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Review Article

Contribution of Oxidative Stress to HIF-1-Mediated Profibrotic Changes during the Kidney Damage

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Hypoxia and oxidative stress are the common causes of various types of kidney injury. During recent years, the studies on hypoxia inducible factor- (HIF-) 1 attract more and more attention, which can not only mediate hypoxia adaptation but also contribute to profibrotic changes. Through analyzing related literatures, we found that oxidative stress can regulate the expression and activity of HIF-1α through some signaling molecules, such as prolyl hydroxylase domain-containing protein (PHD), PI-3K, and microRNA. And oxidative stress can take part in inflammation, epithelial-mesenchymal transition, and extracellular matrix deposition mediated by HIF-1 via interacting with classical NF-κB and TGF-β signaling pathways. Therefore, based on previous literatures, this review summarizes the contribution of oxidative stress to HIF-1-mediated profibrotic changes during the kidney damage, in order to further understand the role of oxidative stress in renal fibrosis.

1. Introduction

The balance of oxygen consumption and supply is essential for all mammalian organs, providing fuel for various physiological metabolic processes and maintaining homeostasis [1]. Kidney, an active metabolic organ, is a great need for oxygen. Thus, there is no doubt that the kidney is also susceptible to hypoxic damage.

There are increasing evidences shown that a variety of pathological factors such as hyperglycemia, hypersaline, hypertension, and infection can induce renal hypoxia and aggravate oxidative stress [2]. Meanwhile, it is demonstrated that acute kidney injury (AKI) and various chronic renal diseases (CKD) are associated with hypoxia and oxidative stress, which are more likely to develop into renal fibrosis eventually [3, 4]. Therefore, we have reasons to believe that hypoxia and oxidative stress may play an important role in the destruction of renal tissue, irreversible loss of kidney function, and the progression of renal fibrosis [5, 6].

Hypoxia inducible factors (HIFs), critical nuclear transcription factors, involved in maintaining O_2 homeostasis were firstly discovered by Semenza in 1992, which have received extensive attention due to their significant role in cellular adaptation to hypoxia in recent years [7, 8]. Based on the difference of α-subunits, HIFs are divided into three subtypes, HIF-1, HIF-2, and HIF-3. The function of HIF-1 and HIF-2 is currently being intensively investigated. An increasing evidence finds that HIF-1 during kidney damage not only mediates hypoxia adaptation but also is associated with inflammation, epithelial-mesenchymal transition (EMT), and extracellular matrix (ECM) deposition, participating in the profibrotic changes [9–12]. And oxidative stress has been also reported to play an important role in this process [2]. HIF-2α plays a dominant role in erythropoietin production [13–15]. Schietke et al. also found that constitutional transgenic overexpression of HIF-2α in distal tubular cells in mice resulted in renal fibrosis [16]. Besides, a recent study has shown that SIRT1 can attenuate renal fibrosis by repressing HIF-2α. The effects of HIFs may be cell type and context dependent. HIF-2α may also be a candidate for studying renal fibrosis [17, 18]. However, HIF-3 is less well known. Other studies have shown that HIF-3α can act as a

target gene of HIF-1 and negatively regulate the activity of HIF-1 and HIF-2 [19].

The present review is aimed at summarizing the profibrotic role and molecular regulation of HIF-1α on kidney damage, illustrating the interaction between HIF-1α and oxidative stress, and providing new insights for renal injury and aberrant tissue repair.

2. The Progression of Renal Fibrosis

Renal fibrosis is the final outcome of various kidney injuries and diseases. Although the reasons for fibrogenesis are diverse in different kidney diseases, the pathological process is similar. Usually, renal fibrosis can be artificially divided into four overlapping stages named as priming, activation, execution, and progression, respectively, according to different characteristics. Priming, the earliest stage of fibrogenesis, inflammatory cells can infiltrate into the kidney and be activated to secrete a variety of factors, such as chemokines, cytokines, and reactive oxygen species because of tissue damage. And then, secreted cytokines stimulate cells to undergo transformation and transdifferentiation to a myofibroblast phenotype, which expresses α-smooth muscle actin and produces a large amount of ECM proteins during the activation phase. In the stage of execution, ECM are accumulated in the interstitials and modified to resist proteolytic enzyme. The last stage of fibrosis is progression, which involves several types of kidney injuries, such as renal tubular atrophy and capillary rarefaction [20–22]. It is worth noting that the pathological process is irreversible once fibrosis emerges. Thus, it is crucial to understand the mechanism of renal fibrosis clearly and prevent fibrogenesis timely at the early stage of renal disease.

3. Oxidative Stress

Under normal physiological conditions, the body can produce a small amount of reactive oxygen species (ROS) [23]. And free radical scavenging enzymes and antioxidants maintain the balance of oxygen metabolism through activating transcription factors, regulating physiological active substances and inflammatory immunity, and promoting cell proliferation and differentiation, which has extensive physiological significance. However, once the levels between ROS and reactive nitrogen species (RNS) and antioxidant defense system cannot keep balance, oxidative stress appears [24, 25].

ROS is the main member inducing oxidative stress *in vivo*, mainly including superoxide anion and hydrogen peroxide. In cells, a large number of ROS are generated by the mitochondrial electron transport chain and cytochrome P450 family, and xanthine oxidoreductase, reduced nicotinamide adenine dinucleotide phosphate oxidase (NOX), nitric oxide synthase, and other catalytic enzymes greatly affect the generation of ROS [26]. RNS is a class of nitric oxide- (NO-) centered derivatives produced by the reaction of NO with ROS, including NO, nitrogen oxygen anion, nitrosothiols, and peroxynitrite. Excessive ROS and RNS can react with intracellular lipids, nucleic acids, and proteins, leading to lipid peroxidation, DNA oxidative damage, and intracellular protein denaturation, causing damage to cellular structure and function [27]. And oxidants can also act as signaling molecules to change intracellular signaling pathways and even gene expression [28]. In addition, oxidative modification can promote abnormal cell growth, inflammation, and other physiological processes [29, 30].

