


Review

Hypoxia-Driven Responses in Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) affects 10% of the population. Fibrosis is the hallmark of CKD, which is marked by the deposit of extracellular matrix (ECM). This response is the final outcome of an unbalanced reaction to inflammation and wound healing and can be induced by a variety of insults, including hypoxia. Vascular damage results in an impaired tissue oxygen supply, inducing immune cell infiltration, tubule injury and the activation of ECM-secreting myofibroblasts. In turn, tubulointerstitial fibrosis development worsens oxygen diffusion. Hypoxia-inducible factor (HIF) is the primary transcriptional regulator of hypoxia-associated responses, such as oxidative stress and metabolic reprogramming, triggering a proinflammatory and profibrotic landscape. In this review, we discuss hypoxia-driven reprogramming in CKD as well as potential therapeutic approaches to target chronic hypoxia.

Keywords: kidney fibrosis; hypoxia; mitochondria; oxidative stress; tubular epithelial cells

1. Chronic Kidney Disease

Chronic kidney disease (CKD) is a clinical setting with a gradual decline in renal function. It has high rates of morbidity and mortality and constitutes a significant medical, social and economic burden. It affects about 10% of the global population and affects roughly 30–40% of patients with high prevalent pathologies, such as diabetes mellitus and hypertension [1]. Acute kidney injury (AKI) is a risk factor for developing CKD, whereas CKD sensitizes patients to AKI [2]. While a lot has been learned about the mechanisms underlying these diseases, the causes predisposing AKI to CKD and vice versa remain largely elusive. High rates of cardiac diseases are reported in CKD patients with chronic inflammation, which may result in a reduced blood supply to the kidneys [3]. Dysregulation of the immune system following AKI could be a major factor contributing to increased risk of CKD based on the incomplete tissue relocation of immune cells after injury [4,5]. Genetic conditions such as polycystic kidney disease (PKD), immune glomerulopathies and exposure to environmental chemicals are less frequent causes of CKD. Within the next 20 years, CKD is ranked to be the fifth leading cause of death worldwide [6]. Although multiple interventions have been used to slow the progression of CKD, including strict control of blood pressure and glycaemia, correction of dyslipidemia, halting of potentially nephrotoxic drugs or smoking, blockade of the renin-angiotensin system to lower glomerular capillary pressure and immunosuppression in some rapidly progressing disorders, none of the current tactics have shown effectiveness to revert the progression to end-stage renal disease (ESRD). Sodium-glucose cotransporter-2 (SGLT2) inhibition showed promising in recent trials. However, most of CKD patients advance toward ESRD, which requires dialysis or kidney transplant [7].

Nephrons are the functional units of the kidney, formed by glomeruli and tubules. The glomerulus retains cells and big proteins while filtering the blood. The filtrate enters the tubule to produce the final urine by eliminating or adding substances to the tubular fluid. Kidneys keep the interior environment in a state of homeostasis by maintaining



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the proper balance of water, minerals, electrolytes and hydrogen ions as well as removing toxins. That is the case of uremic toxins, substances produced by protein metabolism that accumulate in patients with impaired renal function, contributing to CKD progression. Many of these protein-bound uremic toxins are gut-derived from the degradation of aromatic amino acids by intestinal bacteria. The most-studied ones are p-cresol, p-cresyl sulfate, p-cresyl glucuronide, indoxyl sulfate, indole-3-acetic acid, trimethylamine-N-oxide, phenylacetylglutamine and hippuric acid [8]. Regardless of etiology, CKD progression involves the development of tubulointerstitial and glomerular fibrosis. It involves the excessive accumulation of extracellular matrix proteins (ECM), such as fibronectin, proteoglycans and collagens, which replace the cellular living tissue. This is the result of an unbalanced response to inflammation and wound healing that activates ECM-secreting myofibroblasts [9].

Renal injury, caused by toxic compounds, hypoxia or proteinuria, promotes rarefaction of the peritubular microvasculature and damages the tubular epithelium, which leads to its subsequent dedifferentiation or cell death. Reduced number of functional nephrons results in hyperfiltration by the remnant kidney, increasing biomechanical forces that can determine cellular injury. The responses underlying tubular damage are complex, involving oxidative stress, metabolic alterations, cell cycle arrest, dedifferentiation, senescence, inflammatory mediators and epigenetic changes. After the first insult, the remaining cells go through a recovery phase during which regeneration mechanisms are activated to restore epithelial cell characteristics and functions. An incomplete repair promotes fibrosis and CKD progression. By secreting paracrine proinflammatory or profibrotic mediators, sublethal injured tubular epithelial cells (TECs) can act as fibrogenesis initiators [10]. The main profibrogenic cytokine is Transforming growth factor- β (TGF- β) [11]. In addition to a variety of cytokines, such as interleukin 1 (IL-1) and tumor necrosis factor (TNF), other key fibrogenic factors include platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), fibroblast growth factor 2 (FGF2), tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and angiotensin II (Ang II) [12], triggering the activation of TGF- β , Notch, Wnt/ β -Catenin, PDGF and Ang II/Reactive oxygen species (ROS)-signaling pathways. These proinflammatory/profibrotic factors are crucial for kidney fibrosis development by triggering ECM-producing myofibroblast activation, epithelial cell dedifferentiation/apoptosis and inflammatory cell recruitment/activation, perpetuating the fibrotic loop.

2. Hypoxia in the Kidney

Despite the significant blood flow to the kidney (up to 20% of the cardiac output in humans), it is an organ predisposed to suffer hypoxic damage. This is because its inefficient uptake of oxygen delivered by the renal artery (10% at most) due to an arterial-venous diffusional oxygen shunt. Indeed, the particular renal vasculature creates a cortico-medullary pO₂ gradient from approximately 30 mmHg in the cortex to 10 mmHg in the medulla [13,14]. Furthermore, part of the delivered oxygen is consumed in mitochondrial respiration to produce large amounts of adenosine triphosphate (ATP). It is required for the active transport of the proximal tubule, which reabsorbs 80% of the filtrate that traverses the glomerulus. Therefore, both renal architecture and the limited ability of kidney tubules to generate energy under anaerobic conditions make the kidney a highly sensitive organ to changes in oxygen levels [15]. This particular setting facilitates erythropoietin-producing cells residing in the kidney to adjust the generation of erythropoietin (EPO) to variations in oxygen availability [16]. Of interest, the uremic toxin indoxyl sulfate can control the cell survival and differentiation of erythroid progenitors, altering erythropoiesis and contributing to anemia development in CKD patients [17].

