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Endoplasmic Reticulum: The Master Regulator of Stress Responses in Glomerular Diseases

Reiko Inagi

*Division of Nephrology and Endocrinology,
University of Tokyo School of Medicine, Hongo Bunkyo-ku, Tokyo,
Japan*

1. Introduction

The glomerulus is composed of glomerular resident cells, which include podocytes, mesangial cells, and glomerular endothelial cells, and is responsible for glomerular filtration. A range of pathogenic conditions can cause structural and functional damage to these glomerular cells, including hypertension, diabetes, and inflammation; these induce glomerulonephritis, which in turn leads to end-stage renal failure. Extensive investigations have uncovered the molecular mechanisms by which glomerulonephritis progresses, including the contribution of cellular stress signals induced by oxidative stress, hypoxia, or inflammation.

The endoplasmic reticulum (ER) is an organelle that maintains protein homeostasis, which includes regulation of the concentration, conformation, folding, and trafficking of client proteins. ER dysfunction causes an imbalance between protein-folding capacity and protein-folding load, a condition referred to as ER stress. This stress triggers the accumulation of unfolded proteins in the ER and subsequent activation of an intracellular stress signal, the unfolded protein response (UPR). ER stress and the UPR can result from various disturbances, such as hypoxia, glucose deprivation, and oxidative stress. The UPR, which initially serves as an adaptive response to maintain the homeostasis of the ER, induces ER resident chaperones, which act to enhance protein-folding capacity, the activation of pathways that degrade unfolded proteins accumulated in the ER (ERAD), and the attenuation of translation. The physiological level of the UPR transforms to a pathogenic response when ER stress is overwhelming or prolonged. At its pathogenic level, the UPR produces an apoptotic response, namely the activation of UPR-related proapoptotic molecules and inhibition of anti-apoptotic molecules. Accumulating evidence demonstrates that ER stress contributes not only to protein conformational diseases, but also to the progression of various diseases, including cardiac disease, diabetes, cancer, and kidney disease. Given the linkage of ER stress with oxidative stress or hypoxia, both of which are pathogenic, it is hardly surprising that the potential pathophysiological significance of ER stress is evoked across a wide range of diseases.

Recent evidence demonstrates that ER stress is a significant contributor to glomerulonephritis. Podocytes play an important role in the glomerular filtration barrier that is maintained by filtration slits (slit diaphragm), and express various proteins associated

with the slit diaphragm. Congenital nephrotic syndrome is caused by genetic mutation of slit diaphragm-associated molecules, such as nephrin and α -actinin-4. These mutated proteins are misfolded and accumulated in the ER of podocytes, and thereby induce the UPR, namely ER chaperone expression and proapoptotic gene induction. Mesangial cells are responsible for the structural and functional maintenance of glomerular tufts and mesangial cell damage in glomerulonephritis is associated with induction of the UPR, which involves ER chaperone expression and the attenuation of protein translation. The induction level of the UPR increases in parallel with disease progression. These data suggest that the UPR maintains ER homeostasis in glomerular cells and ensures cell survival under pathogenic conditions. ER stress pathophysiologically contributes to tubulointerstitial damage not only in glomeruli, but also tubules. Tubular damage, such as tubular cell death caused by proteinuria, ischemia-reperfusion, or nephrotoxin, predominantly enhances the UPR, especially UPR-induced apoptosis and autophagy.

These findings emphasize not only the importance of ER stress as a new progression factor but also the interesting future possibility of renoprotective strategies which target ER stress. In experimental glomerular and tubular injury model animals, overexpression of GRP78 (glucose-regulated protein 78), a master regulator of UPR, or administration of the chemical compounds that regulate UPR activation shows renoprotective effects. Preconditioning of ER stress with non-nephrotoxic dose of ER stress inducers protects against the podocyte and mesangial cell damage they induced. Interestingly, some oxidative stress inhibitors and advanced glycation inhibitors also act as UPR inhibitors, suggesting a link between oxidative stress, hypoxia, and ER stress. Therapeutic approaches which target ER stress may act by breaking the vicious cycle of this stress signal crosstalk in kidney disease.

Here, I summarize the role of ER stress as the master regulator of the stress response in glomerular disease and the therapeutic possibility of targeting UPR molecules.

2. ER stress and the unfolded protein response (UPR)

The ER plays an important role in the quality control of proteins by the regulating their synthesis, folding and trafficking. ER homeostasis depends on a balance in capacity between protein synthesis and folding. Various disturbances; decrease folding capacity, including folding mutations, hypoxia, or starvation, and thereby induce the accumulation of misfolded protein in the ER, which in turn leads to ER stress. This enforces the cellular stress signal, called the unfolded protein response (UPR) (Ron & Walter, 2007) (Figure 1).

