Proteostasis in Kidney Disease&Fibrosis

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Pathological insults usually disturb the folding capacity of cellular proteins and lead to the accumulation of misfolded proteins in the endoplasmic reticulum (ER), which leads to so-called “ER stress”. Increasing evidence indicates that ER stress acts as a trigger factor for the development and progression of many kidney diseases. The unfolded protein responses (UPRs), a set of molecular signals that resume proteostasis under ER stress, are thought to restore the adaptive process in chronic kidney disease (CKD) and renal fibrosis. Furthermore, the idea of targeting UPRs for CKD treatment has been well discussed in the past decade.

Keywords: unfolded protein responses ; endoplasmic reticulum stress ; fibrosis ; kidney ; proteostasis

1. Introduction

Kidney diseases have recently received considerable attention because the renal function is vulnerable to pathogenic insults, including inflammation, hypoxia, hypertension, and aging. Once acute kidney injury (AKI) occurs, the event frequently leads to the progression of chronic kidney disease (CKD) despite a transient recovery from AKI [1]. Renal tubulointerstitial fibrosis is a common pathway of advanced CKD, which is associated with vasoconstriction, capillary obliteration caused by fibrotic expansion, and finally the formation of a hypoxic microenvironment that worsens renal function [2][3].

There is accumulating evidence indicating that the disruption of endoplasmic reticulum (ER) homeostasis is involved in various pathological processes, including cancer, metabolic diseases, diabetes, neurodegenerative disorders, and liver dysfunction [4]. The unfolded protein responses (UPRs) signaling activated by the ER stress participates in the progression of AKI and CKD [5]. In addition, ER stress is also involved in the progression of organ fibrosis, including those of the kidney, liver, and lung [6]. Because of the limited therapeutic options for the retarding of CKD progression, the modulation of UPRs signaling has become an attractive target for drug discovery [7]. In this mini-review, we discuss the role of UPRs in renal diseases and renal fibrosis, highlight the therapeutic potentials of the modulation of UPRs and the proteostasis of ER, and, in particular, emphasize the role of inositol-requiring protein 1-X-box-binding protein 1 (IRE1-XBP1) signaling.

2. Fundamental Roles of ER Stress and Unfolded Protein Responses

The ER is the organelle where most secretory and transmembrane proteins are synthesized, modified, and folded into their correct conformations. Since the ER plays such an essential role in the maintaining of proteostasis, it must optimally control the quality of protein folding [8]. However, the folding capacity of the ER is susceptible to environmental stress, such as inflammation, oxidative stress, infection, or the deprivation of nutrients, which leads to the abundant accumulation of misfolded or unfolded protein in the ER, which is hence termed the “ER stress” [9]. Restoring the proteostasis of the ER will initiate the signaling of UPRs, thereby reducing protein load, increasing folding ability, or triggering cell apoptosis for as long as overwhelming ER stress persists [8]. Three ER transmembrane proteins, including IRE1, pancreatic eukaryotic translation initiation factor 2-alpha kinase (PKR-like protein kinase, PERK), and activating transcription factor 6 (ATF6), mediate the transduction of UPRs signaling. In normal proteostasis, the immunoglobulin heavy-chain binding protein (BiP) will conjugate with these three transmembrane proteins, and no UPRs cascade will be initiated. When ER stress occurs, BiP acts as an endogenous chaperon that binds to misfolded proteins, and therefore, detaches from the UPRs initiators, resulting in the activation of UPRs signaling [10].

Upon ER stress, IRE1 is activated after the dissociation of BiP, which leads to the conformational change of IRE1. This promotes its dimerization and trans-autophosphorylation, followed by activation of the kinase and RNase domains [11][12]. XBP1 RNA is spliced by unconventional endonuclease, causing a frameshift and generating spliced XBP1 (XBP1s), which possesses a completely different function from its intact form (XBP1u) [13]. XBP1s acts as a transcription activator, upregulating genes that encode ER-associated degradation (ERAD) and chaperone [14][15]. However, the overwhelming

level of ER stress induces the activation of the kinase domain, and then recruits tumor necrosis factor receptor (TNFR)-associated factor-2 (TRAF2), before activating the signaling of c-Jun amino-terminal kinases (JNK), which are pro-apoptosis mediators [16]. In addition, hyper-activation of IRE1α is reported to activate regulated IRE1α-dependent degradation (RIDD) and digest a subset of mRNAs that encode secretory proteins [17][18].