To date, hypoxia along CKD progression is not conclusively demonstrated yet due to the lack of feasible methods. Techniques for assessing hypoxia in tissues include microelectrode-dependent measurements, pimonidazole staining, analysis of the HIF pathway, two-photon phosphorescence lifetime microscopy of oxygen in living animals, blood oxygenation level-

dependent magnetic resonance imaging and positron emission tomography-computed tomography [18]. However, these methodologies have some drawbacks: limited accuracy and specificity, high operating costs and challenging implementation.

2.1. Factors Leading to Hypoxia

Systemic oxygenation is decreased by a combination of physiological, behavioral and environmental risk factors. They include anemia, hyperglycemia, hypertension, hypercholesterolemia, obstructive sleep apnea, smoking, air pollution and atherosclerosis [19–23]. Under prolonged hypoxia, pathological cellular processes are activated, including epithelial apoptosis/dedifferentiation, leukocyte activation/recruitment, fibroblast activation and ECM deposition [24–28]. Additionally, these processes result in renal fibrosis and vasoconstriction, worsening hypoxia by reducing erythrocyte access and limiting oxygen diffusion [29]. This loop acts as a vicious circle that will inevitably result in progressive CKD (Figure 1).

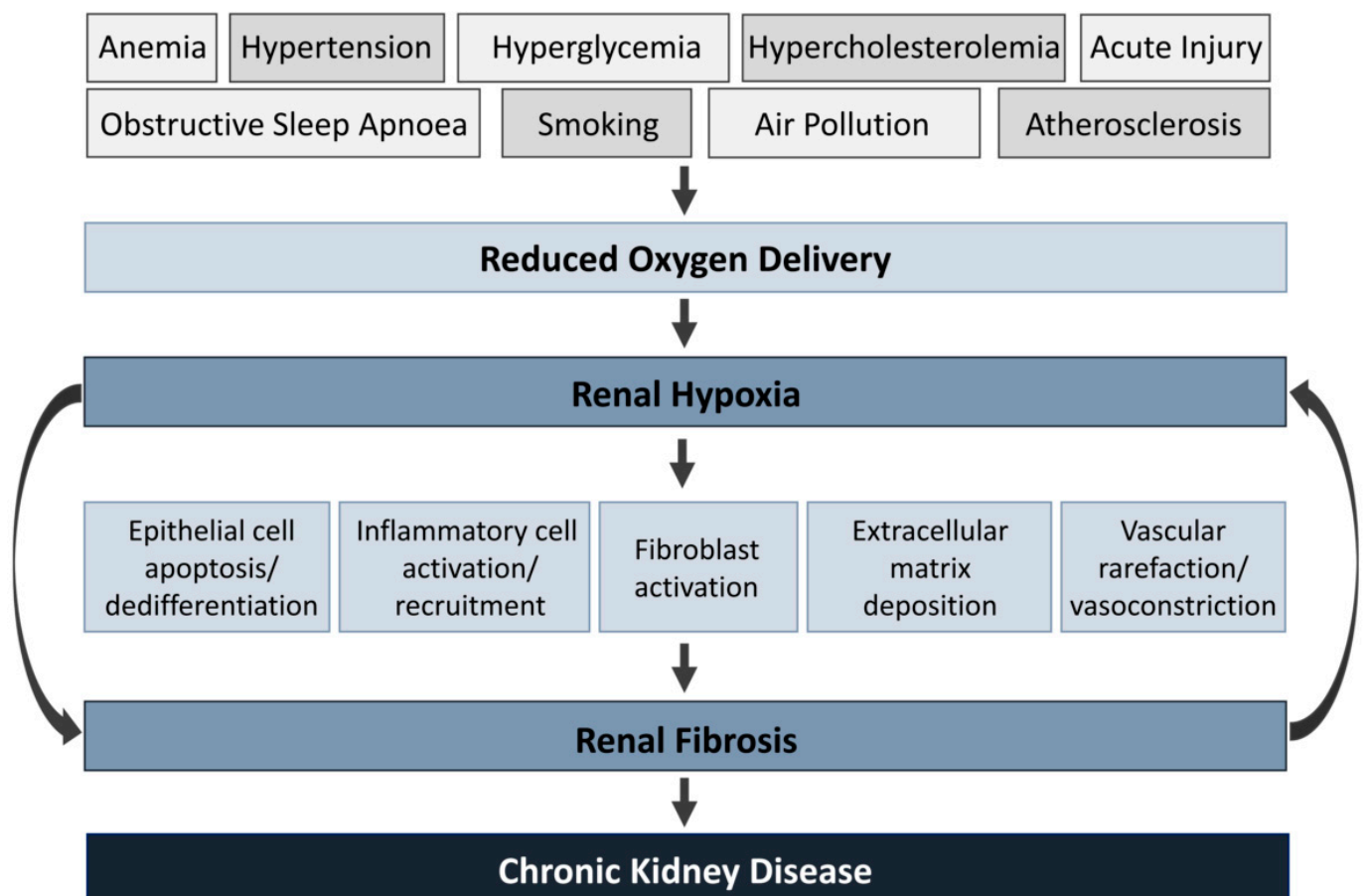


Figure 1. Renal hypoxia in the pathophysiology of CKD progression. Environmental, behavioral and physiologic risk factors reduce systemic oxygenation. It triggers a range of pathological cellular processes including epithelial cell apoptosis/dedifferentiation, inflammatory cell activation/recruitment, fibroblast activation, ECM deposition and vascular rarefaction/vasoconstriction. These processes cause tubulointerstitial fibrosis, further aggravating hypoxia by limiting oxygen diffusion. This vicious cycle results in CKD progression.

2.2. The Hypoxia-Inducible Factor System

The primary regulator of the cellular adaptive response to hypoxia is the hypoxia-inducible factor (HIF) pathway. HIFs are heterodimeric complexes formed by one of the three different oxygen-regulated α subunits (HIF-1 α to -3 α) and one constitutional β subunit (HIF-b), which bind to the transcriptional coactivators C-AMP-Response Element-

binding protein (CREB-binding protein)/binding protein p300 (CBP/p300) in the nucleus, increasing the expression of downstream genes (Figure 2) [30]. In the kidney, HIF-1 α is mainly expressed in TECs under hypoxic conditions, while HIF-2 α is limited to the endothelial and interstitial cells [31]. HIF has >1000 different target genes, including EPO, transferrin, vascular endothelial growth factor (VEGF) and glycolytic enzymes [32]. Genetic ablation of the HIF pathway, either HIF-1 α or HIF-2 α , aggravates renal injury, while global HIF-1 α overexpression is protective [33–35].