The UPR pathway is regulated by three ER resident transducers (ER stress sensors), namely inositol-requiring protein-1 (IRE1), protein kinase RNA (PKR)-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Under normal conditions, they are inactivated by binding with an ER chaperone, glucose-regulated protein 78 (GRP78 or BiP). When unfolded proteins accumulate in the ER lumen, however, they are dissociated from GRP78, activated by dimerization, phosphorylation, or translocation to the Golgi, and then induce signals to attenuate translation or upregulate adaptive UPR target gene expression. The three ER resident transducers induce the ER chaperones to enhance folding capacity and activate the pathway for ER-associated protein degradation (ERAD) to reduce the accumulation of misfolded proteins. The UPR pathway maintains ER homeostasis to ensure cell survival.

When severe ER stress results in excessive or prolonged UPR activation, cells are unable to resolve the protein-folding defect or restore ER homeostasis via the adaptive UPR pathway.

In these circumstances, the proapoptotic UPR mediated by CHOP (CCAAT/enhancer-binding protein homologous protein) or caspase 12 is induced to ensure cell death (Tabas & Ron, 2011). The UPR pathway is thus a double-edged sword for cells under ER stress, and the final outcome represents the sum of the effects of the various possible UPR branches.

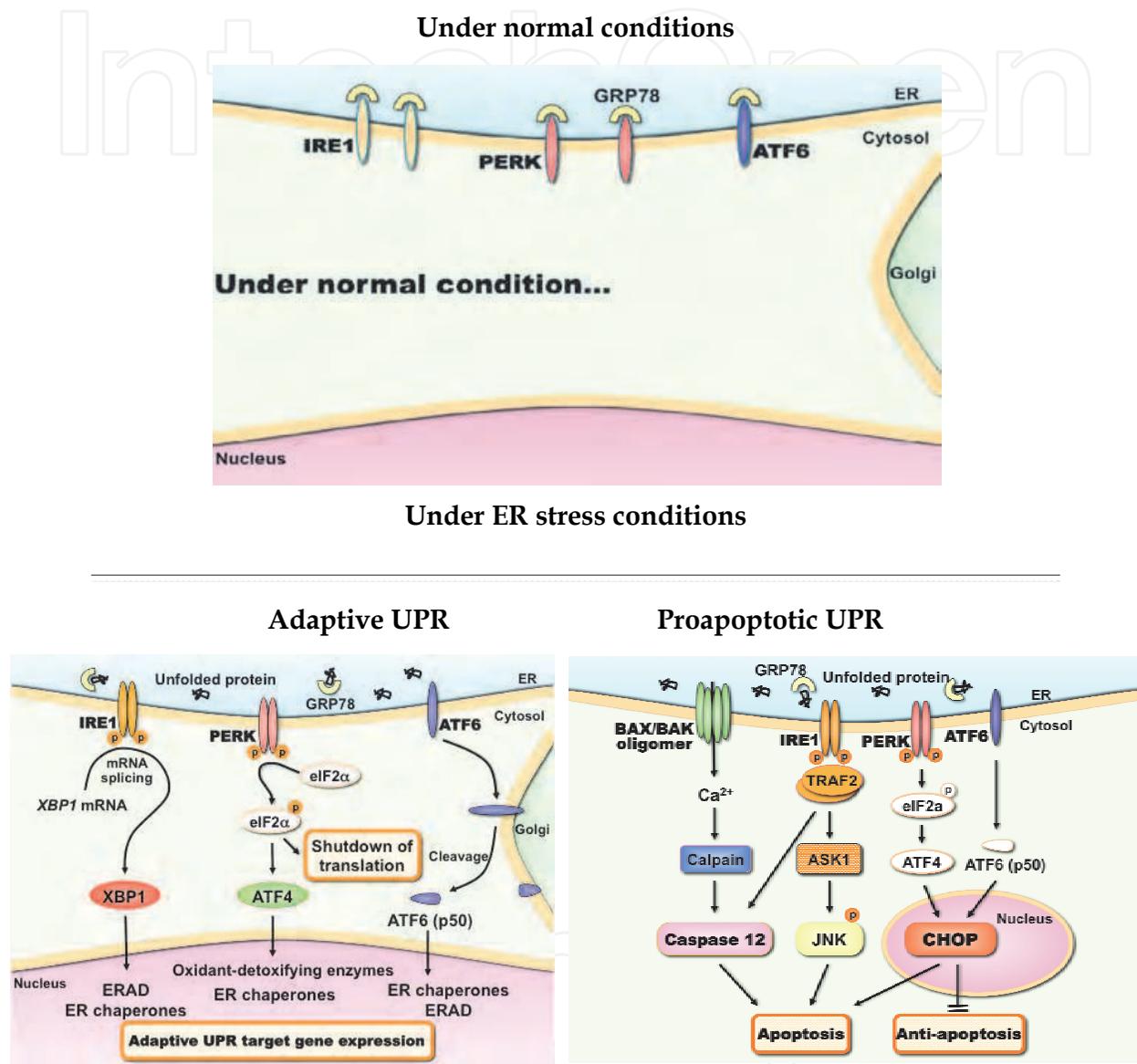


Fig. 1. Unfolded protein response (UPR)