4. Hypoxia Inducible Factor-1

HIF-1 is a basic heterodimeric helix-loop-helix transcription factor and consists of an adjustable oxygen-sensitive α-subunit, HIF-α, and a constitutively expressed β-subunit, HIF-β. Hypoxia is the main regulation factor of physiologic HIF-1 expression. Besides, it is important to notice that HIF-1α overactivation can also be stimulated by some other mechanisms [31, 32].

4.1. Regulation of HIF-1 Hydrolysis. Oxygen-induced hydroxylation is one of the most important regulated pathways for HIF-α. Under normoxia, oxygen-dependent proline degradation domains on HIF-α can be hydroxylated by PHD [33]. Hydroxylated HIF-α can combinate with ubiquitin and be degraded by proteasome following the activation of von Hippel-Lindau tumor suppressor protein (pVHL), with the latter acting as a ubiquitin ligase to promote proteolysis of HIF-α. Factor inhibiting HIF (FIH) can also inhibit the transcriptional activity of HIF-α by hydroxylating asparaginic acid, while, under hypoxic conditions, the activity of PHD and FIH is suppressed, which further inhibits the hydroxylation and hydrolysis of HIF-α. Subsequently, the stabilized HIF-α dimerizes with HIF-β and translocates into the nucleus, activating a targeting gene [34].

4.2. HIF-1 Mediated Profibrotic Change. As a transcription factor, HIF-1 activation can regulate the expression of erythropoietin, vascular endothelial growth factor, endothelin-1, glucose transporters, and some other target genes, affecting erythropoiesis, angiogenesis, and energy metabolism, during which it governs the initial adaptation process to hypoxia, improves tissue oxygenation and cell survival, and to some extent offsets some harmful effects [9–11]. Although HIF-1 can reduce hypoxic-related damage under short-term hypoxia, increasing findings have suggested that HIF-1 can also play a significant role in the initiation and progression of kidney disease [12, 35–37]. Wang et al. demonstrated that chronic ischemia-induced overactivation of HIF-1α in the kidney mediates chronic renal damage [32]. Kimura et al. performed 5/6 nephrectomy on normal and VHL-knockout mice, finding that HIF-1 expression was stable and interstitial fibrosis was significantly severe in tubular epithelial cells of VHL-deleted mice [38]. And Baumann et al. found that knockout of the podocyte HIF-1α gene can prevent glomerular type I collagen accumulation and glomerulosclerosis [35]. Thus, HIF seems to promote the formation and development of fibrosis during kidney damage. Generally, renal fibrosis is characterized by inflammation, myofibroblast transformation, and extracellular matrix deposition [20, 21, 22]. Many researches have also demonstrated that HIF-1 may promote extracellular matrix remodeling to mediate renal fibrosis by

inducing inflammation, EMT, collagen deposition, and ECM stiffening [39–41].

5. Contribution of Oxidative Stress to HIF-1-Mediated Profibrotic Changes

It has been described that during hypoxia, mitochondria increased the production of ROS, leading to inhibition of PHD activity and subsequent stabilization of HIF-1α protein [41]. Wang et al. have also demonstrated that ANG II stimulated H_2O_2 production, which inhibited PHD activity and thereby upregulated HIF-1α levels and consequently activated the tissue inhibitor of metalloproteinase, resulting in collagen I/III accumulation in cultured renal medullary interstitial cells [31]. PHD2 is the main subtype of renal PHD, mainly expressed in renal medulla. High salt intake initially increased renal tubular activity and decreased renal medullary oxygen level, thereby inhibiting PHD2 activity and activating HIF-1α-mediated adaptive genes. Proteins encoded by these genes produced medullary protective factors including NO, which in turn inhibited PHD2 [42]. Additional studies have suggested the involvement of PI-3K and ERK in NO-mediated HIF-1α accumulation [43, 44]. Others have also reported an increase in transcription of HIF-1α under hypoxia by ROS through induction of PI-3K/AKT and ERK phosphorylation [45, 46]. Oxidative factors can regulate the expression and activity of HIF-1 via PHD, ERK, and PI-3K/AKT.

While there is impaired PHD2 response to high salt in Dahl rats, increased oxidant stress might be one of the mechanisms. It is possible that high salt-induced oxidative stress induces PHD2 and thereby reduces HIF-1α levels in the renal medulla in Dahl S rats. Because of superoxide anion, it has been demonstrated to stimulate PHDs and thereby inhibit HIF-1α [47, 48]. Therefore, details of oxidative stress and PHD activity need to be clarified in future investigations. The relationship of oxidative stress and HIF-1 might be complex than our imagination. For example, it may be different in diverse animal models or distinct periods of diseases.

5.1. OS/NF-κB/HIF-1 Signaling. Normally, inflammatory response is a process that the body resists to pathogen infection, which is controllable. However, if inflammatory response lasts a long time, it will cause damage and diseases to the body [49]. It is accepted that hypoxia is a common feature and an important cause of most inflammation. Studies have found that most kidney damage started with inflammation [50]. The nuclear factor-kappa B (NF-κB) pathway is necessary for the expression of various proinflammatory factors under hypoxia, including TNF-α, IL-8, and IL-1β [51].

The study conducted by Jin and his colleagues has demonstrated that the oxidative stress/NF-κB signal pathway contributed to the formation of unilateral ureteral obstruction renal interstitial fibrosis [52]. Under hypoxic environment, excessive ROS can activate the NF/κB signaling pathway and then promote the expression of HIF-1α [53]. HIF-1α and NF-κB signaling is highly dependent. Hypoxia and/or inflammation lead to increased NF-κB and CCAAT/enhancer-binding protein delta (CEBPD) activity. CEBPD subsequently binds to the HIF-1α promoter and regulates HIF-1α signaling, thereby promoting inflammatory cell infiltration and inflammatory cytokine secretion in the renal tubulointerstitial region [54]. Zhao et al. showed that HIF-1α was upregulated in the kidneys of wild-type aristolochic acid nephropathy mice, accompanied by proximal tubular cell G2/M arrest and renal fibrosis [36]. Greijer and van der Wall have suggested that HIF-1 may inhibit the expression of cyclin-dependent kinase 1 and cyclins B1 and D1, leading to cell cycle G2/M arrest and promoting apoptosis in renal tubules [55]. Apoptosis induced by HIF-1 can release inflammatory mediators such as IL-1β and TNF-α, altering local renal microenvironment to trigger inflammation and fibrosis [56–58]. What is more, it has been shown that inflammatory cytokines can upregulate HIF-1α by MAPKp38 and via PI-3K/AKT phosphorylation [59].