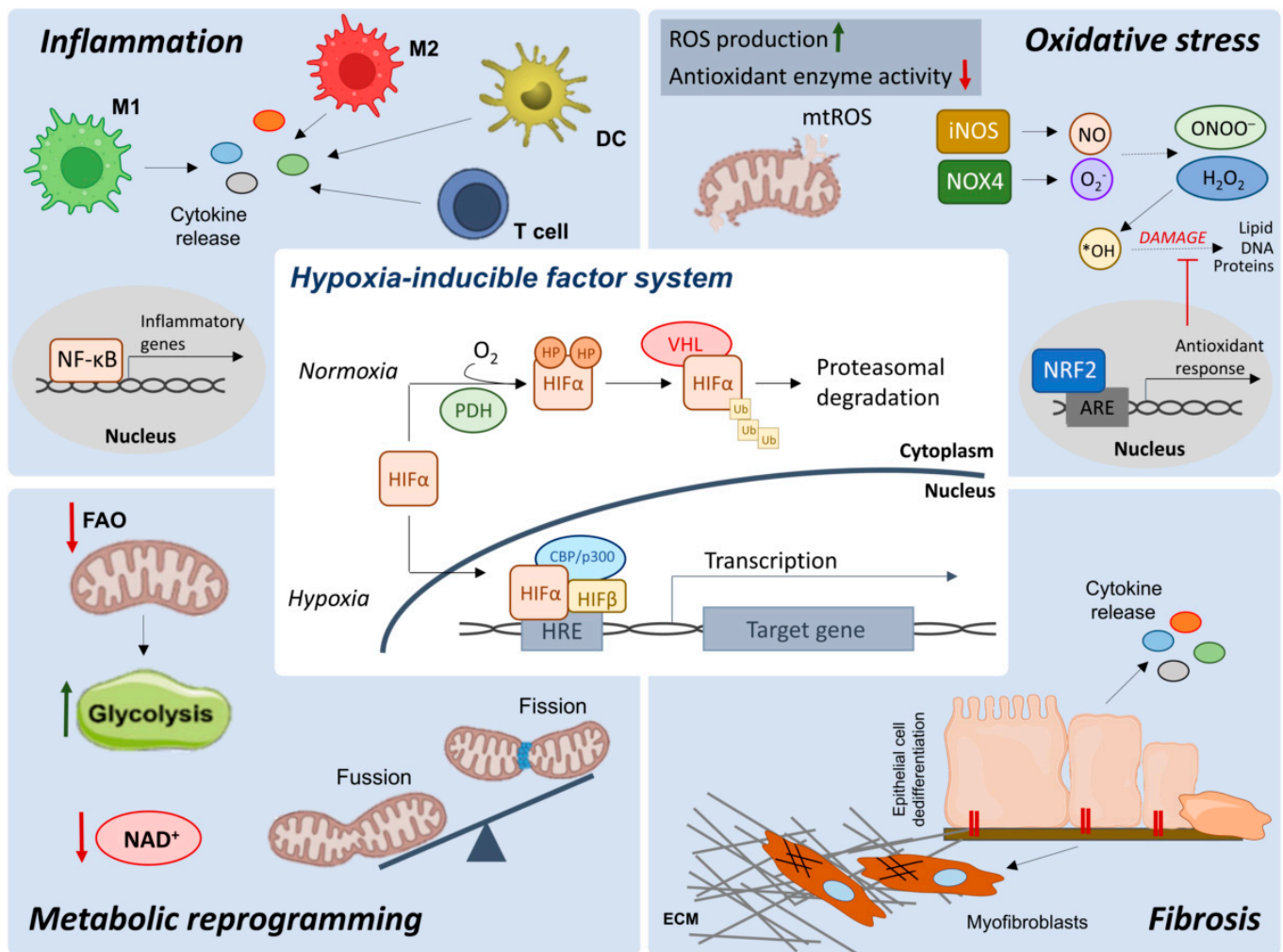


Figure 2. Effects and mechanisms of hypoxia on the progression of CKD. Hypoxia activates the Hypoxia-inducible factor (HIF) system, which triggers a transcriptional adaptive response regulating inflammation, metabolism, oxidative stress and fibrosis. Black arrows and red blunt arrows represent positive and negative regulation, respectively. Green and red arrows represent enhanced and decreased cellular processes, respectively. ARE: Antioxidant response element, CBP/p300: C-AMP-Response Element-binding protein (CREB-binding protein)/binding protein p300, DC: Dendritic cell, ECM: Extracellular matrix, FAO: Fatty acid oxidation, HIF α : Hypoxia Inducible Factor Subunit Alpha, HIF β : Hypoxia Inducible Factor Subunit Beta, HP: Hydroxyproline, HRE: Hypoxia response element, iNOS: Inducible nitric oxide synthase, M1: M1 macrophage type 1, M2: Macrophage type 2, mtROS: Mitochondrial reactive oxygen species, NAD⁺: Nicotinamide adenine dinucleotide, NF- κ B: Nuclear factor kappa B, NRF2: Nuclear factor erythroid 2-related factor 2, PDH: Pyruvate dehydrogenase complex, VHL: Von Hippel–Lindau Tumor Suppressor, Ub: Ubiquitin.

The oxygen-dependent control of the HIF pathway is based on prolyl-4-hydroxylase domain (PHD1–3) enzymes and the asparagine hydroxylase factor inhibiting HIF (FIH) [36]. In normoxia, PHDs hydroxylate specific proline residues on HIF- α , which is recognized by

von Hippel–Lindau tumor suppressor protein (VHL), triggering its proteasomal degradation via polyubiquitination. FIH-dependent asparagine hydroxylation of HIF- α prevents its interaction with CBP/p300, reducing HIF transactivation activity [37]. HIF-PHDs can be inhibited by structural analogs of 2-oxoglutarate, the intermediates of the Krebs cycle succinate and fumarate, ROS and nitric oxide, which results in HIF stabilization in normoxic conditions [38–40].

Accumulating evidence suggests that HIF- α can also be regulated by oxygen-independent degradation mechanisms. Thus, the heat-shock protein (HSP) 90, which stabilizes HIF-1, competes with the receptor of activated protein kinase C 1 (RACK1) to bind to HIF-1 and elongin C, triggering the ubiquitination of HIF-1 [41]. Post-translational modifications of HIF-1 α and HIF-2 α at specific residues through phosphorylation, acetylation, S-nitrosylation and sumoylation can also affect HIF protein stability and activity [42–45]. Additionally, it has been shown that HIF- α is subject to control at transcriptional and translational levels through the nuclear factor- κ B (NF- κ B) or the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathways [46,47]. There is also evidence of HIF-independent gene regulation under hypoxia through more than 20 transcription factors [48–50].

HIF accumulation takes place at certain stages of CKD and is expected to protect from hypoxia. Nevertheless, its activation may be suboptimal [51]. Indoxyl sulfate also upregulates CBP/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2 (CITED2) via post-transcriptional mRNA stabilization, which in turn can inhibit the interaction of p300 with HIF-1 α C-terminal transactivation domain, suppressing HIF-1 activity [52].