Under normal conditions (upper panel), the ER stress sensors IRE1, PERK, and ATF6 are inactivated by binding with ER chaperone GRP78. When an imbalance between protein synthesis and folding capacity under ER stress causes the accumulation of unfolded proteins in the ER, however, these sensors are dissociated from GRP78 and activated by dimerization and phosphorylation (IRE1 and PERK) or translocation and cleavage (ATF6), thereby inducing the adaptive UPR for cell survival (lower left panel). The adaptive UPR consists of 1) translation attenuation to ensure a balance of protein synthesis and folding, 2) induction of ER chaperone expression to enhance folding capacity, and 3) activation of the ER-

associated protein degradation (ERAD) system to reduce unfolded protein accumulation. In stark contrast, prolonged or severe UPR activation leads to induction of the proapoptotic UPR, which is mediated by CHOP and caspase 12 for cell death (lower right panel). The balance of UPR states contributes to the consequence of ER stress. IRE1, inositol-requiring protein-1; PERK, protein kinase RNA (PKR)-like ER kinase; ATF6, activating transcription factor 6; GRP78, glucose-regulated protein 78; CHOP, CCAAT/enhancer-binding protein homologous protein. (modified from Reiko Inagi, *Curr Opin Pharmacol*, 2009 with permission)

2.1 Adaptive UPR: IRE-XBP, PERK-eIF2 α , and ATF6 pathways

The IRE1 pathway is initiated by the RNAase activity of IRE1, which induces mRNA splicing in X-box-binding protein 1 (XBP1), thereby creating a potent transcriptional activator (XBP1s) of genes which encode ERAD components and ER chaperones such as GRP78, GRP94, and calreticulin. The IRE1-XBP1 pathway serves mainly as an ER homeostatic response to ER stress by degrading or refolding misfolded proteins accumulated in the ER lumen. Recent publication of the crystal structure and autophosphorylation mechanism of IRE1 protein has provided new insights into the regulation mechanism of IRE1-XBP1 axis and subsequently the entire UPR (Lee et al, 2008; Ali et al, 2011).

The PERK pathway alleviates the ER burden by reducing the frequency of initiation of mRNA translation, thereby decreasing the influx of new proteins into the ER. PERK is a Ser/Thr protein kinase whose active homodimer phosphorylates and inactivates eukaryotic initiation factor 2 α (eIF2 α), thereby shutting off protein translation globally and reducing protein load on the ER. In addition to this function, the PERK-eIF2 α pathway activates in parallel activating transcription factor 4 (ATF4), and thereby selectively induces UPR-inducible gene expression, including ER chaperones, as well as antioxidant enzymes, such as glutathione S-transferase and hemoxygenase 1 (HO-1), to protect cells from both oxidative as well as ER stresses (Bardag-Gorce et al, 2010). Although PERK and IRE1 share functionally similar ER-luminal sensing domains and are both simultaneously activated in cellular paradigms of ER stress *in vitro*, they are selectively engaged *in vivo* by the physiological stress of unfolded proteins.

The ATF6 pathway is activated by its translocation to the Golgi where it is cleaved by S1P and S2P (site-1 and site-2 proteases). The cytosolic fragment of cleaved ATF6 (p50) further translocates to the nucleus, where it subsequently activates the transcription of its target genes, which encode ER chaperones and ERAD components.

2.2 Proapoptotic UPR: CHOP and IRE1-TRAF2 pathways

ER stress-induced apoptosis is mainly mediated by CHOP, also referred to as GADD153 (growth arrest and DNA damage 153). CHOP, a transcription factor which induces several proapoptotic factors, occurs downstream of the PERK (PERK-ATF4 pathway) and ATF6 pathways in the proapoptotic UPR axis. The CHOP pathway also down-regulates anti-apoptotic Bcl-2, leading to enhanced oxidant injury and apoptosis. These findings are consistent with the previous observation that overexpression of Bcl-2 specifically in the ER protects renal tubular cells against ER stress-induced apoptosis (Bhatt et al, 2008).