Nevertheless, HIF can also inhibit renal inflammation by regulating Bcl-2 family genes, interacting with p53 or targeting mitochondrial enzymes to reduce tubular cell death [60, 61]. It can be seen that due to the complexity of the occurrence and development of inflammation, HIF-1α may play different roles in different stages of its development, which needs further study.

5.2. OS/HIF-1α /TGF-β Signaling. The activation of the NF/kB signaling pathway also plays an important role in the process of EMT and renal interstitial fibrosis in renal tubules [62]. EMT and ECM deposition are the key during renal aberrant trauma repair, which leads to fibrosis [63, 64]. During the process of EMT, proteins, such as e-cadherin, normally expressed by epithelial cells are lost and cell transdifferentiation markers, such as α-smooth muscle actin and fibroblast-specific protein 1, are obtained. An interesting finding shows that HIF-1α inhibited by short hairpin RNA can block the increasing expression of α-smooth muscle actin (SMA) in rats with a clipped kidney [32]. Higgins et al. found that activation of HIF-1 signaling in renal epithelial cells was associated with the development of chronic renal disease [64]. Experimental studies have shown that HIF-1 can activate various transcriptional regulators to promote mesenchymal transition by upregulating lysyl oxidase-like 2, B lymphoma Mo-MLV insertion region homolog1 (Bmi1), and Twist [12, 65, 66]. It has been demonstrated that HIF-1α stimulated collagen accumulation by activation of fibrogenic factors, such as connective tissue growth factor, plasminogen activator inhibitor, tissue inhibitor of metalloproteinase, and collagen proline and lysine hydroxylase [35, 67–69].

Transforming growth factor- (TGF-) β is considered to be the prototypical cytokine in renal fibrosis, which not only regulates the transformation of epithelial-mesenchymal cells to form myofibroblasts but also regulates the production and degradation of ECM [70, 71]. Zhou et al. indicate that ROS and HIF participate in hypoxia-induced TGF-β production [72]. HIF-1 accumulation can significantly enhance TGF-β expression [73–75]. TGF-β can upregulate gene expression of Nox4 NADPH oxidase or directly activate NADPH oxidase to generate ROS, which was reported to stabilize HIF-1α by decreasing PHD2 to reduce HIF-1α prolyl

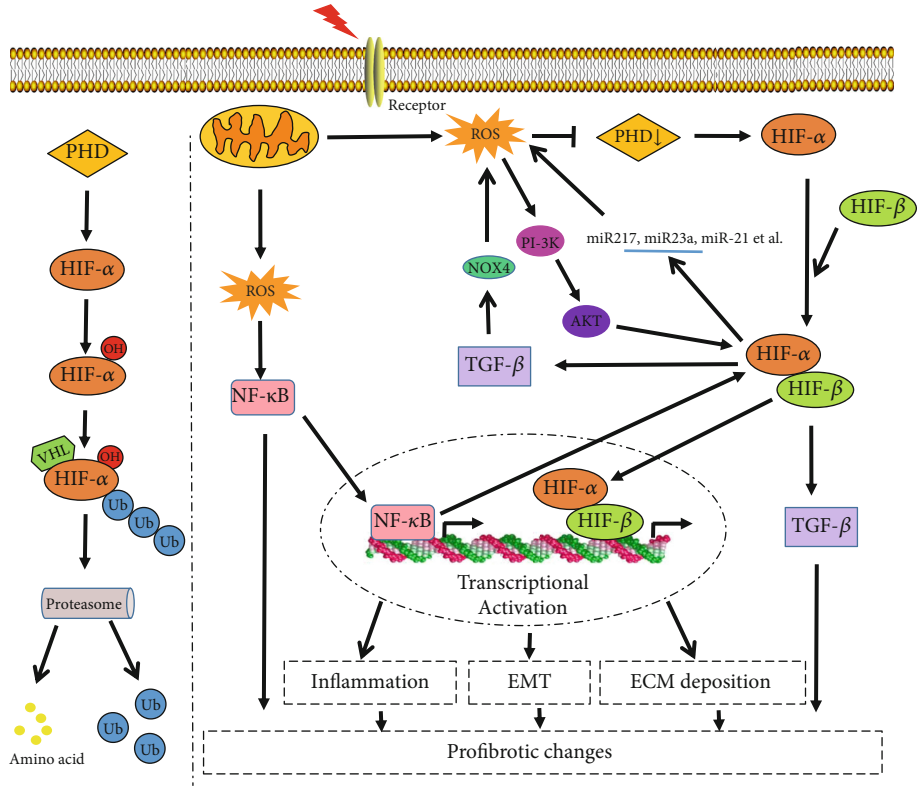

Figure 1: Contribution of oxidative stress to HIF-1-mediated profibrotic changes during the kidney damage. (1) Under normoxia, HIF-α can be hydroxylated by PHD. Hydroxylated HIF-α can combinate with ubiquitin and be degraded following the activation of VHL, (2) while, under stress conditions such as hypoxia or inflammation, the increased ROS can suppress the activity of PHD, which further inhibits the hydroxylation and hydrolysis of HIF-α. (3) Meanwhile, excessive ROS can activate NF/κB signaling and then promote the expression of HIF-α. (4) Stabilized HIF-α dimerizes with HIF-β and translocates into the nucleus, activating a targeting gene. HIF-1 can promote apoptosis and lead to the release of inflammatory mediators such as IL-1β and TNF-α, triggering inflammation, while inflammation can aggravate hypoxia and oxidative stress further. Besides, HIF-1 may promote EMT and ECM deposition to mediate profibrotic changes by activating various transcriptional regulators and fibrogenic factors. (5) HIF-1 accumulation can also significantly enhance TGF-β expression. TGF-β can upregulate gene expression of Nox4 NADPH oxidase or directly activate NADPH oxidase to generate ROS, which may form a vicious cycle to lead to renal fibrosis. (6) In addition, HIF-1 can also regulate the expression of various microRNAs such as miR217, miR23a, and miR-21, then affecting the generation of ROS and promoting the development of fibrosis via activating PI-3K signaling.