2.3. Effects of Hypoxia

2.3.1. Inflammation

Hypoxia is associated with inflammation in models of progressive kidney disease. Immune cells can contribute not only to O₂ deprivation at the site of inflammation, but also alter many of their responses to hypoxia, either promoting or repressing inflammation [5]. Renal inflammation, characterized by the infiltration of macrophages, neutrophils and lymphocytes, is present in kidney disease animal models and human renal biopsies (Figure 2). Inflammatory cells initiate phagocytosis and secrete inflammatory and profibrotic cytokines [53]. TGF- β , mainly released by macrophages and injured tubules, promotes renal wound healing by stimulating myofibroblast proliferation and reducing the production of extracellular matrix-degrading proteinases [54]. Renal cell death occurs by apoptosis or necrosis in response to renal insults, such as ischemia or toxic agents. Damage-associated molecular patterns (DAMPs) generated by necrotic TECs stimulate Toll-like receptors on renal parenchymal cells and local immune cells to produce proinflammatory cytokines and chemokines [55]. The immunomodulatory medication Thalidomide attenuated macrophage infiltration and reduced kidney interstitial fibrosis [56]. KIM-1 expressed by injured tubules mediates small extracellular vesicle uptake by recognizing phosphatidylserine, a ligand of KIM-1, amplifying tubule inflammation induced by hypoxia [57]. Specific deletion of TGF- β RII in macrophages prevents from interstitial fibrosis following renal ischemia–reperfusion injury (IRI) [58]. Interleukin-1 receptor-associated kinase-M is linked to the transformation of macrophages from a M1 inflammatory to an M2 prorepair phenotype. Genetic ablation of this kinase led to a persistent M1 activation and severe fibrosis following IRI [59].

The transcription factor CCAAT/enhancer-binding protein δ (CEBPD) links hypoxia and inflammation in TECs in both acute and chronic hypoxic settings. Even under normoxic conditions, inflammatory stimuli like interleukin-1 can induce CEBPD, increasing HIF-1 expression, which in turn stimulates infiltration/activation of inflammatory cells. Importantly, hypoxia can induce CEBPD expression through NF- κ B-dependent pathways [60]. The effect of HIF seems to largely depend on the target cell type. HIF-1 and HIF-2 activation has particular roles based on the macrophage phenotype, as HIF-1 is more related to M1

and HIF-2 to M2 [61]. In the mouse unilateral ureteral obstruction (UUO) model, HIF activation via myeloid-specific VHL-deletion not only decreased inflammation but had no discernible impact on renal fibrosis [62]. In contrast, global or conditional knockout of HIF in myeloid cells (driven by Lysozyme M promoter which targets macrophages and neutrophils) exhibited more severe inflammation [63]. Under ischemic conditions, neutrophils migrate into the renal interstitium, where they can harm TECs and peritubular capillary endothelial cells by releasing cytokines, chemokines, proteases and ROS. Adenosine 2A receptor agonists lessen neutrophil transmigration and improve renal function [64]. Blocking neutrophil integrin activation prevents neutrophil recruitment and reduces IRI [65]. Hypoxia induces neutrophil viability through HIF-1 α -dependent NF- κ B activity. HIF-1 boosts the expression of antimicrobial molecules in neutrophils [66]. Under hypoxic conditions, it has been demonstrated that the neutrophil-activating and survival factor MIP-1 (macrophage inflammatory protein-1) is induced, acting as an alternative mediator of neutrophil survival [67]. Furthermore, neutrophils also shape the tissue microenvironment by depleting local molecular oxygen [68]. In endothelial cells, inactivation of HIF-2 α , but not HIF-1 α , enhanced inflammatory cell infiltration. This was reversed by neutralizing vascular cell adhesion molecule-1 (VCAM1) and very late antigen-4 (VLA4) using specific antibodies [69]. CD8⁺ T cells immune response is also strengthened by the HIF-1 α induced polarization of Th1 cells to Th2, together with regulatory T cell proliferation [70].

2.3.2. Oxidative Stress

Oxidative stress is a condition where the level of ROS or reactive nitrogen species (RNS) surpasses the cellular counteracting antioxidant capacity to scavenge them. Electrophiles include the superoxide radical, hydrogen peroxide (H₂O₂) and the hydroxyl radical, while RNS, such as peroxynitrite (ONOO⁻), nitrogen dioxide (\bullet NO₂) and dinitrogen trioxide (N₂O₃), are formed by reactions involving superoxide and nitric oxide (\bullet NO) [71]. The \bullet NO radical is produced by three L-arginine-dependent nitric oxide synthase (NOS) isoforms, all expressed in the kidney. It plays a role in controlling hypertension and acting as a powerful vasodilator. These reactive species can react with cellular macromolecules, such as lipids, proteins or DNA, altering their function. They can trigger the oxidation or nitration of amino acids like tyrosine, cysteine, methionine and tryptophan.

Mitochondria electron-transport chain (ETC) leakage, membrane-bound NADPH oxidases (NOXs) and endoplasmic reticulum (ER) are the primary sources of the majority of intracellular ROS [72]. The most abundant endogenous antioxidant is Glutathione (GSH) [73]. Other non-enzymatic antioxidants involve the synthesis of nucleophiles such as ascorbate, tocopherols and retinol. Nuclear factor erythroid 2-related factor 2 (Nrf2)-induced antioxidant protection is the main antioxidative response. NRF2 is sequestered in the cytosol by KEAP1. When ROS interact with certain cysteine residues in KEAP1, NRF2 is able to go into the nucleus and activate cytoprotective genes by attaching to antioxidant response elements (ARE). Other antioxidant enzymes include the NOX:quinone oxidoreductase1 (NQO1), glutathione S-transferase (GSTs), glutathione peroxidase (GPx), catalase and peroxiredoxin (PRx)/thioredoxin (TRx) [74].