The IRE1-TRAF2 pathway is another proapoptotic UPR branch. The cytoplasmic domain of activated IRE1 interacts with the adaptor factor TRAF2 (tumor necrosis factor receptor-

associated factor 2), leading to activation of both the caspase 12-dependent and JNK-mediated apoptotic pathways. Several components of the caspase cascade are reported to be involved in ER stress-induced apoptosis. In particular, caspase 12, which is associated with the ER membrane, is a proximal regulator of ER stress-induced caspase activation followed by apoptosis. Caspase 12 is expressed in rodents but not primates, and caspase 4 is instead thought to contribute to ER stress-induced apoptosis in human cells.

ER stress-induced dysfunction of ER Ca^+ homeostasis also contributes to apoptosis through multiple pathways. Ca^+ leaked from the ER lumen enters the mitochondria, depolarizes the inner mitochondrial membrane, and generates mitochondrial ROS. This enhanced ROS production is associated with a vicious cycle of oxidative stress in both the ER and mitochondria, where it activates several apoptotic pathways, including the caspase 9-mediated or BAX/BAK-mediated pathways. This dispensation with dysfunctional cells represents a last resort on the part of multicellular organisms.

3. Pathophysiology of ER stress in kidney disease

It was recently established that ER stress is induced in various kidney diseases (Inagi, 2010). This is not entirely unexpected given that ER function is easily influenced by various cellular stresses. Further, ER stress contributes to disease progression in cardiac, vascular, and metabolic diseases, all of which are linked to the development of kidney disease. ER stress and consequent imbalance of UPR is one of the potent pathogenic mechanisms of kidney disease.

The initial filtrating component of functional nephrons are the glomeruli, which are capillary tufts that receive their blood supply from afferent arterioles of the renal circulation. The specialized capillary bed in each glomerulus consists of a network of interconnected loops surrounded by Bowman's capsule. Podocytes, which play an important role in the filtration barrier, have foot processes that extend over the glomerular basement membrane. These foot processes are bridged by slit diaphragms (filtration barrier) which connect adjacent foot process and thereby act to prevent larger molecules filtering into Bowman's capsule. Mesangial cells, some of which have phagocytic properties, are located between the capillary loops, and form the central stalk of the glomerulus. These form part of the functional nephron unit and interact closely with endothelial cells and indirectly with podocytes. Recent evidence increasingly emphasizes the link between ER stress and both glomerular cell damage and tubulointerstitial injury.

3.1 Podocytes and ER stress

Mutation of components of the slit diaphragms, including nephrin and alpha-actinin-4, leads to congenital nephrotic syndromes. These mutations are mostly associated with conformational abnormalities. Thus, they induce defects in the related protein trafficking and retention of mutant proteins in the ER, and thereby lead to ER stress in podocytes. Indeed, Cybulsky and colleagues have demonstrated that mice overexpressing human mutated alpha-actinin-4 develop the pathological and functional features of congenital nephrotic syndrome, including podocyte injury and proteinuria. They also show associated ER stress, namely an increase in ER chaperones and adaptive and proapoptotic UPR molecules (Cybulsky et al, 2009), suggesting that ER stress in podocytes contributes to congenital nephrotic syndrome. We have also demonstrated that ER stress is induced by malformed protein accumulation in podocytes, and that this leads to proteinuria. We

previously established a transgenic rat in which the protein encoded by the transgene (megsin, a kidney specific serine protease inhibitor) is consistently malformed and polymerized under overexpression conditions and accumulated in the ER lumen of podocytes (Inagi et al, 2005a). Pathological changes in these podocytes, such as ER dilation, were associated with severe proteinuria. Importantly, these transgenic rats showed an increase in ER chaperone expressions in damaged podocytes, including GRP78 or oxygen-regulated protein 150 (ORP150) (Inagi et al, 2005b). Collectively, these data suggest that the decline in protein-folding capacity in podocytes triggers cellular dysfunction which in turn results in derangement of the structure of slit diaphragms and thereby causes proteinuria.

We have also established an advanced diabetic nephropathy model mouse, which develops severe albuminuria and renal damage with all of the characteristics of human advanced diabetic nephropathy, such as acellular nodule-like lesions (Inagi et al, 2006). Immunohistochemistry for the detection of GRP78 revealed that these changes were associated with ER stress mainly in podocytes. (Inagi R, unpublished data)

ER stress induction in podocytes was further confirmed by studies utilizing the XBP1-venus fusion Tg mouse, which is an ER stress monitoring mouse (Iwawaki et al, 2004). These mice produce XBP1-GFP fusion protein only when XBP1 is activated by alternative splicing under ER stress conditions, and not under normal conditions. On treatment with anti-GBM antibody, a model of rapidly progressive glomerulonephritis, untreated mice showed the basal level of GFP expression in podocytes. In contrast, this expression was significantly increased in the diseased mice in association with proteinuria. This finding suggests that the XBP-1 axis is activated in damaged podocytes.