hydroxylation [76]. Das et al. found that the expression of NOX4 caused by TGF-β activation can be reduced by blocking Smad2 or Smad3, which suggested that TGF-β/Smad2/3 upregulated NOX4 and induced ROS generation, such as H_2O_2, which played an important role in the progression of renal fibrosis [76–78]. In TGF-β-treated renal tubular epithelial and mesangial cells, mammalian target of rapamycin complex-1 and Smad3 can also interact to increase the expression of HIF-1 and collagen [79]. Thus, TGF-β and ROS/HIF may form a feedback loop to maintain a prolonged signaling cascade initiated by either ROS/HIF or TGF-β.

5.3. miRNA/OS/HIF Signaling. The researches focused on the role of microRNA and HIF-1 during renal disease have also become more and more popular in recent years. MicroRNAs (miRNAs), small noncoding RNA molecules, can combine with 3′ untranslated regions of their target messenger RNA to inhibit their translation and thus regulate gene expression. A large number of studies show that miRNAs, such as miR217, miR23a, and miR-155, are closely related to the occurrence and development of renal fibrosis [80–84]. Recent studies have found that microRNA can regulate the expression or activity of HIF-1 by interfering with ROS production.

Increased miR-217 promotes inflammation and fibrosis in rats' glomerular mesangial cells cultured with high glucose through upregulating ROS, activating HIF-1 signaling pathway, and mediating cell apoptosis [80, 81]. miR-23a regulates cardiomyocyte apoptosis by suppressing the expression of MnSOD [82]. Li et al. also suggested that HIF-1 can induce exosome miR-23a expression, mediating the interaction between tubule epithelial cells and macrophages in tubule interstitial inflammation [83]. Xie et al. demonstrated that HIF-1α can increase the level of miR-155, thus promoting ETM and fibrosis both *in vivo* and *in vitro* [84], while miR-155-5p inhibitor treatment significantly decreased ROS generation and H_2O_2 concentration in HK-2 cells incubated with oxalate [85]. Therefore, we speculate that miR-155-5p mediated EMT by upregulating ROS, thereby activating HIF-1 signaling, which may form a vicious cycle.

In addition, miR-21 in extracellular vesicles may induce EMT through enhancing HIF-1α expression, and caloric restriction alleviates aging-related fibrosis of the kidney through downregulation of miR-21 [86]. It has also been shown that miR-21 is induced by H_2O_2 in vascular smooth muscles [87]. miR-21 silencing enhanced mitochondrial function, which reduced mitochondrial ROS production and thus preserved tubular functions. It is possible that the interplay between miR-21 and ROS may lead to the activation of AKT and ERK pathways and contribute to miR-21 regulation of HIF-1α [88].

6. Conclusion

With the aging of the social population, more and more patients now suffer from diabetes, hypertension, chronic kidney disease, and fibrosis, especially in developed countries [89–91]. Hypoxia and oxidative stress play an indispensable role in the occurrence and development of renal damage induced by these factors [92]. ROS accumulation during hypoxia promotes inflammation through activating NF-κB and mediating crosstalk with HIF-1 signaling. Besides, ROS can stabilize HIF, inducing TGF-β gene expression. Elevated TGF-β levels sustain the ROS production, maintaining prolonged ROS/HIF/TGF-β signaling. The possible interaction between microRNA and HIF-1 may provide a sight for revealing the profibrotic changes of HIF-1. The crosstalk of HIF-1 with other classical intracellular fibrogenic signaling pathways may be necessary to amplify fibrotic pathological response (Figure 1).

However, the results on studying the role of HIF-1 in renal fibrosis seem to be much more complex. Kapitsinou et al. found that the stable expression of HIF can inhibit cell apoptosis and inflammatory response and significantly reduce AKI-related renal fibrosis [93]. In addition, HIF-1 has been found to contribute to the activation of forkhead box O3, leading to increased autophagy and reduced oxidative damage, thus playing a role in renal protection [94]. Inconsistent results may be caused due to diverse experimental conditions, nature and duration of animal models, and methods of manipulating HIF activity. It is worth noting that these harmful or protective mediators are not always easily distinguished. The overall effect depends on the intensity and duration of their expression.

Data Availability

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

The work was conceived by HZ, RX, and ZW, the draft was written by HZ and RX, and the manuscript was revised by ZW. All authors reviewed and approved the final version of the manuscript for publication.

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References

[1] N. R. Prabhakar and G. L. Semenza, "Oxygen sensing and homeostasis," *Physiology (Bethesda)*, vol. 30, no. 5, pp. 340–348, 2015.

[2] T. Honda, Y. Hirakawa, and M. Nangaku, "The role of oxidative stress and hypoxia in renal disease," *Kidney Research and Clinical Practice*, vol. 38, no. 4, pp. 414–426, 2019.

[3] W. M. Bernhardt, V. Câmpean, S. Kany et al., "Preconditional activation of hypoxia-inducible factors ameliorates ischemic acute renal failure," *Journal of the American Society of Nephrology*, vol. 17, no. 7, pp. 1970–1978, 2006.

[4] Z. L. Li and B. C. Liu, "Hypoxia and renal tubulointerstitial fibrosis," *Advances in Experimental Medicine and Biology*, vol. 1165, pp. 467–485, 2019.

[5] K. Richter and T. Kietzmann, "Reactive oxygen species and fibrosis: further evidence of a significant liaison," *Cell and Tissue Research*, vol. 365, no. 3, pp. 591–605, 2016.