The manner of activation of PERK is similar to the way in which IRE is activated. After dimerization and trans-autophosphorylation, PERK suppresses global protein translation by phosphorylating the α subunit of eukaryotic translation initiation factor-2 (eIF2α) [19]. However, ATF4, a critical transcriptional regulator in the PERK-eIF2α pathway, is upregulated by ribosomal skipping [20]. Following the activation of downstream stress-induced redox proteins, C/EBP-homologous protein (CHOP) [21], which is well recognized as a pro-apoptotic protein that mediates UPR-related cell death [22], directly activates both growth arrest and DNA damage-inducible protein-34 (GADD34) [23], the protein that dephosphorylates the phospho-eIF2α in cells under ER stress and helps cells to recover from translational inhibition [23].

Activated ATF6 translocates from the ER to the Golgi apparatus, and is cleaved by site-1 and site-2 proteases in the Golgi apparatus [24][25], thereby generating the cleaved fragment of ATF6 (cATF6), and then cATF6 enters the nucleus to activate the genes that enhance protein folding, including BiP, GRP94, calreticulin, protein disulfide isomerase (PDI), and XBP1 [26][27][28][29].

The three-branch axis orchestrates the process of UPRs, and their interdependency in terms of regulation is well documented. For instance, the downstream target genes of ATF6 can be compensated by XBP1 during acute silence of ATF6 [30]. Inhibition of PERK leads to the compensatory activation of XBP1s, and the inhibition of IRE1α contributes to the sustained activation of PERK and CHOP [31]. In addition, hyperactivation of IRE1α is found in the XBP1 deletion hepatocyte [32]. Recent evidence demonstrated that cell fate is determined by elaborate ER compensation during ER stress.

3. Homeostatic Role of Proteolysis through Adaptive UPRs Activation in Disease Progression

ERAD plays a pivotal role in the removal of misfolded protein to maintain the homeostasis and cell survival of ER. The process of ERAD is initiated by unfolded substrate recruitment, assisted by chaperones such as Bip and the ER degradation-enhancing alpha-mannosidase-like protein (EDEM) protein family. The tagged protein is eventually degraded by the 26S proteasome and resolves ER stress [33][34]. However, it may shut down the capacity of ERAD and activate apoptotic ER stress during the overloading of misfolded/unfolded proteins, as well as during oxidative stress or heat shock states [35]. Various ERAD-deficient mouse models developed organ dysfunction, including enteritis, obesity, and glucose intolerance [36][37][38]. In addition, ERAD inhibition was identified as a therapeutic target in cancer treatment [39][40]. Furthermore, the enhancement of ERAD through the overexpression of XBP1s reduced amyloid β-peptide accumulation in an Alzheimer's disease model [41][42].

4. ER Stress-Mediated Autophagy and Proteostasis

There is strong evidence supporting the crosstalk between ER stress and autophagy [43][44][45]. Autophagy is triggered by a mechanistic rapamycin (mTOR) inhibition target and involves sequential steps, including the initiation of phagophore, which begins with Unc-51-like autophagy activating the complex formation and nucleation of kinase 1 (ULK1). Then, the autophagosome membrane elongation is assisted by the conjugation of autophagy-related protein (ATG) to LC3 phosphatidylethanolamine (PE) and the lysosome, and finally, proteolytic degradation is initiated [46].

The interplay between ER stress and autophagy has been frequently mentioned. For example, the accumulation of cytosol calcium from ER will activate UPRs, followed by the inhibition of mTOR and the induction of autophagy [47]. Margariti et al. and Ogata et al. demonstrated that autophagy transcriptionally induced the activation of beclin-1 via the IRE1/XBP1s and IRE1/JNK axis [48][49]. B'chir et al. elegantly showed that induction of PERK/eIF2α/ATF4 axis is essential for ATGs genes expression [50]. Furthermore, Fang et al. and Qi et al. showed that the chemical chaperone 4-PBA and TUDCA can attenuate STZ and obesity-induced diabetic nephropathy, extracellular matrix deposition, and autophagy in an ER-stress-dependent manner [51][52]. All of the above-mentioned reports support the connection between ER stress and autophagy.