Taken together, our and previous findings demonstrating UPR activation in other podocyte-injury disease models (e.g., membranous nephropathy and minimal change nephrotic syndrome) highlight the link between ER stress and podocyte homeostasis, and that the ER stress state in podocytes might be changed by these various factors.

3.2 Mesangial cells and ER stress

Mesangioproliferative glomerulonephritis, which is caused by mesangial cell damage, is one of the major glomerulonephritises. We previously demonstrated that ER chaperone expression was significantly increased in the damaged mesangial area in anti-Thy1 nephritis rats, a representative mesangioproliferative glomerulonephritis model (Inagi et al, 2008). For example, immunohistochemistry for the detection of GRP78 and ORP150 followed by quantitative morphometry confirmed that the UPR for the induction of ER chaperone expression was markedly enhanced as the disease progressed. Similar results were observed by Western blot analysis followed by densitometry utilizing isolated glomeruli in experimental rats. Further, another adaptive UPR axis for translation attenuation was also significantly increased, as estimated by the phosphorylation of PERK and eIF2 α . These data emphasize the association between mesangial cell damage and ER stress, and that significant activation of the adaptive UPR axis contributes to the progression of glomerulonephritis. Given that oxidative stress is also induced in anti-Thy1 nephritis rats, mesangial cell damage may be orchestrated by the link between ER stress and oxidative stress as pathogenic mediators.

This evidence from a rat disease model might be consistent with evidence that ER stress estimated by GRP78 and CHOP expression is higher in patients with proliferative glomerulonephritis than in those with other glomerular diseases (Markan et al, 2009).

Trigger	Disease state	References
Folding mutant proteins		
	Congenital nephrotic syndrome	Cybulsky AV et al., Am J Physiol-Renal 2009
ATP depletion		
	Puromycin nephrosis	Nakajo A et al., J Am Soc Nephrol 2007
Complement (C5b-9)		
	Heymann nephritis	Cybulsky AV et al., J Biol Chem 2002
Oxidative stress (ROS), fatty acid		
	Diabetic nephropathy	Morse E et al., Am J Physiol-Renal 2010
Lowering of folding capacity		
	Proteinuria	Inagi R et al., Kidney Int 2005

Table 1. Triggers for ER stress in podocytes

Various pathogenic factors trigger ER stress in podocytes. Heymann nephritis and puromycin nephrosis are representative experimental animal disease models which mimic human membranous nephropathy and minimal change nephrotic syndrome, respectively.

3.3 Tubular cells and ER stress

Several disturbances have been shown to induce ER stress in tubules as cellular damage progresses. (Table 2) Among them, we showed that the proapoptotic UPR axis, which is predominantly mediated by caspase 12, is induced by proteinuria and contributes to tubular cell death in a minimal change nephrotic syndrome model rats (puromycin nephropathy) (Ohse et al, 2006). In chronic kidney disease, we further showed that uremic toxin might act as an ER stress inducer. In particular, in chronic kidney disease model rats (5/6-nephrectomized rats), CHOP-positive tubular cells were significantly increased in parallel with the accumulation of a representative uremic toxin, indoxyl sulfate, in the serum (Kawakami et al, 2010). These changes were ameliorated by the administration of a uremic toxin absorbent, AST-120, clearly suggesting the causal effect of indoxyl sulfate in ER stress induction in tubular cells.

Not only in experimental animals but also in humans, mRNA levels of ER chaperons (GRP78 and ORP150) and UPR transcription factors (XBP1 and CHOP) in tubules is increased in patients with both advanced diabetic nephropathy and minimal change nephrotic syndrome as compared with healthy individuals (Lindenmeyer et al, 2008).

Disease site (trigger)	Consequence(s)	Reference
Ischemia-reperfusion (hypoxia)	ORP150 ↑	Bando Y, et al, FASEB J 2004
Minimal change nephrotic syndrome (proteinuria)	GRP78 ↑, ORP150 ↑, CHOP ↑, caspase 12 ↑	Ohse T, et al, Kidney Int 2006
	GRP78 ↑, ORP150 ↑, XBP1 ↑, CHOP ↑	Lindernmeyer MT, et al., J Am Soc Nephrol 2008
Diabetic nephropathy (hyperglycemia)	GRP78 ↑, ORP150 ↑, XBP1 ↑, CHOP ↑	Lindernmeyer MT, et al., J Am Soc Nephrol 2008
Tubular injury (nephrotoxin, cyclosporine)	GRP78 ↑, CHOP ↑	Pallet N, et al., Autophagy 2009
Chronic kidney disease (uremic toxin, indoxyl sulfate)	GRP78 ↑, CHOP ↑	Kawakami T, et al., Am J Physiol-Renal 2010

Table 2. Triggers for ER stress in tubular cells.