[6] I. A. Darby and T. D. Hewitson, "Hypoxia in tissue repair and fibrosis," *Cell and Tissue Research*, vol. 365, no. 3, pp. 553–562, 2016.

[7] G. L. Semenza, "Hydroxylation of HIF-1: oxygen sensing at the molecular level,," *Physiology (Bethesda)*, vol. 19, pp. 176–182, 2004.

[8] H. Choudhry and A. L. Harris, "Advances in hypoxia-inducible factor biology," *Cell Metabolism*, vol. 27, no. 2, pp. 281–298, 2018.

[9] E. Moore and R. Bellomo, "Erythropoietin (EPO) in acute kidney injury," *Annals of Intensive Care*, vol. 1, no. 1, p. 3, 2011.

[10] A. Agarwal and H. S. Nick, "Renal response to tissue Injury," *Journal of the American Society of Nephrology*, vol. 11, no. 5, pp. 965–973, 2000.

[11] C. Warnecke, Z. Zaborowska, J. Kurreck et al., "Differentiating the functional role of hypoxia-inducible factor (HIF)-1alpha and HIF-2alpha (EPAS-1) by the use of RNA interference: erythropoietin is a HIF-2alpha target gene in Hep3B and Kelly cells," *FASEB Journal*, vol. 18, no. 12, pp. 1462–1464, 2004.

[12] R. Schietke, C. Warnecke, I. Wacker et al., "The Lysyl Oxidases LOX and LOXL2 Are Necessary and Sufficient to Repress E-cadherin in Hypoxia:," *Journal of Biological Chemistry*, vol. 285, no. 9, pp. 6658–6669, 2010.

[13] R. Hafizi, F. Imeri, R. H. Wenger, and A. Huwiler, "S1P stimulates erythropoietin production in mouse renal interstitial fibroblasts by S1P1 and S1P3 receptor activation and HIF-2alpha stabilization," *International Journal of Molecular Sciences*, vol. 22, no. 17, p. 9467, 2021.

[14] S. Zhu, L. Wu, J. Zhang et al., "Collagen hydrolysate corrects anemia in chronic kidney disease via anti-inflammatory renoprotection and HIF-2α-Dependent erythropoietin and

hepcidin regulation," *Journal of Agricultural and Food Chemistry*, vol. 68, no. 42, pp. 11726–11734, 2020.

[15] D. F. Higgins, K. Kimura, M. Iwano, and V. H. Haase, "Hypoxia-inducible factor signaling in the development of tissue fibrosis," *Cell Cycle*, vol. 7, no. 9, pp. 1128–1132, 2008.

[16] R. E. Schietke, T. Hackenbeck, M. Tran et al., "Renal tubular HIF-2α expression requires VHL inactivation and causes fibrosis and cysts," *PLoS One*, vol. 7, no. 1, p. e31034, 2012.

[17] P. Li, Y. Liu, X. Qin et al., "SIRT1 attenuates renal fibrosis by repressing HIF-2α," *Cell Death Discovery*, vol. 7, no. 1, p. 59, 2021.

[18] S. Y. Pan, P. Z. Tsai, Y. H. Chou et al., "Kidney pericyte hypoxia-inducible factor regulates erythropoiesis but not kidney fibrosis," *Kidney International*, vol. 99, no. 6, pp. 1354–1368, 2021.

[19] T. Tanaka, M. Wiesener, W. Bernhardt, K. U. Eckardt, and C. Warnecke, "The human HIF (hypoxia-inducible factor)-3α gene is a HIF-1 target gene and may modulate hypoxic gene induction," *Biochemical Journal*, vol. 424, no. 1, pp. 143–151, 2009.

[20] J. P. Thiery, H. Acloque, R. Y. Huang, and M. A. Nieto, "Epithelial-mesenchymal transitions in development and disease," *Cell*, vol. 139, no. 5, pp. 871–890, 2009.

[21] Y. Liu, "Cellular and molecular mechanisms of renal fibrosis," *Nature Reviews Nephrology*, vol. 7, no. 12, pp. 684–696, 2011.

[22] S. G. Mansour, J. Puthumana, S. G. Coca, M. Gentry, and C. R. Parikh, "Biomarkers for the detection of renal fibrosis and prediction of renal outcomes: a systematic review," *BMC Nephrology*, vol. 18, no. 1, p. 72, 2017.

[23] J. Pi, Q. Zhang, J. Fu et al., "ROS signaling, oxidative stress and Nrf2 in pancreatic beta-cell function," *Toxicology and Applied Pharmacology*, vol. 244, no. 1, pp. 77–83, 2010.

[24] N. S. Chandel, D. S. McClintock, C. E. Feliciano et al., "Reactive Oxygen Species Generated at Mitochondrial Complex III Stabilize Hypoxia-inducible Factor-1α during Hypoxia:," *Journal of Biological Chemistry*, vol. 275, no. 33, pp. 25130–25138, 2000.

[25] H. Zhang, H. M. Zhang, L. P. Wu et al., "Impaired mitochondrial complex III and melatonin responsive reactive oxygen species generation in kidney mitochondria of db/db mice," *Journal of Pineal Research*, vol. 51, no. 3, pp. 338–344, 2011.

[26] M. Sedeek, R. Nasrallah, R. M. Touyz, and R. L. Hebert, "NADPH oxidases, reactive oxygen species, and the kidney: friend and foe," *Journal of the American Society of Nephrology*, vol. 24, no. 10, pp. 1512–1518, 2013.

[27] J. Martinez-Useros, W. Li, M. Cabeza-Morales, and J. Garcia-Foncillas, "Oxidative stress: a new target for pancreatic cancer prognosis and treatment," *Journal of Clinical Medicine*, vol. 6, no. 3, p. 29, 2017.

[28] H. Ha, M. R. Yu, Y. J. Choi, M. Kitamura, and H. B. Lee, "Role of high glucose-induced nuclear factor-kappaB activation in monocyte chemoattractant protein-1 expression by mesangial cells," *Journal of the American Society of Nephrology*, vol. 13, no. 4, pp. 894–902, 2002.

