal may also activate BH3-only "sensitizer" proteins such as Bcl-2-associated agonist of cell death (Bad), Noxa, and Hrk, that do not efficiently activate Bax and Bak, but inhibit the activity of pro-survival Bcl-2 family proteins, which results in the release of BH3-only "activators" to trigger MOMP (Singh et al., 2019).

The effect of HIF-1α stabilization on this caspase-dependent pathway is paradoxical, which depends on how it regulates different members of the Bcl-2 family (Sendoel and Hendgartner, 2014). It may promote apoptosis via downregulation of Bcl-2 (Carmeliet et al., 1998) and induction of BNIP3 (Bcl-2/adenovirus EIB 19kD-interacting protein 3), Nip3-like protein X (NIX) (Bruick et al., 2000; Guo et al., 2001; Sowter et al., 2001) and Noxa (Kim et al., 2004). Conversely, it may also inhibit apoptosis via induction of Bcl-2 (Sasabe et al., 2005), Mcl-1 (Liu et al., 2006; Sharma et al., 2011; Palladino et al., 2012), and Bcl-xL (Chen et al., 2009; Menrad et al., 2010), and downregulation of Bid (Erler et al., 2004), Bax (Hansson et al., 2002; Menrad et al., 2010), and Bak (Menrad et al., 2010). Whether the effect of HIF-1 regulation promotes or inhibits apoptosis depends on the cellular context (Carmeliet et al., 1998).

It has been reported that p53 can induce pro-apoptotic BH3-only proteins such as Puma, Noxa and Bax to trigger apoptosis. The regulatory effect of HIF-1α on p53 is achieved through at least three different types of interactions between the two proteins. First, two proteins interact via a direct binding of the oxygen-dependent degradation (ODD) domain of HIF-1α to p53 (Hansson et al., 2002; Sánchez-Puig et al., 2005). Second, both transcription factors require p300/cyclic AMP response element binding protein (CREB) binding protein (CBP) as a coactivator, suggesting that both compete with each other for p300/CBP (Schmid et al., 2004). Third, HIF-1α target genes could directly or indirectly affect the response of p53 to HIF-1α. Context-dependent regulation between HIF-1α and p53 may have pro- or anti-apoptotic effect. In the rat proximal TECs with chronic hypoxia, the induction of HIF-1 can stabilize p53, transactivate Bax mRNA expression and elevate caspase-9 activity (Tanaka et al., 2003). Conversely, in RCC4 cells under prolonged hypoxia condition, p53 overexpression or stabilization can downregulate HIF-1, which impedes the increase in caspase-3 activity and the loss of mitochondrial membrane potential (Schmid et al., 2004). However, it seems that the anti-apoptotic effect of HIF-1 associated with p53 in TECs has not yet been reported.

In addition, the apoptosis-inducing factor (AIF)/Endonuclease (Endo) G-mediated mitochondria apoptosis pathway is caspase-independent. Endo G released from mitochondria translocates into the nuclei, where it cleaves chromatin DNA into nucleosomal fragments independent of caspases. AIF, similar to Endo G, manifests mitochondrion-nucleus relocation as a component of caspase-independent apoptosis pathway (Li et al., 2001). As an upstream of AIF/Endo G, BNIP3 is proved to participate in regulating the caspase-independent apoptosis. BNIP3 is a hypoxia-inducible pro-apoptotic member of the Bcl-2 family of proteins and HIF-1α can directly bind to the BNIP3 promotor region and regulate BNIP3 expression (Wang et al., 2014; Drake et al., 2017; Chen et al., 2018). The caspase-independent pathway plays a critical role in renal TECs damage. BNIP3 protein levels and the nuclear translocation of AIF and Endo G are increased during cadmium-induced rat proximal TECs apoptosis, whereas BNIP3 silencing decreases the nuclear translocation of AIF and Endo G (Liu et al., 2016). Accordingly, HIF-1 may affect the nuclear translocation of AIF/Endo G by regulating BNIP3 expression. The apoptosis of TECs induced by renal stones is also mediated by the HIF-1/BNIP3 pathway (Peng et al., 2019). But no studies have shown that this signaling pathway is related to TECs apoptosis in AKI model such as ischemia reperfusion injury (IRI).