3.4 Other kidney cells and ER stress

While ER stress is induced in retinal endothelial cells and pericytes in diabetic retinopathy, the role of ER stress in glomerular endothelial or tubulointerstitial cells is still unclear. Tubulointerstitial cells are heterogeneous, and a certain subpopulation of these cells includes pericyte-like cells producing erythropoietin (EPO). The role of ER stress in tubulointerstitial cells is an interesting issue, particularly its contribution to the regulation of EPO expression. Recently, it was demonstrated that renal anemia is not due to loss of EPO-producing cells but rather derangement of the oxygen-sensing mechanism which regulates EPO expression (Bernhardt et al, 2010). We investigated the effect of ER stress on EPO production in an EPO-producing hepatic cell line, HepG2. Hypoxia-induced EPO mRNA expression was significantly blunted by ER stress in HepG2 when the cells were treated with the ER stress inducer tunicamycin under low oxygen tension (Chiang CK, et al., unpublished data). Our observations suggest that renal pathogens, which can trigger ER stress, derange renal EPO production capacity and may thereby enhance the development of renal anemia. Further studies of the suppressive mechanism of this finding are under way.

4. ER stress and other stress signals

It is known that ER stress is initiated by hypoxia or oxidative stress and vice versa. Hypoxia and oxidative stress induce the cellular stress signals, namely the hypoxia-inducible factor (HIF) and NF-E2-related factor 2 (Nrf2) pathways, respectively. Imbalance of these stress

signals contributes to the pathological features of various kidney diseases (e.g., diabetic nephropathy, ischemia-reperfusion injury, glomerulonephritis) (Nangaku, 2006), which are also associated with ER stress. This suggests that the UPR, HIF, and Nrf2 pathways are linked, and that stress signal crosstalk might orchestrate the disease progression.

4.1 UPR and HIF pathway

Hypoxia, leading to the loss of energy, initiates a defect in protein-folding capacity, and thereby induces UPR activation. In tumor cells, for example, the hypoxic microenvironment brought on by poor vascularization brings about ER stress due to the loss of energy for protein folding. It has now been established that not only the HIF pathway but also the UPR is crucial to the survival of tumor cells against their hypoxic microenvironment: increased expression of ER chaperones, which enhances protein-folding capacity, is observed in a wide range of human cancers, and expression level correlates with tumor progression, metastasis, and drug resistance (Lee, 2007).

Further, it has also been demonstrated that the HIF pathway upregulates the expression of the UPR molecules, indicating the presence of molecular crosstalk between the HIF and UPR pathways. Cultured endothelial cells under hypoxia showed an increased in GRP78, GRP94 and caspase 12 expressions. A chemical stabilizer of HIF, CoCl_2 , also increased the expression of both GRP78 and GRP94, revealing that HIF activation alters UPR state (Ostergaard et al, 2009). Conversely, ER stress by tunicamycin and brefeldin A triggered HIF-1 α mRNA expression in the human hepatocyte cell line HepG2 under hypoxia (Werno et al, 2008). These findings suggest the presence of positive feedback between the HIF pathway and the UPR under hypoxic conditions and the possibility of indirect regulation of the HIF pathway by the UPR. In addition, one study demonstrated that certain UPR molecule expression is translationally regulated by an HIF regulator: ATF4, a UPR transcription factor, alters its protein stability through interaction of the zipper II domain of ATF4 with the oxygen sensor prolyl-4-hydroxylase domain 3 (PHD3) (Koditz et al, 2007). PHDs are well-known regulators of HIF, and treatment with the PHD inhibitor increased ATF4 protein levels. These data demonstrate that PHD-dependent oxygen-sensing recruits both the HIF and ATF4 systems in parallel. To further emphasize the biological significance of interaction between the HIF and ER stress pathways, studies utilizing *C. elegans* showed that HIF-1 deficiency extended lifespan in a UPR transducer IRE-1-dependent manner (Chen et al, 2009)