[29] P. D. Ray, B. W. Huang, and Y. Tsuji, "Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling," *Cellular Signalling*, vol. 24, no. 5, pp. 981–990, 2012.

[30] J. L. Barnes and Y. Gorin, "Myofibroblast differentiation during fibrosis: role of NAD(P)H oxidases," *Kidney International*, vol. 79, no. 9, pp. 944–956, 2011.

[31] Z. Wang, L. Tang, Q. Zhu et al., "Hypoxia-inducible factor-1α contributes to the profibrotic action of angiotensin II in renal medullary interstitial cells," *Kidney International*, vol. 79, no. 3, pp. 300–310, 2011.

[32] Z. Wang, Q. Zhu, P. Li et al., "Silencing of hypoxia-inducible factor-1α gene attenuates chronic ischemic renal injury in two-kidney, one-clip rats," *American Journal of Physiology - Renal Physiology*, vol. 306, no. 10, pp. F1236–F1242, 2014.

[33] G. H. Fong and K. Takeda, "Role and regulation of prolyl hydroxylase domain proteins," *Cell Death and Differentiation*, vol. 15, no. 4, pp. 635–641, 2008.

[34] A. J. Majmundar, W. J. Wong, and M. C. Simon, "Hypoxia-inducible factors and the response to hypoxic stress," *Molecular Cell*, vol. 40, no. 2, pp. 294–309, 2010.

[35] B. Baumann, T. Hayashida, X. Liang, and H. W. Schnaper, "Hypoxia-inducible factor-1α promotes glomerulosclerosis and regulates _COL1A2_ expression through interactions with Smad3," *Kidney International*, vol. 90, no. 4, pp. 797–808, 2016.

[36] H. Zhao, N. Jiang, Y. Han et al., "Aristolochic acid induces renal fibrosis by arresting proximal tubular cells in G2/M phase mediated by HIF-1α," *FASEB Journal*, vol. 34, no. 9, pp. 12599–12614, 2020.

[37] M. Nangaku, C. Rosenberger, S. N. Heyman, and K. U. Eckardt, "Regulation of hypoxia-inducible factor in kidney disease," *Clinical and Experimental Pharmacology and Physiology*, vol. 40, no. 2, pp. 148–157, 2013.

[38] K. Kimura, M. Iwano, D. F. Higgins et al., "Stable expression of HIF-1alpha in tubular epithelial cells promotes interstitial fibrosis," *American Journal of Physiology - Renal Physiology*, vol. 295, no. 4, pp. F1023–F1029, 2008.

[39] S. Shu, Y. Wang, M. Zheng et al., "Hypoxia and hypoxia-inducible factors in kidney injury and repair," *Cell*, vol. 8, no. 3, p. 207, 2019.

[40] M. Liu, X. Ning, R. Li et al., "Signalling pathways involved in hypoxia-induced renal fibrosis," *Journal of Cellular and Molecular Medicine*, vol. 21, no. 7, pp. 1248–1259, 2017.

[41] K. Louis and A. Hertig, "How tubular epithelial cells dictate the rate of renal fibrogenesis?," *World Journal of Nephrology*, vol. 4, no. 3, pp. 367–373, 2015.

[42] Z. Wang, Q. Zhu, M. Xia, P. L. Li, S. J. Hinton, and N. Li, "Hypoxia-inducible factor prolyl-hydroxylase 2 senses high-salt intake to increase hypoxia inducible factor 1alpha levels in the renal medulla," *Hypertension*, vol. 55, no. 5, pp. 1129–1136, 2010.

[43] K. B. Sandau, H. G. Faus, and B. Brüne, "Induction of hypoxia-inducible-factor 1 by nitric oxide is mediated via the PI 3K pathway," *Biochemical and Biophysical Research Communications*, vol. 278, no. 1, pp. 263–267, 2000.

[44] K. Kasuno, S. Takabuchi, K. Fukuda et al., "Nitric Oxide Induces Hypoxia-inducible Factor 1 Activation That Is Dependent on MAPK and Phosphatidylinositol 3-Kinase Signaling," *Journal of Biological Chemistry*, vol. 279, no. 4, pp. 2550–2558, 2004.

[45] N. Koshikawa, J. Hayashi, A. Nakagawara, and K. Takenaga, "Reactive Oxygen Species-generating Mitochondrial DNA Mutation Up-regulates Hypoxia-inducible Factor-1α Gene Transcription via Phosphatidylinositol 3-Kinase-Akt/Protein Kinase C/Histone Deacetylase Pathway," *Journal of Biological Chemistry*, vol. 284, no. 48, pp. 33185–33194, 2009.

[46] J. du, R. Xu, Z. Hu et al., "PI3K and ERK-induced Rac1 activation mediates hypoxia-induced HIF-1α expression in MCF-7 breast cancer cells," *PLoS One*, vol. 6, no. 9, p. e25213, 2011.

[47] M. Callapina, J. Zhou, T. Schmid, R. Kohl, and B. Brune, "NO restores HIF-1α hydroxylation during hypoxia: Role of reactive oxygen species," *Free Radical Biology and Medicine*, vol. 39, no. 7, pp. 925–936, 2005.

[48] Y. EMORI, T. MIZUSHIMA, N. MATSUMURA et al., "Camostat, an oral trypsin inhibitor, reduces pancreatic fibrosis induced by repeated administration of a superoxide dismutase inhibitor in rats," *Journal of Gastroenterology and Hepatology*, vol. 20, no. 6, pp. 895–899, 2005.

[49] X. M. Meng, G. L. Ren, L. Gao et al., "NADPH oxidase 4 promotes cisplatin-induced acute kidney injury via ROS- mediated programmed cell death and inflammation," *Laboratory Investigation*, vol. 98, no. 1, pp. 63–78, 2018.

[50] O. M. Akchurin and F. Kaskel, "Update on inflammation in chronic kidney disease," *Blood Purification*, vol. 39, no. 1-3, pp. 84–92, 2015.