A growing body of evidence has demonstrated that HIF-1 is involved in several signal pathways associated with apoptosis. In AKI, Wnt/β-catenin signaling promotes TECs survival through activation of Akt and survivin to inhibit apoptosis. Akt regulates the activity of phosphorylated-Bad and Bcl-2 to prevent mitochondrial death cascade thereby promoting cell survival (Chen et al., 2019) and survivin blocks caspase-3 and caspase-9 activation (Al-Bataineh et al., 2016). The transcriptional activity of HIF-1α can be enhanced by β-catenin and the activation of HIF-1 can directly increase the transcription of TCF/LEF genes to promote activation of β-catenin signaling (Mazumdar et al., 2010; Zhang et al., 2013). This mutual regulation between HIF-1 and β-catenin promotes cell adaptation to hypoxia and survival. In addition, PI3K/Akt signaling also plays a critical role in cell survival by blocking apoptotic pathway since it links extracellular survival signal with intracellular apoptosis-related pathway (Chen et al., 2014; Mahfouz et al., 2017). It has been reported that the activation of PI3K/Akt signaling in response to hypoxia leads to upregulation of HIF-1α expression at the level of translation in cancer cells (Vasseur et al., 2009). However, the direct interaction between HIF-1 and Akt or survivin in apoptosis of TECs during AKI or CKD has not been reported.

HIF-1 and autophagy

Autophagy occurs in most tissues under physiological conditions. It enables the renewal of cellular components (Maiuri et al., 2007; Mariño et al., 2014; Kim and Lee, 2014) and regulates cell adaptation to or defense against adverse environment (Bellot et al., 2009; Mazure and Pouysségur, 2009), which is critical for intracellular homeostasis.

Several key molecules participate in the initiation, execution and completion of autophagy. The inducer of autophagy relieves the inhibitory interaction of mammalian target of rapamycin (mTOR) complex 1 (mTORC1) with ULK1/2 complex, allowing ULK1/2 complex to increase the activity of Beclin-1/class III PI3K complex. The interaction of Beclin-1 with several enhancing (UVRAG, Bif1 and Ambra1) or inhibiting (Rubicon, Bcl-2 and Bcl-xL) factors may modulate its binding to the catalytic unit of PI3K, Vps34, the lipid kinase activity of which is essential for autophagy. In addition to these two complexes, the formation of autophagosome requires the participation of two ubiquitin-like protein (Atg12 and Atg8/LC3) conjugation systems and two transmembrane proteins (Atg9 and VMP-1). Both conjugation systems are indispensable for the biogenesis of the isolation membrane. The Atg8/LC3 system is required for the transport and maturation of the autophagosome and the selection of autophagic cargo. The fully mature autophagosome fuses with Rab7-positive late endosome to form amphisome. Finally, autophagosome or amphisome fuses its external membrane with the membrane of acidic lysosome to acquire hydrolytic activity, degrades cargo, and recycles essential biomolecules to the cytoplasm (Kroemer and Mariño, 2010).

Autophagy may promote cell survival or induce cell death under pathological conditions, which depends on environmental stressors (Chen et al., 2013). For example, the effect of autophagy induced by hypoxia is related to the degree and duration of hypoxic stress. Studies have suggested the beneficial effects of autophagy on the recovery of proximal tubule from acute ischemic injury. Under moderate hypoxia conditions, suitable level of autophagy is protective by renewing damaged cellular components, whereas excessive autophagy induced by severe and prolonged hypoxia may result in cell death (Xie et al., 2018). The appropriate autophagy induced in renal proximal TECs has the potential to protect against IRI (Kimura et al., 2011; Jiang et al., 2012). The autophagy activity of proximal TECs declines with aging, so the kidneys of elderly people show stress susceptibility to AKI (Huber et al., 2012; Decuypere et al., 2015; Kaushal and Shah, 2016).

There are two classical pathways for autophagy regulation: AMPK-dependent and HIF-1α-dependent (Hamacher-Brady et al., 2007; Ravikumar et al., 2010; Zhao et al., 2012). The pro-death autophagy owing to severe and prolonged hypoxia is predominantly mediated by AMPK/mTOR pathway, and hypoxia is a potent stimulus for AMPK activation, which is independent of HIF-1 activity (Papandreou et al., 2008). AMPK is a major regulator of energy homeostasis. Activation of AMPK can inhibit mTORC1, and dissociate it from the ULK1/2 complex, which triggers autophagy (Kroemer and Mariño, 2010). The pro-survival autophagy caused by short-term hypoxia is mediated by the HIF-1α-dependent pathway (Papandreou et al., 2008; Chen et al., 2013). The HIF-1α-dependent pathway is a canonical pathway for regulating autophagy during the process of renal IRI, in which the moderate activation of autophagy is able to eliminate damaged mitochondria and protect renal TECs from hypoxic stress (Brooks et al., 2009; Isaka et al., 2011).