4.2 UPR and oxidative stress

Oxidative stress as well as hypoxia initiates ER stress (Malhorta & Kaufman, 2007). Nitric oxide (NO), produced in excessive levels following ischemia, contributes to ER stress. Ischemia-reperfusion-induced activation of the PERK-eIF2 α axis for translation attenuation is blocked in endothelial or neuronal NO synthase (NOS) knockout mice with bilateral carotid artery occlusion (DeGracia & Montie, 2004). Consistent with this, the NO-releasing reagent SNAP activates the PERK pathway, indicating that NO plays a role in the ischemia-reperfusion-induced UPR. Pretreatment with neuroprotective levels of an NOS inhibitor recovered the proapoptotic UPR state induced by a ischemia-induced defect in ER Ca^{2+} homeostasis, which occurs due to Ca^{2+} leakage into the cytosol and subsequent uptake into mitochondria, resulting in mitochondrial ROS generation. The aberrant NO production seen in hypoxia, which alters calcium homeostasis in both the ER and mitochondria, may initiate a vicious cycle of ER stress, oxidative stress, and apoptosis.

Under oxidative stress, reactive oxygen species (ROS) interfere with not only cellular redox-dependent reactions but also protein-folding capacity, including protein disulfide bonding,

ultimately resulting in protein misfolding in the ER. Studies utilizing the overexpression of anti-oxidant enzymes have emphasized the linkage of oxidative stress to the ER stress response. The ischemia-induced ER stress response was markedly less pronounced in animals overexpressing copper/zinc superoxide dismutase (Cu/Zn-SOD), suggesting that superoxide radicals play a role in this pathological process (Hayashi et al, 2003). Further, cadmium caused the generation of ROS with subsequent induction of ER stress in a cultured renal proximal tubular cell line, which in turn led to apoptosis; this cadmium-induced ER stress and apoptosis were significantly attenuated by manganese SOD overexpression (Yokouchi et al, 2008). Paradoxically, ER stress also increases intracellular ROS production: increased protein disulfide bonding enhances ROS production in the ER lumen, and alteration of ER Ca⁺ homeostasis increases cytosolic Ca⁺, thereby stimulating mitochondrial ROS production. Of particular note, recent studies have demonstrated that the accumulation of intracellular ROS is attenuated by the adaptive UPR through PERK activation, which simultaneously activates an anti-oxidative stress signal, the Nrf2 pathway, and maintains redox homeostasis, thereby ensuring cell survival. The antioxidant effects of the PERK axis of the UPR are supported by the finding that PERK-deficient cells exposed to tunicamycin, an ER stress inducer, showed a toxic accumulation of intracellular ROS compared to wild-type cells (Cullinan & Diehl, 2006). Translation attenuation through the PERK-eIF2 α pathway effectively prevents the misfolded protein-inducible oxidative stress and maintains the cell (Back et al, 2009).

4.3 UPR and advanced glycation

Under oxidative stress conditions with hyperglycemia, proteins and DNA are non-enzymatically modified by oxidative glycation, which occurs mainly due to increased ROS generation, and converted to advanced glycation endproducts (AGEs). Advanced glycation is one of the major pathophysiological posttranslational modifications and induces the derangement of protein functions or apoptosis. Functional abnormalities of glycated proteins perturb cellular homeostasis and increase mitochondrial ROS generation, accelerating the vicious cycle of oxidative stress and thereby enhancing subsequent glycation modification. From the viewpoint that ER stress is predominantly induced by hypoxic or oxidative stress, it is reasonable to speculate the presence of a link between advanced glycation and ER stress on the disease development and progression caused by these disturbances.

It has been reported that AGEs induce ER stress directly. Among findings, it is reported that glycated serum albumin (AGE-bovine serum albumin) induces ER stress, as estimated by GRP78 expression, and apoptosis in a dose- and time-dependent manner in mouse podocytes via an increase in intracellular Ca²⁺ concentration. ER stress inhibitor taurine-conjugated ursodeoxycholic acid (TUDCA), which acts as a chaperone that promotes the folding and trafficking of unfolded or misfolded proteins, prevents AGE-induced apoptosis, suggesting that this apoptosis is mediated by the apoptotic UPR pathway (Chen et al., 2008). Like glycated albumin, extracellular matrix is frequently modified by advanced glycation in the skin of diabetic patients. The advanced-glycated type I collagen also causes proapoptotic UPR-mediated apoptosis via CHOP activation in dermal fibroblasts, suggesting a pathophysiological role for the link between advanced glycation and ER stress in diabetic wounds (Loughlin & Artlett, 2010).

5. Therapeutic approach targeting ER stress in kidney disease

Accumulating evidence, including ours, has recently indicated the therapeutic benefits of targeting ER stress in various diseases, including cardiac, vascular, and metabolic diseases as well as kidney disease. Therapeutic modalities which targeting ER stress are summarized

in Table 3. While artificial modulation of ER stress may provide protection to various kinds of cells (Kim et al, 2008), this chapter focuses on the beneficial effects on kidney disease.