5. UPRs and Systemic Fibrosis Progression

Many studies proposed the relationship between UPRs and organ fibrosis [6][53]. Familial interstitial pneumonia (FIP), a class of interstitial pneumonitis that may be caused by the genetic mutation in surfactant protein C (SPC) [54], suggests a potential connection between organ fibrosis and ER stress. SPC is secreted by type II alveolar epithelial cells in order to maintain alveolar distensibility. In vitro studies revealed that the mutation of SPC in the carboxyl domain leads to its accumulation, in a misfolded form, in the ER lumen [55]; furthermore, tissue samples from FIP patients with SPC mutation showed prominent expression of BiP, and XBP1 expression co-localized with fibrotic areas [56].

In murine models of cardiac fibrosis, subcutaneous injection of isoproterenol and angiotensin II-induced fibrosis activated UPR signaling and upregulated the pro-apoptotic expression of CHOP. In these models, the severity of fibrosis was attenuated through the administration of chemical chaperone 4-phenylbutyric acid (4-PBA) [57][58].

6. UPRs in Renal Disease and Fibrosis

Renal fibrosis is the final common pathway of CKD and end-stage renal disease (ESRD) [59], which results from the loss of parenchymal due to the occurrence of natural senescence, diabetes, or acute kidney insults. It has been well documented that AKI is recognized as a cause of long-term risk of CKD or ESRD and maladaptive repair of kidney injury, leading to renal fibrosis and the transition from AKI to CKD [60][61]. Myofibroblasts play a critical role in the inducing of excessive deposition of the extracellular matrix, which contributes to renal fibrosis. Myofibroblasts can originate from the activation of renal interstitial fibroblasts, perivascular fibroblasts, pericytes, and bone marrow-derived mesenchymal cells, as well as the transition of endothelial cells or tubular epithelial cells [62][63][64][65][66]. Recent studies revealed that perivascular fibroblasts and pericytes, but not injured tubular epithelial cells, transdifferentiate into myofibroblasts and contribute to fibrosis in renal fibrosis animal models. However, an emerging concept is that kidney damage caused by AKI or unresolved injuries leads to prolonged cell arrest in the cell cycle G2/M phase and leads to the appearance of profibrotic and proinflammatory features in tubule cells. Profibrogenic growth factors and inflammatory cytokines secreted from injured tubules can stimulate the proliferation of fibroblasts and the production of extracellular matrix, and eventually contribute to progressive renal fibrosis. In addition, many publications also revealed that UPRs signaling is involved in the progression of renal diseases, which is triggered by hypoxia, oxidative stress, inflammation, high glucose, and functional genetic deficiency of the glomerular protein [67].

6.1. Disturbance of UPR Contributes to AKI-to-CKD Transition

Renal ischemia-reperfusion injury is a common cause of AKI that results in hypoxia, and ER stress is well recognized as the initial response to ischemia-reperfusion injury [68][69]. A calcitonin/calcitonin gene-related peptide, namely intermedin, ameliorates renal ischemia-reperfusion injury by inhibiting ER stress-mediated apoptotic signaling, for example, the expression of CHOP and caspase-12 [70]. The unilateral ureteral obstruction (UUO) model activated all three effectors of the UPR signaling during the development of renal fibrosis. The pro-apoptotic signals, such as CHOP, caspase-12, JNK, and Bax, were also increased [65]. Furthermore, Fan and Xiao et al. showed that the dysregulation of UPRs was correlated to the severity of the progression from AKI to CKD in humans, with upregulated expression of Bip, p-PERK, and CHOP and reduced expression of XBP1s in patients with progressive AKI renal biopsy [71]. Jao et al. revealed that the dysregulation of UPRs induced the accumulation of lipids, as well as renal fibrosis [72]. The renal fibrosis induced in the UIRI mice model coincides with the accumulation of lipids and the activation of ATF6 in tubular epithelial cells. Furthermore, ATF6 knockout mice demonstrated less tubulointerstitial fibrosis and lipid accumulation through the activation of PPARα.