Oxidative stress is involved in AKI to CKD progression (Figure 2). Oberg et al. compared the levels of three oxidative stress indicators (plasma protein carbonyl group content, plasma-free F2-isoprostane content and plasma protein reduced thiol content) in patients with stage 3–5 CKD and found that they had greater levels of oxidative stress [75]. The kidney is particularly susceptible to damage from oxidative stress because of its high levels of oxidation inside the mitochondria [76]. The substantial immunological response that occurs in sepsis-induced AKI promotes the activation of inducible NOS synthase and the overproduction of NO, which leads to endothelial damage, localized hypoxia and ROS [77]. Cisplatin-induced AKI is characterized by the generation of mitochondrial ROS (mtROS), reduced mitochondrial membrane potential and mitochondrial swelling [78]. While it is generally accepted that ROS increases during reoxygenation following hypoxia, it is more controversial whether ROS are elevated during hypoxia. Such increased mtROS

and mitochondrial calcium content cause MPTP opening and the activation of different cell death pathways [79]. Additionally, mtROS also stimulates renal inflammation and NLRP3 activation [80]. Consistently, hyperactivation of Nrf2 in tubules halts the progression of tubular damage by suppressing IRI-mediated ROS during the early progressive phase in the IRI model [81]. Studies have reported reduced NO bioactivity in CKD patients [82]. This is due to compromised NO generation, increased metabolism or increased levels of NOS inhibitors. An imbalance of vasoactive substances triggers aberrant intrarenal vasoconstriction, which can also cause chronic hypoxia in the kidney. In addition to constrict glomerular arterioles, Ang II hampers the efficient utilization of oxygen in TECs through the production of oxidative stress by stimulating NADPH oxidase activity. It results in decreased NO bioavailability through peroxynitrite formation [83]. Because NO inhibits mitochondrial respiration, depletion of NO may accelerate mitochondrial respiration and decouple it from chemical energy use, which would result in tissue hypoxia [84]. Kidney damage induced by indoxyl sulfate may also operate through this mechanism [85]. In the hypoxic kidney, the stress-responsive transcription factor FoxO3 is activated in TECs likely as an adaptation to counteract hypoxic insults, attenuating CKD. Hypoxia inhibits FoxO3 prolyl hydroxylation and subsequent degradation, promoting autophagy and reducing oxidative injury [86].

In addition, mitochondrial dysfunction interferes the communication between mitochondria and ER, leading to tubular inflammation and fibrosis. ER controls protein synthesis, folding and degradation through the unfolded protein response (UPR) pathway. It promotes cellular survival by restoring ER and mitochondrial homeostasis through different signaling networks, which include ATF6 p50, XBP1 and ATF4, but if impaired, the UPR induces inflammation and cell death [87].

2.3.3. Metabolic Reprogramming

TECs need a huge amount of energy to cope with their reabsorption function. Although TECs reabsorb a lot of glucose, they barely consume it but are highly dependent on fatty acid oxidation (FAO), which makes them extremely vulnerable to hypoxia [88]. In particular, the mature nephron's inability to produce anaerobic energy in combination with its basal low pO_2 point to the S3 region of the proximal tubule as the main site for hypoxia-based damage [89,90]. During AKI and CKD, TECs are prone to metabolic reprogramming (Figure 2). Although FAO is transiently activated in PTECs (marked by Perilipin 2 (PLIN2) expression, a marker of intracellular lipid droplets) at the earliest stages of IRI and is linked with effective repair [91], its failure is considered a potential pathogenic component in the onset of renal disease. It involves the shift from FAO to glycolysis due to hypoxia, mitochondrial malfunction and disordered nutrient-sensing pathways [92]. HIF-1 α enhances glucose uptake by promoting the expression of glucose transporters. By upregulating pyruvate dehydrogenase kinase (PDK) expression, HIF-1 can also boost lactate dehydrogenase (LDH) expression to promote the conversion of pyruvate to lactic acid and prevent it from entering the TCA cycle. HIF-1 also activates PKM2, the key enzyme in the glycolytic metabolism [93]. These changes are a double-edged role. On the one hand, increased glycolysis acts as a compensatory mechanism for ATP synthesis to maintain the normal function of the surviving TECs, playing also a protective role against antioxidative stress [94]. The activity of hexokinase (HK), a crucial enzyme in glycolysis, was significantly elevated in a sepsis-induced AKI animal model. This increased the flow of the pentose phosphate pathway (PPP), which keeps glutathione in its reduced state, thereby protecting the kidney from peroxide damage [95,96]. On the other hand, long-term shutdown of FAO and enhanced glycolysis lead to a proinflammatory response, lipid accumulation and fibrosis, contributing to AKI to CKD transition [97]. To fulfill the rapid energy demand associated with the ECM synthesis phenotype, myofibroblasts also undergo metabolic reprogramming marked by enhanced aerobic glycolysis [98]. In addition to provide a rapid energy-generating mechanism compared to oxidative phosphorylation (OXPHOS), glycolysis yields by-products such as lactate that control fibrosis [99]. It has been discovered that

chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII), a transcription factor that directly regulates PGC-1 α expression, causes a metabolic reprogramming in myofibroblast that favors glycolysis and the production of profibrotic mediators [100]. Aerobic glycolysis inhibition has evolved as an antifibrotic therapy by reducing myofibroblast activation [101–103].

The pathophysiology of AKI to CKD transition is significantly influenced by the dysregulation of nicotinamide adenine dinucleotide (NAD⁺) metabolism, most likely due to the combination between decreased NAD⁺ synthesis and increased NAD⁺ consumption. NAD⁺ participates in metabolic activities including glycolysis, tricarboxylic acid (TCA) cycle and OXPHOS by acting as an electron carrier and forming nicotinamide adenine dinucleotide (NADH) [104]. NAD⁺ is an essential substrate for a number of crucial enzymes, including sirtuins. It controls mitochondrial homeostasis, cell senescence and DNA repair [105]. Reduced renal NAD⁺ may enhance vulnerability to AKI due to an impaired de novo NAD⁺ production pathway linked to kidney damage or aging [106]. AKI syndrome triggers accelerated consumption of NAD⁺ by poly (ADP-ribose) polymerases (PARP) and CD38 enzymes, contributing to reduce NAD⁺ availability. Treatment with TES-1025, a selective inhibitor of α -amino- β -carbox- γ -muconate- ϵ -semialdehyde decarboxylase (ACMSD), a limiting enzyme in de novo NAD⁺ synthesis, rescued renal NAD⁺ decline and attenuated kidney injury [107,108]. In AKI and CKD models, nicotinamide mononucleotide (NMN) supplementation promoted the NAD⁺ salvage synthesis pathway and resulted in antifibrosis, antiaging and anti-inflammatory benefits [109,110].

Gluconeogenesis is also impaired during AKI. In experimental and human AKI, renal glucose release and lactate uptake were reduced, a metabolic change linked to patient mortality. Approximately 40% of endogenous gluconeogenesis is produced by the kidneys, which is involved in normoglycaemia during fasting and stress conditions. The generation of glucose from lactates is an energy-consuming process [111]. In AKI, severe lack of renal ATP supply is accompanied by NAD⁺ depletion [112]. Therefore, shifts from FAO to glycolysis, with concomitant impaired of NAD⁺ metabolism and gluconeogenesis seem to be cellular adaptations to the pathological environment.