[51] X. Chen, X. Li, W. Zhang et al., "Activation of AMPK inhibits inflammatory response during hypoxia and reoxygenation through modulating JNK-mediated NF-κB pathway," *Metabolism - Clinical and Experimental*, vol. 83, pp. 256–270, 2018.

[52] H. Jin, Y. Wang, D. Wang, and L. Zhang, "Effects of Qingshen granules on the oxidative stress-NF/kB signal pathway in unilateral ureteral obstruction rats," *Evidence-based Complementary and Alternative Medicine*, vol. 2018, 2018.

[53] A. Quercioli, G. Luciano Viviani, F. Dallegri, F. Mach, and F. Montecucco, "Receptor activator of nuclear factor kappa B ligand/osteoprotegerin pathway is a promising target to reduce atherosclerotic plaque calcification," *Critical Pathways in Cardiology*, vol. 9, no. 4, pp. 227–230, 2010.

[54] J. Yamaguchi, T. Tanaka, N. Eto, and M. Nangaku, "Inflammation and hypoxia linked to renal injury by CCAAT/enhancer-binding protein δ," *Kidney International*, vol. 88, no. 2, pp. 262–275, 2015.

[55] A. E. Greijer and E. van der Wall, "The role of hypoxia inducible factor 1 (HIF-1) in hypoxia induced apoptosis," *Journal of Clinical Pathology*, vol. 57, no. 10, pp. 1009–1014, 2004.

[56] C. C. Scholz, M. A. S. Cavadas, M. M. Tambuwala et al., "Regulation of IL-1 -induced NF- B by hydroxylases links key hypoxic and inflammatory signaling pathways," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 46, pp. 18490–18495, 2013.

[57] L. Liu, P. Zhang, M. Bai et al., "p53 upregulated by HIF-1α promotes hypoxia-induced G2/M arrest and renal fibrosis in vitro and in vivo," *Journal of Molecular Cell Biology*, vol. 11, no. 5, pp. 371–382, 2019.

[58] A. Sendoel and M. O. Hengartner, "Apoptotic cell death under hypoxia," *Physiology (Bethesda)*, vol. 29, no. 3, pp. 168–176, 2014.

[59] J. WESTRA, E. BROUWER, R. BOS et al., "Regulation of cytokine-induced HIF-1 Expression in rheumatoid synovial fibroblasts," *Annals of the New York Academy of Sciences*, vol. 1108, no. 1, pp. 340–348, 2007.

[60] R. Provenzano, A. Besarab, C. H. Sun et al., "Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD," *Clinical Journal of the American Society of Nephrology*, vol. 11, no. 6, pp. 982–991, 2016.

[61] B. De Vries, R. A. Matthijsen, T. G. Wolfs, A. A. Van Bijnen, P. Heeringa, and W. A. Buurman, "Inhibition of complement factor C5 protects against renal ischemia-reperfusion injury: inhibition of late apoptosis and inflammation," *Transplantation*, vol. 75, no. 3, pp. 375–382, 2003.

[62] Z. Wang, Z. Chen, B. Li et al., "Curcumin attenuates renal interstitial fibrosis of obstructive nephropathy by suppressing epithelial-mesenchymal transition through inhibition of the TLR4/NF-κB and PI3K/AKT signalling pathways," *Pharmaceutical Biology*, vol. 58, no. 1, pp. 828–837, 2020.

[63] M. Mack and M. Yanagita, "Origin of myofibroblasts and cellular events triggering fibrosis," *Kidney International*, vol. 87, no. 2, pp. 297–307, 2015.

[64] D. F. Higgins, K. Kimura, W. M. Bernhardt et al., "Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition," *Journal of Clinical InvestigationJournal of Clinical Investigation*, vol. 117, no. 12, pp. 3810–3820, 2007.

[65] M. H. Yang and K. J. Wu, "TWIST activation by hypoxia inducible factor-1 (HIF-1): implications in metastasis and development," *Cell Cycle*, vol. 7, no. 14, pp. 2090–2096, 2008.

[66] S. Sun, X. Ning, Y. Zhang et al., "Hypoxia-inducible factor-1α induces Twist expression in tubular epithelial cells subjected to hypoxia, leading to epithelial-to-mesenchymal transition," *Kidney International*, vol. 75, no. 12, pp. 1278–1287, 2009.

[67] X. Li, H. Kimura, K. Hirota et al., "Synergistic effect of hypoxia and TNF-α on production of PAI-1 in human proximal renal tubular cells," *Kidney International*, vol. 68, no. 2, pp. 569–583, 2005.

[68] T. Tanaka, "Expanding roles of the hypoxia-response network in chronic kidney disease," *Clinical and Experimental Nephrology*, vol. 20, no. 6, pp. 835–844, 2016.

[69] J. T. Norman, I. M. Clark, and P. L. Garcia, "Hypoxia promotes fibrogenesis in human renal fibroblasts," *Kidney International*, vol. 58, no. 6, pp. 2351–2366, 2000.

[70] S. W. Chea and K. B. Lee, "TGF-beta mediated epithelial-mesenchymal transition in autosomal dominant polycystic kidney disease," *Yonsei Medical Journal*, vol. 50, no. 1, pp. 105–111, 2009.

[71] C. L. Belmiro, R. G. Gonçalves, E. O. Kozlowski et al., "Dermatan sulfate reduces monocyte chemoattractant protein 1 and TGF-β production, as well as macrophage recruitment and myofibroblast accumulation in mice with unilateral ureteral obstruction," *Brazilian Journal of Medical and Biological Research*, vol. 44, no. 7, pp. 624–633, 2011.

[72] G. Zhou, L. A. Dada, M. Wu et al., "Hypoxia-induced alveolar epithelial-mesenchymal transition requires mitochondrial ROS and hypoxia-inducible factor 1," *American Journal of Physiology - Lung Cellular and Molecular Physiology*, vol. 297, no. 6, pp. L1120–L1130, 2009.

[73] R. Kalluri and E. G. Neilson, "Epithelial-mesenchymal transition and its implications for fibrosis," *Journal of Clinical Investigation*, vol. 112, no. 12, pp. 1776–1784, 2003.