The production of reactive oxygen species (ROS) during renal ischemia-reperfusion injury also causes the pathogenesis of CKD progression [73]. Antioxidant therapy for CKD patients showed significant benefits, including attenuation of the risk of ESRD development, reduced serum creatinine levels, and improved creatinine clearance [74]. The production of ROS interferes with cellular redox-dependent metabolism and protein-folding capacity, resulting in the accumulation of misfolded proteins in the ER [75]. The antioxidative effects of UPRs were also found during the stimulation of cells against ROS [76]. Nuclear factor E2-related factor 2 (Nrf2) is an antioxidative transcription regulator that resists oxidative stress through the activation of antioxidative genes, such as catalase, heme oxygenase-1 (HO-1), and superoxide dismutase [77]. In terms of the connection between Nrf2 and three branches of UPRs initiators, it was demonstrated that Nrf2 is the downstream target of the ATF6 [78], IRE1/JNK [76], and PERK pathways [79]. The PERK-Nrf2 pathway, for example, plays an essential role in the maintenance of redox homeostasis, as shown by the fact that a deficiency of PERK leads to the accumulation of ROS in cells [80]. Cadmium induces kidney injury through the generation of ROS and leads to ER stress-mediated apoptosis [81]. This evidence suggests that ER stress is an important pathogenic mediator of renal diseases.

7. Therapeutic Strategies: Targeting the IRE1-XBP1 and PERK-eIF2α Axis

7.1. IRE1-XBP1 Axis of UPRs

The XBP1 arm of the UPRs is generally recognized as cytoprotective. As mentioned above, the three UPRs branches are all activated in the UUO model [65]. In this model, XBP1s has been downregulated during the development of renal fibrosis, which ARB could reverse. Somlo and colleagues reported that site-specific deficiency of XBP1 in podocytes resulted in severe albuminuria, glomerulosclerosis, and kidney fibrosis in a Sec63 and XBP1 double knockout model [82][83]. In this first part of the study, the authors demonstrated the accumulation of unfolded proteins without proteinuria or pathological features in podocyte-specific Sec63 or XBP1s single knockout mice. However, podocyte-specific Sec63 and XBP1s double-knockout mice developed defects in the integrity of the glomerular filtration barrier and progressive tubulointerstitial fibrosis in association with the loss of podocytes, which occurred through the activation of the JNK-apoptotic pathway in 2-month-old mice. Moreover, the re-expression of XBP1s in vivo completely rescues chronic tubulointerstitial kidney injury in XBP1 and Sec63 double knockout mice. Madhusudhan et al. also revealed an essential role of XBP1 in DN. They demonstrated that sXBP1 lies downstream of insulin signaling, and attenuates insulin signaling in podocytes through the genetic ablation of the insulin receptor or the regulatory subunits phosphatidylinositol 3-kinase (PI3K) p85α or p85β, which impair sXBP1 nuclear translocation and exacerbate DN [84]

6.2. Dysregulation of UPR Mediates Renal Fibrosis in Diabetic Nephropathy and Podocyte Defect Mice Model

Diabetic nephropathy (DN) accounts for up to 40% of incident ESRD [85]. In the streptozotocin (STZ)-induced DN model, the upregulation of BiP and CHOP, and the activation of PERK signaling, are observed in 22-month-old mice with DN accompanied by tubulointerstitial fibrosis and extensive inflammatory cell infiltration [86]. The renal renin-angiotensin system (RAS) is well known for governing blood pressure and the homeostasis of target organs. In the cascade of RAS, angiotensin II is the key regulator that contributes to vasoconstriction. In addition, the proinflammatory and profibrogenic effects of angiotensin II are widely discussed in the progression of CKD [87]. Therefore, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) are the standard treatments for hypertension or heart failure patients. Evidence showed that ACEIs reduce the apoptosis of renal tubular cells and suppress the signaling of UPRs, as demonstrated by, for example, the activation of phospho-eIF2α and phospho-PERK in STZ-induced diabetic rat models [88]. Human kidney biopsy samples demonstrated that diabetic nephropathy had higher expression of BiP, XBP1, and CHOP, which is consistent with in vitro findings. In addition, albumin and high glucose administration induced the activation of ER stress in human and rodent renal tubules [89]. Furthermore, the deletion of podocyte-specific IRE1a and XBP1s in mice led to more severe cases of albuminuria, glomerular basement membrane thickening, and ER stress induction [84][90].

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