In AKI to CKD transition, TECs display imbalance in mitochondrial quality control, characterized by altered mitochondrial biosynthesis, increased mitochondrial fission, decreased mitochondrial fusion and decreased mitophagy [113–115]. Another significant component that promotes this metabolism reprogramming is maladjustment of the nutrient-sensing mTOR/AMP-activated protein kinase (AMPK) signaling pathways, involved in maintaining renal energy homeostasis. mTOR complex 1 (mTORC1) increases HIF-1 α translation, leading to an increased expression of the glycolytic enzymes HK and PKM2 along CKD progression [116]. When the ATP/AMP ration drops, AMPK increases ATP production by enhancing mitochondrial biosynthesis, FAO and OXPHOS. AMPK also inhibits the mTOR signaling pathway. In the cisplatin-induced AKI model, AMPK activation was reduced, which caused the overactivation of the mTOR signaling pathway and autophagy suppression. By contrast, AMPK activation shielded TECs and protected from fibrosis development in several AKI models [117,118].

Importantly, substantial changes in cell metabolism also accompany the phenotypic and functional alterations during transitions of other cell types involved in CKD. Thus, proinflammatory M1 macrophages primarily rely on glycolysis and have two breaks on the TCA cycle. By contrast, macrophages acquiring a M2 phenotype, with an important role in wound healing and resolving inflammation, are more dependent on OXPHOS. Although the activation of M1-like proinflammatory macrophages may be favored by ROS generation also contributing to their increased glycolysis and TCA blockage via HIF-1 α stabilization, they are also important for M2 macrophage differentiation, suggesting a differential spatial and temporal role [119].

2.3.4. Fibrosis

Hypoxia triggers fibroblast activation which leads to ECM deposition. Fibrosis, in turn, exacerbates hypoxia by reducing the efficiency of oxygen diffusion by extending the distance between capillaries and TECs (Figure 2). Activated HIF binds to the promoters of profibrogenic genes and matrix-modifying factors including matrix metalloproteinase 2, tissue inhibitor of metalloproteinase 1 (TIMP-1), collagen I, plasminogen activator inhibitor-1 (PAI-1) and CTGF, resulting in the accumulation of ECM in the tubulointerstitium [24]. In this line, genetic deletion of HIF-1 α in TECs reduced the number of S100A4-positive fibroblasts [120]. In the endothelium, persistent HIF-1 α expression, induced by specific knockdown of PHD-2, caused endothelial–mesenchymal transition (EndoMT) and renal fibrosis [121]. Hypoxia stimulated endothelial PDGF- β production, triggering the proliferation of mesangial cells [122].

Besides the direct transcription activation of fibrogenic factors, HIF can interact with diverse profibrotic signaling pathways, including TGF- β , Notch, NF- κ B and PI3K/Akt pathways, further regulating renal fibrosis [123]. HIF-1 α can form a complex with Smad family member 3 (SMAD3), enhancing the expression of COL1A2 [124]. Conversely, the interaction between mTORC1 and SMAD3 under TGF- β treatment enhances HIF-1 induction and downstream collagen expression [125]. One possible mechanism is that TGF- β 1-induced SMAD2/3 activation inhibits PHD2 expression [126]. Of importance, translational HIF regulation by TGF- β 1 is cell type-specific. In TECs, HIF-1 α expression is stimulated by TGF- β 1/SMAD3 signaling, while HIF-2 induction is more prevalent in mesangial cells [127,128]. HIF accumulation not only induces TGF- β 1, but also markedly increases Notch3 transcription [121]. Additionally, in the Ang II infusion model of hypertensive CKD, HIF-1 α was demonstrated to be crucial to initiate glomerular injury and renal fibrosis by inducing the expression of vasoactive proteins [129]. Hypoxia causes renal fibrosis by activating the HIF-1 α /HIF-1/NF- κ B signaling, upregulating tissue inhibitor metalloproteinases 1, which may prevent ECM degradation [130]. Furthermore, HIF can also interact with PI3K/Akt to control fibrosis. HIF-1 induction in TECs activates the transcription of Bmi-1, which modulates PI3K/Akt signaling and promotes Snail-mediated TEC dedifferentiation [131].

2.4. Influence of Renal Hypoxia in AKI to CKD Progression

AKI consists in the sudden and persistent impairment of renal function that can be reversible if treated promptly and effectively. Clinical and animal research have demonstrated that AKI can eventually lead to CKD, even if followed by a full recovery of renal function. Of note, AKI severity and the frequency of AKI episodes predict the subsequent onset of CKD [132].

Historically, AKI models have been divided into two categories: ischemic and non-ischemic models [133]. However, hypoxia and HIF expression are not limited to the acute stage of ischemic AKI. HIF staining disappears 24 h after AKI induction. It is interesting to note that HIF reappeared between days 3 and 7 after AKI induction in the IRI model [33,134]. Human kidney transplant recipients have also reported similar delays in HIF activation and up to 5 weeks after an AKI episode [135]. These findings might potentially point to hypoxia as a side effect of tissue regeneration following kidney transplantation.

In response to nitric oxide synthase inhibition, folic acid nephropathy and IRI, mouse kidneys show a decrease in microvascular density. Although it is likely that HIF increases angiogenic factors like VEGF, which restore capillary density, this adaptation process typically fails because injured TECs are unable to produce sufficient VEGF [136]. Of note, prolonged hypoxia leads to the renal downregulation of the proangiogenic isoform 164 and the upregulation of the dys-angiogenic isoforms 120 and 188 of VEGF-A [137]. The inflammatory environment may contribute to the suppression of VEGF expression. Antiangiogenic factors (e.g., thrombospondin 1 and endostatin) are increased in several kidney disorders [138,139]. Furthermore, the incapability of endothelial progenitor cells potentially underlies poor capillary repair [140]. Complementarily, Kramann et al. proposed that the

mechanism underlying capillary rarefaction is pericyte detachment from nearby capillary endothelial cells [141].

This persistent hypoxia induces several pathological processes including proinflammatory adhesion molecules and chemokines, which result in the accumulation of immune cells in the kidney [142]. Hypoxia induces leukocyte adherence to endothelial cells by activating 2-integrin [143]. Palm et al. demonstrated that dinitrophenol-induced renal hypoxia led macrophages to gather in the kidney [144]. Further, Polichnowski et al. suggested that capillary loss causes localized hypoxia that limits tubule regeneration [145]. Many in vitro studies have also shown that hypoxic injury causes apoptosis and TEC dedifferentiation. In AKI, recruited inflammatory cells and dedifferentiated TECs produce profibrotic cytokines, such as TGF- β , contributing to activate fibroblasts [146]. Under hypoxic conditions, these cells produced more collagen and tissue inhibitor of metalloproteinase 1 [24]. In turn, tubulointerstitial fibrosis exacerbates hypoxia because it widens the distance between capillaries and TECs, decreasing the effectiveness of oxygen transport [130]. CKD progresses as a result of the vicious cycle of tubulointerstitial fibrosis and hypoxia (Figure 1).