It has been reported that Sestrin2 and BNIP3 can regulate autophagy (Ishihara et al., 2013). The expression of Sestrin2 is upregulated mainly by p53 but also by HIF-1α since the promoter of Sestrin2 gene contains a functional HRE (Budanov and Karin, 2008; Essler and Dehne, 2009). The regulation of autophagy by Sestrin2 is achieved by inhibiting mTOR signaling (Budanov and Karin, 2008). It has been demonstrated that autophagy, especially mitophagy (defined as the selective degradation of mitochondria by autophagy), is induced by the p53-Sestrin2 pathway in renal TECs during AKI (Ishihara et al., 2013). BNIP3 is a downstream target of HIF-1, and the mRNA and protein expression of BNIP3 is induced in a HIF-1α-dependent manner in the cultured renal proximal TECs exposed to hypoxia. BNIP3-induced autophagosomes predominantly localize in the mitochondria, suggesting that BNIP3

may selectively induce mitophagy (Ishihara et al., 2013). BNIP3 can upregulate the expression of Beclin-1 and Atg5 (Zhang et al., 2008). Overexpression of BNIP3 dissociates Bcl-2/Beclin-1 or Bcl-xL/Beclin-1 interaction, leading to the release of Beclin-1. Then, as a key component of Beclin-1/PI3K complex, Beclin-1 triggers autophagy (Bellot et al., 2009). It is unclear whether BNIP3 directly induces autophagy or whether autophagy is caused by mitochondrial damage induced by BNIP3. Based on the results of existing studies, BNIP3-mediated mitochondrial damage through opening the mitochondrial permeability transition pore (MPTP) may be the cause of enhanced autophagy (Mazure et al., 2009). Mitophagy mediated by HIF-1α/BNIP3 functions as a protective stress response by removing dysfunctional mitochondria (Ravikumar et al., 2010; Zhao et al., 2012). In addition to hypoxia, HIF-1α/BNIP3 pathway can protect renal TECs from other types of stress, such as H_2O_2 treatment or serum deprivation (Ishihara et al., 2013; Zhao et al., 2016).

BNIP3-like protein (BNIP3L), also known as NIX, is also a direct target gene of HIF-1 (Guo et al., 2017). Interestingly, BNIP3 and NIX can regulate both apoptosis and autophagy during hypoxia. Under anoxic circumstances, a crosstalk between apoptosis and autophagy is established (Gyongyosi et al., 2018). The cytoprotective effect of autophagy can be mediated by negative modulation of apoptosis, while apoptotic signaling can be inhibited by autophagy (Gordy and He, 2012; Mariño et al., 2014). The function of Beclin-1 in autophagy is inhibited by apoptotic signaling since Beclin-1 can be cleaved by caspases, and the C-terminal cleavage product of Beclin-1 can target mitochondria to directly induce the release of cytochrome c, thus inhibiting autophagy and enhancing apoptosis. Conversely, full-length Beclin-1 suppresses apoptosis by mediating the autophagic degradation of activated caspase 8 (Gordy and He, 2012; Gyongyosi et al., 2018). The potential role of BNIP3, NIX, and Beclin-1 in autophagy in TECs in response to the injury induced by cisplatin is HIF-1-dependent (Liu et al., 2015). Further study on the mechanism of HIF-1 in regulating autophagy and the crosstalk between autophagy and apoptosis will be helpful to fully understand the role of HIF-1 in TECs during kidney injury.

HIF-1 and inflammation

Hypoxia and inflammation often coexist and interact with each other. Hypoxia can initiate and amplify inflammatory process via recruiting inflammatory cells and promoting the production and secretion of inflammatory factors. Conversely, inflammation, by activating hypoxic signaling pathways, can aggravate hypoxia-induced injury (Nizet and Johnson, 2009; Melillo, 2011; Eltzschig and Carmeliet, 2011; Haase, 2015).