[74] C. Sahlgren, M. V. Gustafsson, S. Jin, L. Poellinger, and U. Lendahl, "Notch signaling mediates hypoxia-induced tumor cell migration and invasion," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 17, pp. 6392–6397, 2008.

[75] N. Kushida, S. Nomura, I. Mimura et al., "Hypoxia-inducible Factor-1α activates the transforming growth Factor-β/SMAD3 pathway in kidney tubular epithelial cells," *American Journal of Nephrology*, vol. 44, no. 4, pp. 276–285, 2016.

[76] R. Das, S. Xu, X. Quan et al., "Upregulation of mitochondrial Nox4 mediates TGF-β-induced apoptosis in cultured mouse podocytes," *American Journal of Physiology - Renal Physiology*, vol. 306, no. 2, pp. F155–F167, 2014.

[77] R. Das, S. Xu, T. T. Nguyen et al., "ERK1/2-mTORC1-Nox4 Axis in TGF-β1-induced Podocyte Apoptosis," *Journal of Biological Chemistry*, vol. 290, no. 52, pp. 30830–30842, 2015.

[78] H. E. Boudreau, B. W. Casterline, B. Rada, A. Korzeniowska, and T. L. Leto, "Nox4 involvement in TGF-beta and SMAD3-driven induction of the epithelial-to- mesenchymal transition and migration of breast epithelial cells," *Free Radical Biology and Medicine*, vol. 53, no. 7, pp. 1489–1499, 2012.

[79] B. Rozen-Zvi, T. Hayashida, S. C. Hubchak, C. Hanna, L. C. Platanias, and H. W. Schnaper, "TGF-β/Smad3 activates mammalian target of rapamycin complex-1 to promote collagen production by increasing HIF-1α expression," *American Journal of Physiology - Renal Physiology*, vol. 305, no. 4, pp. F485–F494, 2013.

[80] Y. Shao, C. Lv, C. Wu, Y. Zhou, and Q. Wang, "Mir-217 promotes inflammation and fibrosis in high glucose cultured rat glomerular mesangial cells via Sirt1/HIF-1α signaling pathway," *Diabetes/Metabolism Research and Reviews*, vol. 32, no. 6, pp. 534–543, 2016.

[81] J. Sun, Z. P. Li, R. Q. Zhang, and H. M. Zhang, "Repression of miR-217 protects against high glucose-induced podocyte injury and insulin resistance by restoring PTEN-mediated autophagy pathway," *Biochemical and Biophysical Research Communications*, vol. 483, no. 1, pp. 318–324, 2017.

[82] B. Long, T. Y. Gan, R. C. Zhang, and Y. H. Zhang, "miR-23a regulates cardiomyocyte apoptosis by targeting manganese superoxide dismutase," *Molecules and Cells*, vol. 40, no. 8, pp. 542–549, 2017.

[83] Z. L. Li, L. L. Lv, T. T. Tang et al., "HIF-1α inducing exosomal microRNA-23a expression mediates the cross-talk between tubular epithelial cells and macrophages in tubulointerstitial inflammation," *Kidney International*, vol. 95, no. 2, pp. 388–404, 2019.

[84] S. Xie, H. Chen, F. Li, S. Wang, and J. Guo, "Hypoxia-induced microRNA-155 promotes fibrosis in proximal tubule cells," *Molecular Medicine Reports*, vol. 11, no. 6, pp. 4555–4560, 2015.

[85] K. Jiang, J. Hu, G. Luo et al., "miR-155-5p promotes oxalate- and calcium-induced kidney oxidative stress injury by suppressing MGP expression," *Oxidative Medicine and Cellular Longevity*, vol. 2020, 2020.

[86] J. R. Liu, G. Y. Cai, Y. C. Ning et al., "Caloric restriction alleviates aging-related fibrosis of kidney through downregulation of miR-21 in extracellular vesicles," *Aging (Albany NY)*, vol. 12, no. 18, pp. 18052–18072, 2020.

[87] Y. Lin, X. Liu, Y. Cheng, J. Yang, Y. Huo, and C. Zhang, "Involvement of MicroRNAs in Hydrogen Peroxide-mediated Gene Regulation and Cellular Injury Response in Vascular Smooth Muscle Cells," *Journal of Biological Chemistry*, vol. 284, no. 12, pp. 7903–7913, 2009.

[88] I. G. Gomez, D. A. MacKenna, B. G. Johnson et al., "Anti-microRNA-21 oligonucleotides prevent Alport nephropathy progression by stimulating metabolic pathways," *Journal of Clinical Investigation*, vol. 125, no. 1, pp. 141–156, 2015.

[89] L. Zhang, F. Wang, L. Wang et al., "Prevalence of chronic kidney disease in China: a cross-sectional survey," *Lancet*, vol. 379, no. 9818, pp. 815–822, 2012.

[90] P. Romagnani, G. Remuzzi, R. Glassock et al., "Chronic kidney disease," *Nature Reviews. Disease Primers*, vol. 3, no. 1, p. 17088, 2017.

[91] S. G. Coca, S. Singanamala, and C. R. Parikh, "Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis," *Kidney International*, vol. 81, no. 5, pp. 442–448, 2012.

[92] K. Shoji, T. Tanaka, and M. Nangaku, "Role of hypoxia in progressive chronic kidney disease and implications for therapy," *Current Opinion in Nephrology and Hypertension*, vol. 23, no. 2, pp. 161–168, 2014.

[93] P. P. Kapitsinou, J. Jaffe, M. Michael et al., "Preischemic targeting of HIF prolyl hydroxylation inhibits fibrosis associated with acute kidney injury," *American Journal of Physiology - Renal Physiology*, vol. 302, pp. F1172–F1179, 2012.

[94] L. Li, H. Kang, Q. Zhang, V. D. D'Agati, Q. Al-Awqati, and F. Lin, "FoxO3 activation in hypoxic tubules prevents chronic kidney disease," *Journal of Clinical Investigation*, vol. 129, no. 6, pp. 2374–2389, 2019.