Increasing evidence has shown that proinflammatory and profibrotic gene expression is also regulated by hypoxia-induced epigenetic alterations. HIF-1 binds to the promoters of histone demethylases JMJD1A and JMJD2B, inducing their expression. In turn, it increases the expression of downstream genes by reducing promoter histone methylation [147,148]. In particular, chromosomal conformation capture tests demonstrated that the interaction between HIF-1 and lysine-specific demethylase 3A may cause a significant shift in chromatin conformation, leading to the erasure of suppressive histone marks [149]. Three weeks after IRI, proinflammatory and profibrotic genes, such as monocyte chemoattractant protein-1, TGF- β 1 and collagen III, showed increased expression along with enhanced level of gene-activating histone modification (e.g., H3K4m3 or H3K9/14ac). Promoters of those genes also showed increased binding of chromatin-remodeling enzymes, such as Brahma-related gene 1 [150]. Zager et al. showed that IRI triggers endothelin-1 (ET-1) expression, which leads to gene-activating histone modifications close to the transcriptional start site of the ET-1 gene. This may exacerbate renal hypoxia by inducing vasoconstriction [151].

3. Hypoxia as a Therapeutic Target in CKD

Given that renal hypoxia is a final common path in CKD development and that the genetic suppression of the HIF pathway aggravates renal injury, HIF activation/stabilization is suggested as a potential therapy for CKD (Table A1) [152]. Dimethyloxalylglycine (DMOG), a competitive inhibitor of HIF- α prolyl hydroxylase (HIF-PH), improved proteinuria, mitochondrial function and cell survival in the rat subtotal nephrectomy model [153]. In hypertensive rats, DMOG also reduced glomerulosclerosis, fibrosis and proteinuria [154]. This effect was not observed in DMOG-treated animals lacking endothelial HIF-2 [69]. In the streptozotocin (STZ)-induced diabetic nephropathy rat model, cobalt chloride (CoCl₂), another inhibitor of HIF hydroxylation, improved GFR, albuminuria and tubulointerstitial damage [155]. Additionally, CoCl₂ had a protective effect in the Thy1 nephritis rat model, in the subtotal nephrectomy rat model and in Type 2 diabetic nephropathy [156,157]. Beside the beneficial effects of cobalt in experimental animals, long-term administration to humans has adverse effects. In this regard, the new HIF-PHD inhibitors (HIF-PHIs) roxadustat, daprodustat, vadadustat and enarodustat improved renal anemia and exerted a positive effect on the hemoglobin rate in CKD patients [158–164]. Enoradustat also reduced albuminuria and alleviated renal damage in the diabetic nephropathy ob/ob model [165]. Enoradustat was similarly protective in the rat subtotal nephrectomy model, decreasing fibrosis and inflammation [166].

While the pre-stimulation of the HIF pathway both genetically and pharmacologically reduces AKI episodes, its beneficial role in CKD progression is still controversial and mainly relies on pre-ischemic activation [167]. Schley et al. found that HIF-PHIs cause renal mononuclear phagocytes to adopt an anti-inflammatory phenotype [168]. By contrast, some other CKD preclinical studies showed that HIF-signaling activation in the kidney

appears to be deleterious, as evidenced the stabilization of HIF-1 by genetic deletion of VHL in a 5/6 renal ablation model and the administration of an anti-HIF-1 α drug in the UUO model [169]. Genetic endothelial-specific knockout of PHD2 (leading to constitutive HIF-1 α and HIF-2 α stabilization) also induced fibrosis and worsened kidney damage [121]. Similarly, genetic HIF-2a overexpression in the tubules exacerbated renal fibrosis [170]. Therefore, the role of HIF activation is likely to depend on the pathological context, cell type and timing. Additional investigation is necessary to clarify the implications and mechanisms of HIF-PHIs on CKD progression.

Strategies directed towards the preservation of peritubular capillaries early in the AKI process lead to maintaining renal oxygen levels and exert a protecting role in AKI to CKD transition. Thus, treatment with the angiogenic factors VEGF-121 or angiopoietin-1 administered early during injury suppressed AKI to CKD transition in the IRI model, by attenuating the loss of peritubular capillaries and subsequent tubulointerstitial fibrosis [171–173]. Protein kinase C comprises a superfamily of serine-threonine kinases with diverse functions in signal transduction and cellular regulation. Inactivation of PKC isoforms were shown to alleviate many diabetes- or hyperglycemia-associated vascular dysfunctions in the kidney [174]. Blocking PKC α signaling with the chemical inhibitor Go6976 also inhibited fibroblast activation and renal fibrosis [175]. Targeting fibrosis has been mainly addressed by blocking the TGF- β signaling pathway. It includes several strategies including Smad agonists/inhibitors and neutralizing antibodies against receptors/cytokines. However, the pleotropic nature of this pathway has limited their application due to potential side effects [176].

SGLT2 inhibitors (SGLT2is), a new class of antihyperglycemic drugs which act by targeting glucose reabsorption, also lessen principal kidney and cardiovascular problems in CKD patients [177]. Studies have suggested that SGLT2i may reduce cortical oxygen consumption. Reduced oxygen pressure could activate the HIF-signaling pathway and imitate systemic hypoxia [178,179]. In the IRI model, SGLT2i was also discovered to prevent renal capillary rarefaction and subsequent hypoxia and fibrosis. However, further research is required to decipher the renoprotective mechanisms of SGLT2 inhibition associated with tissue oxygenation [180].

Multiple substances directed to target mitochondria and correct imbalanced bioenergetics seem to prevent CKD progression. The PPAR α agonists fenofibrate and clofibrate attenuated acute renal tubule injury by increasing FAO rate and inhibiting nuclear factor kappa-B (NF- κ B) activity, oxidative stress, cellular apoptosis and fibrosis [181,182]. Additionally, promoting mitochondrial biosynthesis is a promising approach to block AKI to CKD progression [183]. In several AKI models, resveratrol (an SIRT1 agonist) and AICAR (an AMPK agonist) improved mitochondrial fitness and protected from renal fibrosis [184,185]. Mdivi-1, an inhibitor of mitochondrial fission protein DRP1, exerts a beneficial effect in several kidney diseases, attenuating tubular cell apoptosis and maintaining mitochondrial structure [186]. Enhancing mitophagy in TECs is also an effective strategy to treat AKI to CKD progression [115]. Berberine (BBR), a quaternary ammonium isoquinoline alkaloid, reduced cisplatin-induced TEC cytotoxicity by inducing mitophagy through the PINK1/Parkin signaling pathway [187]. Finally, a novel mitochondrial protectant, SS-31 (D-Arg-dimethylTyr-Lys-Phe-NH₂), specifically binds to cardiolipin in the mitochondrial inner membrane to stabilize the mitochondrial structure, reducing ROS production. It was shown to prevent tubular apoptosis, interstitial fibrosis and glomerulosclerosis [188,189]. Although early restoration of TEC metabolism offers a promising therapeutic approach for AKI, the translation of drugs that target mitochondria and bioenergetics into the clinic is limited due to adverse off-target effects [190]. In addition, available studies have focused only on TECs, so whether other renal cell types undergo metabolic changes needs to be further explored.