Plenty of evidence has indicated that hypoxia is an important inducer of kidney tubulointerstitial inflammation (TI), and as a common pathological process in both AKI and CKD, TI can deteriorate the damage of TECs and trigger the development of interstitial fibrosis (Nangaku, 2006; Tanaka et al., 2014; Jang and Rabb, 2015; Li et al., 2019). Under hypoxia state, TECs contribute to TI by promoting infiltration of inflammatory cells into the sites of tissue damage (Lv et al., 2017; Baek et al., 2015). Upregulation of HIF-1α mRNA expression in TECs has been observed in the kidneys with IRI or nephropathy from UUO, and the activity of HIF-1α is associated with the severity of TI (Li et al., 2019).

It has been suggested that hypoxia-induced HIF-1α promotes TI via exosome-mediated crosstalk between TECs and intrarenal macrophages. For example, HIF-1α appears to mediate the secretion of microRNA (miRNA)-23a-enriched exosomes derived from TECs under hypoxia, resulting in the entry of these exosomes into recipient macrophages, thus activating macrophages (Li et al., 2019). Macrophages are the major contributor to both acute and chronic TI, and depletion of macrophages could protect the kidney from injury induced by hypoxia (Lu et al., 2012). Another example, under hypoxia microenvironment, TECs-derived exosomal miR-19b-3p can be internalized by macrophages to target NF-κB/SOCS1, leading to M1 phenotype polarization, so the exosome/miR-19b-3p/SOCS1 axis plays a critical role in M1 macrophage activation and TI (Lv et al., 2020). Therefore, the TECs-medicated activation of macrophages via HIF-1/exosome/miRNA pathway seems to be a major pattern of hypoxia-induced TI. However, miR-21 upregulated by HIF-1α inhibits the programmed cell death 4 (PDCD4)/NF-κB pathway in TECs. Since NF-κB is a positive regulator for the maturation of dendritic cells (DCs), miR-21 overexpression in the kidney with IRI may prevent DCs maturation and repress the inflammatory response in a HIF-1α-dependent way (Song et al., 2018).

In addition to hypoxia, inflammation is also believed to induce the expression of HIF-1. CCAAT/enhancer-binding protein d (CEBPD), as a transcription factor of inflammatory response gene, is considered to be a novel regulator of HIF-1 since CEBPD can be induced not only by inflammation, but also by hypoxia. Studies have demonstrated that CEBPD expression in TECs is increased in systemic hypoxia and many types of kidney diseases including renal artery stenosis, IRI, cisplatin nephrotoxicity, and 5/6 nephrectomy (Kapitsinou et al., 2014). In TECs, CEBPD is rapidly induced by inflammatory cytokines such as IL-1β in a NF-κB-dependent manner, and then CEBPD directly binds to HIF-1α promoter and enhances its transcription (Yamaguchi et al., 2015). In the inflammatory process, lipopolysaccharide or ROS also increases HIF-1α mRNA expression in macrophages through activating a NF-κB-binding site in HIF-1α gene promoter (Bonello et al., 2007; Litvak et al., 2009; Fitzpatrick et al., 2011). Hypoxia- or inflammation-induced expression of

CEBPD and subsequent expression of HIF-1 require the activation of NF-κB, which provides a potential link between hypoxia and inflammation through the crosstalk between macrophages and TECs. In addition, overexpression of CEBPD partially rescues HIF-1α protein expression restricted by the inactivation of NF-κB, indicating that CEBPD is a key mediator in the regulation of HIF-1α by NF-κB. The induction of CEBPD in proximal TECs in the kidney with acute or chronic hypoxia augments HIF-1α expression, thereby regulating adaptive response to hypoxia at the molecular, cellular, and tissue levels. Hence, the CEBPD/HIF-1 pathway activated in TECs is NF-κB-dependent and plays an important role in the cellular protection against kidney injury from hypoxia or inflammation (Yamaguchi et al., 2015).

The effect of HIF-1 in TECs on TI seems to be puzzling and contradictory. Further studies are needed to reveal the regulatory mechanism of HIF-1 signaling between hypoxia and inflammation and its effect on repair in AKI and fibrosis in CKD.