Targeting hypoxia-associated oxidative stress in CKD using antioxidants has also emerged as a potential therapeutic strategy. Nrf2–ARE axis activation triggers strong antioxidative effects [191]. Therefore, the pharmacological stimulation of this system may be a promising target. Bardoxolone methyl, a Nrf2 activator that inhibits Keap1 through modifying Keap1-cysteine-151, was reported to increase glomerular filtration rate (GFR) in diabetic CKD patients on different clinical trials [192]. Inhibitors of xanthine oxidase, an enzyme involved in purine catabolism producing ROS, ameliorate renal damage and reduce uric acid levels, proinflammatory mediators and ROS [193]. That is the case of allopurinol, which slows down renal disease progression in CKD patients [194]. The inhibition of NOX enzymes has emerged as a promising approach to target ROS. Although NOX2 is also expressed, NOX4 is the most prevalent type in the kidney. [195]. Oral administration of APX-115, a pan-inhibitor of NOX enzymes, reduced fibrosis in the murine model of STZ-induced kidney disease [196]. Setanaxib (GKT137831), a first-in-class, dual inhibitor of NOX1/4, also showed renoprotective effects in this model [197]. Treatment of db/db mice with GKT136901, a NOX1/NOX4 inhibitor, blocked renal NOX4-dependent fibrotic signaling after exposure to high glucose [198]. Of note, H₂S donors, such as sodium thiosulfate, maintain redox homeostasis by ROS scavenging and modifying cysteine residues on key signaling molecules, which exerts renal protection [199,200]. Vitamin E reduced cardiovascular disease and myocardial infarction events in hemodialysis patients [201]. A moderate dose of Vitamin C might be beneficial for CKD patients with iron deficiency [202]. CoQ10 supplementation restored the metabolic profile of CKD patients [203]. In renal IRI and Ang II-infused mouse models, pre-administration of MitoQ reduced oxidative damage and apoptosis by reducing aberrant mitochondrial fission and restoring mitophagy by activating the NRF2 pathway [204,205]. Plant-derived polyphenols, such as quercetin, curcumin and resveratrol, have also emerged as promising antioxidant agents with renoprotective effects [206]. Rassaf et al. discovered that supplementation with cocoa flavanol resulted in a reduction in endothelial dysfunction in ESRD patients [207]. However, well-powered clinical studies are still needed to obtain a meaningful evaluation of the effects of Nrf2 system-targeting compounds.

4. Conclusions

Renal hypoxia has emerged as a key mediator of CKD progression. Impaired oxygen supply leads to capillary rarefaction, tubular dedifferentiation, inflammatory reactions and fibrosis that in turn, contribute to worsen hypoxic conditions [208]. HIF is a master transcriptional regulator of cellular adaptation to hypoxia. Given experimental data suggesting suboptimal HIF activation in CKD, its stabilization is a novel and promising therapeutic target. Nevertheless, the majority of approaches are preventive, in which HIF is activated before the onset of AKI or CKD. Therefore, therapeutic strategies, in which HIF is activated after AKI occurs would be more clinically relevant to target AKI to CKD progression [209]. Due to discrepancies from such strategies, numerous challenging questions have emerged: what is the mechanism that links hypoxia and renal inflammation in the kidney? What is the cell type-specific spatiotemporal responsive pattern to hypoxia in the kidney? Is it possible to predict the outcome of kidney damage in response to hypoxia by developing early biomarkers and better resolution methods to monitor hypoxia? And, what is the long-term impact of the novel class of medications targeting HIF-PHIs on the development of AKI-CKD, considering its effectiveness in treating anemia?

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Appendix A

Table A1. Pharmacological agents modulating the HIF pathway in rodent models of CKD.

Treatment	Mecanism of Action	Effects	Experimental Model	Reference
CoCl ₂	Transcriptional HIF-1 α upregulator	- Improved renal function. - Attenuated renal tubulointerstitial fibrosis.	Subtotal nephrectomy in rats	[210,211]
		- Reduced proteinuria and histological kidney injury.	Hypertensive type 2 diabetic rats (SHR/NDmcr-cp)	[158]
		- Increased renal function. - Reduced proteinuria and tubulointerstitial damage.	Streptozotocin-induced diabetic nephropathy rats	[156]
		- Attenuated tubulointerstitial fibrosis.	Uninephrectomized Thy1 nephritis rats	[157]
DMOG	Prolyl hydroxylase inhibitor	- Improved renal function, proteinuria and fibrosis.	DOCA-salt hypertensive rats	[155]
		- Attenuated glomerulosclerosis and interstitial fibrosis.	Dahl salt-sensitive rats	[212]
Deferoxamine	Iron chelator, Transcriptional HIF-1 α upregulator	- Prevented tubulointerstitial fibrosis.	Unilateral ureteral obstruction	[213]
Enarodustat	Prolyl hydroxylase inhibitor	- Reduced albuminuria and endothelial damage.	BTBR ob/ob mice	[166]
		- Attenuated fibrosis and inflammation.	Subtotal nephrectomy in rats	[167]
Roxadustat	Prolyl hydroxylase inhibitor	- Improved renal function. - Reduced tubulointerstitial damage.	Adenine-induced nephropathy	[169]
YC-1	HIF-1 β inhibitor	- Reduced ECM accumulation, albuminuria and oxidative stress.	Type 1 diabetic mouse model OVE26	[214]
Zinc	Blocks nuclear translocation of HIF-1 β	- Attenuated tubular dedifferentiation and tubulointerstitial fibrosis.	Streptozotocin-induced diabetic nephropathy rats	[215]

The studies showing a protective role of HIF activation are highlighted in green and those with a detrimental role are highlighted in red. DMOG: Dimethylaloxoylglycine, DOCA: Deoxycorticosterone acetate, ECM: Extracellular matrix, HIF α : Hypoxia Inducible Factor Subunit Alpha, HIF β : Hypoxia Inducible Factor Subunit Beta, YC-1: 3-(5'-hydroxymethyl-2'-furyl)-1-benzyl indazole.

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