HIF-1 and metabolism

Under normal oxygen tensions, there are three steps of aerobic oxidation of glucose: (i) glucose in cytoplasm is converted into pyruvate by glycolysis; (ii)pyruvate enters mitochondria for oxidative decarboxylation to form acetyl-CoA, a process catalyzed by pyruvate dehydrogenase (PDH) complex; and (iii)acetyl-CoA enters the citric acid cycle and is coupled for oxidative phosphorylation. Electron transport through this chain eventually results in the donation of electron to oxygen and ATP production. While under hypoxia microenvironment, HIF-1 activates glycolytic genes which is considered critical for metabolic adaptation to hypoxia through increased conversion of glucose to pyruvate and subsequently to lactate (Kim et al., 2006). Current studies on the role of HIF-1 activation in metabolic pattern transformation are almost limited to AKI, and there are few related studies on CKD. In AKI, metabolic alteration is beneficial for TECs to adapt to hypoxia (Schley et al., 2011). During IRI, stabilized activity of HIF-1 can mediate the changes of metabolic patterns in TECs, which has cytoprotective action. However, reduced activity of HIF-1 is associated with more severe injury (Hill et al., 2008; Schley et al., 2011; Fahling et al., 2013).

During hypoxia, stabilized HIF-1α enters the nucleus to bind to HRE in the promoter region of its downstream target genes associated with glucose metabolism, including (i) glucose transporter GLUT1, which increases glucose uptake; (ii) glycolytic enzymes like lactate dehydrogenase A (LDHA), enolase, and pyruvate kinase M2 (PKM2), which convert pyruvate to lactate; and (iii) regulatory kinases such as pyruvate dehydrogenase kinase 1 (PDK1) (Luo and Semenza, 2012; Semenza et al., 2012). PDK1 inactivates PDH, resulting in the inhibition of tricarboxylic acid cycle. In addition, PKM2 is a PHD3-stimulated coactivator of HIF-1α. The activation of HIF-1 promotes the transcription of genes encoding PKM2 and PHD3, and PHD3 binds to PKM2 to stimulate its function as a coactivator of HIF-1α, which depends upon the hydroxylase activity of PHD3 and the presence of two proline residues in PKM2. This positive feedback loop can further expand the role of HIF-1 (Luo et al., 2011; Luo and Semenza, 2012).

Hypoxia-induced intracellular lipid accumulation is due to an increase in the uptake of fatty acid via the HIF-1-dependent transcription of fatty acid binding protein (FABP), including FABP3, FABP4 and FABP7 (Bensaad et al., 2014; Lee et al., 2017). Interruption of this pathway decreases lipid accumulation but increases cellular ROS, suggesting that hypoxia-driven lipid accumulation may serve as a protective barrier against toxicity induced by oxidative stress (Bensaad et al., 2014). Carnitine palmitoyltransferase 1A, the rate-limiting enzyme in the process of fatty acid entry into mitochondria for beta oxidation, is a direct target of transcriptional repression by HIF-1 through promoter silencing (Du et al., 2017).

Hence, HIF-1 contributes to the adaptive adjustment of metabolic pattern by promoting the alteration from aerobic oxidation to glycolysis and increasing the storage of fatty acid. Several studies have focused on the effect of HIF-1 on metabolic pattern changes in TECs during AKI. The upregulation of glycolytic gene expression regulated by HIF-1 may facilitate the preservation of ATP generation, which is a key condition for cell survival after hypoxia (Fahling et al., 2013). The shift of cellular metabolism from oxidative phosphorylation to anaerobic glycolysis is critical for TECs to achieve hypoxia tolerance in AKI, and HIF-1 mediates this shift through increasing the expression of several enzymes in glycolytic pathway (Kapitsinou and Haase, 2015). Studies on the role of HIF-1 in regulating the storage of fatty acid is mainly in the field of tumor, but there are few studies on its role in TECs during AKI.

Mucin 1 (Muc1), a transmembrane protein mainly expressed on apical surface of distal tubule and collecting duct in adult kidney and in proximal tubule during development, is identified as a downstream target of HIF-1 (Chaika et al., 2012). Muc1 is induced during kidney IRI and is involved in the changing of glucose metabolism. Muc1 can bind, stabilize and enhance HIF-1α occupancy and activity on the promoter of glycolytic genes in a hypoxia-dependent manner (Chaika et al., 2012), thereby promoting the recovery of kidney TECs via metabolic regulation (Pastor-Soler et al., 2015).

How the increased activity of HIF-1 in TECs during different types of AKI and CKD modulates cellular metabolism and in turn affects kidney function is worthy of further study.

HIF-1 and cell cycle arrest

Kidney repair following AKI involves epithelial

plasticity, i.e., epithelial to mesenchymal transition (EMT) and its reverse process, mesenchymal to epithelial transition (MET) (Gibier et al., 2017). As a typical example of cellular plasticity that dedifferentiates epithelial cells to a mesenchymal phenotype, the EMT program is characterized by cell cycle arrest and cessation of proliferation, which is similar to other programs of differentiation and dedifferentiation (Prakash et al., 2019). After AKI, transient dedifferentiation of kidney TECs is favorable, in which cells simultaneously express both mesenchymal and epithelial markers, followed by re-differentiation to achieve epithelial repair (Chaika et al., 2012). However, the continuous epithelial dedifferentiation involved in cell cycle arrest appears to promote the progression to CKD (Chawla, 2011). In common models of AKI such as ischemia, toxic exposure and obstruction, the production of profibrotic cytokines and the progression of fibrosis are related to the cell cycle arrest of proximal TECs in G2/M (Yang et al., 2010).

The cell cycle arrest induced by temporary hypoxia is reversible, which facilitates cell repair and prevents the proliferation in response to DNA damage caused by hypoxia (Stark and Taylor, 2006). However, the extent of reversibility is reduced with longer or more severe hypoxic conditions such as severe AKI (Green et al., 2001; Canaud et al., 2019). Severe AKI promotes TECs cell cycle arrest in G2/M phase persistently, with secretion of profibrotic factors leading to renal fibrosis (Canaud et al., 2019). Targeting TECs cell cycle arrest due to hypoxia may be an attractive therapeutic strategy to prevent progressive CKD (Fine et al., 2000; Mazumdar et al., 2010; Zhou et al., 2010; Canaud and Bonventre, 2015).

As a downstream target of HIF-1, p53 plays a key role in the regulation of cell cycle arrest in G2/M during hypoxia. The expression of p53 in TECs is transcriptionally upregulated by HIF-1α, and the p53-driven G2/M arrest is due to its regulation of genes related to cell cycle progression such as cyclins and cyclin-dependent kinase (CDK) (Xia et al., 2009; Liu et al., 2019a,b). An orderly progression between four distinct cell cycle phases, termed G1, S, G2, and M, is tightly controlled at 'checkpoints' by the interplay of various cyclins and their associated CDKs (Morgan, 1997). The catalytic subunits of CDK cannot act alone and their ability to trigger cell cycle events is completely dependent on the associated cyclin subunits, which facilitate the cell cycle progression (Morgan, 1997). In hypoxic TECs, p53 upregulation can suppress the expression of CDK1 and cyclins B1 and D1, leading to cell cycle (G2/M) arrest or delay, and persistent arrest in G2/M phase of cell cycle driven by p53 further results in tubulointerstitial fibrosis through activating profibrogenic signaling molecules including TGF-β and CTGF (Xia et al., 2009; Liu et al., 2019a,b).

Studies have suggested that miRNA is involved in the regulation of hypoxia-induced cell cycle arrest. Under hypoxia or ischemia conditions, HIF-1α can bind to the promoter region of miR-191 and elevate its expression in hepatocytes and miR-191 functions as an inhibitory effector on cell cycle progression (Pan et al., 2019). Similar regulatory correlation between HIF-1α and miR-210 is found in lung cancer cells (Wang et al., 2011). In one study, the expression of Stathmin (STMN)-1, a cell cycle positive regulator that plays an important role in the formation of a normal mitotic spindle, is suppressed by the upregulation of miR-493 induced by HIF-1α in HK2 cells under hypoxia conditions. It is suggested that miR-493-STMN-1 pathway contributes to the hypoxia-induced TECs G2/M cell cycle arrest and renal fibrosis (Liu et al., 2019a,b).

Conclusion

In the hypoxic microenvironment of kidney tissue in AKI and CKD, HIF-1 regulates the expression of multiple downstream target genes and participates in the regulation of several cellular processes in TECs. While making cells adapt to the hypoxic microenvironment, HIF-1 is also involved in the development and progression of kidney diseases. Although HIF-1 has been shown to be cytoprotective in AKI, the stable expression of HIF-1 in TECs promotes interstitial fibrosis (Hung et al., 2013). A comprehensive understanding of the molecular mechanisms and pathophysiological effects mediated by HIF-1 may be helpful to explore effective therapeutic targets to improve the recovery of AKI and delay the progression of CKD.

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