Modality	Function(s)
ER chaperone overexpression	
GRP78	Translation shutdown ↑
ORP150	Protein folding ↑
Chemical chaperones	
4-PBA	Protein folding ↑ , ERAD ↑ , caspase 12 ↓
TUDCA	Adaptive UPR ↑ , proapoptotic UPR ↓
Chemical compounds	
DTTox	GRP78 ↑
BIX	GRP78 ↑
Salubrinal	Adaptive UPR (PERK-eIF2 α) ↑
Benzodiazepinones	IRE1/TRAF2/ASK1 ↓
Methoxyflavone	GRP78 ↑
ER stress preconditioning	
ER stress inducers	Basal adaptive UPR ↑
Others	
Anti-oxidative stress compounds	
TM2002	Oxidative stress ↓
Butylated hydroxyanisole	Protein-folding capacity ↑
Anti-hypoxia compound (HIF stabilizer)	
Dimethylxalylglycine	proapoptotic UPR (CHOP) ↓ , GRP78 ↑ , ATF4 ↑
Anti-inflammatory drug	
Mizoribine	Intracellular energy for protein folding ↑
Anti-hypertensive drug	
Angiotensin II type 1 receptor blocker	proapoptotic UPR (CHOP) ↓

Table 3. Therapeutic modalities targeting ER stress.

Abberant UPR state, which contributes to the progression of various diseases, is suppressed by ER chaperone overexpression, the chemical chaperones themselves, or chemical compounds which selectively activate the adaptive UPR axis or suppress the apoptotic UPR axis. ER stress preconditioning upregulates the basal UPR state and protects cells from various pathogenic stresses.

5.1 ER chaperones and chemical chaperones

ER chaperone overexpression (e.g., GRP78 and ORP150) and chemical or pharmaceutical chaperones (e.g., 4-phenyl butyric acid (PBA), TUDCA, and dimethyl sulfoxide) stabilize protein conformation, enhance ER protein-folding capacity to normalize the imbalance of protein synthesis and folding, and thereby maintain ER homeostasis. In particular, protein folding augmentation therapies utilizing these UPR modulators or chemical chaperones may improve conditions associated with protein misfolding, such as congenital nephrotic syndromes, which are caused by a defect in the retention and accumulation of mutant proteins in the ER of podocytes.

As the evidences for the effectiveness of ER chaperone enhancement in the kidney, ORP150 transgenic mice showed resistance to renal ischemia-reperfusion injury (Bando et al, 2004). 4-Phenylbutyric acid (4-PBA), a chemical chaperone, rescues mutated nephrin, which is associated with misfolding and mislocalization, from the ER to the cell surface, suggesting the beneficial effect of protein folding augmentation therapy in congenital nephrotic syndrome (Liu et al, 2004). 4-PBA also exerts a marked renoprotective effect possibly by modulating ER stress and the related inflammatory cascade in diabetic nephropathy (Qi et al, 2011). Endogenous bile acids and derivatives such as ursodeoxycholic acid and its taurine-conjugated derivative (TUDCA) can also modulate ER function, restore glucose homeostasis in type 2 diabetic mice, and thereby ameliorate the development of diabetic complications, including diabetic nephropathy in these animals (Xie et al, 2002; Ozcan et al, 2006; Ozcan et al, 2009). In studies of TUDCA therapy for obese men and women, TUDCA has consistently shown promise as an effective pharmacological approach to the treatment of insulin resistance and obesity-related disease including chronic kidney disease (Kars et al, 2010). Unlike 4-PBA, however, TUDCA has not been shown to act as a chaperone that promotes the folding and trafficking of malformed proteins; instead, it is likely to increase folding capacity, possibly by enhancing the ERAD pathway (ER-associated malformed protein degradation system). Murine podocytes suffered from ER stress-induced apoptosis on exposure to advanced glycation end product (AGE)-modified bovine serum albumin, but TUDCA prevented this apoptosis by suppressing the apoptotic UPR activation (Chen et al, 2008).

Aberrant UPR state, which contributes to the progression of various diseases, is suppressed by ER chaperone overexpression, the chemical chaperones themselves, or chemical compounds which selectively activate the adaptive UPR axis or suppress the apoptotic UPR axis. ER stress preconditioning upregulates the basal UPR state and protects cells from various pathogenic stresses.

5.2 Chemical UPR modulators

Chemical compounds which selectively activate the adaptive UPR branches act as enhancers of translation attenuation as well as of ER chaperone expression. Other chemical compounds which suppress the proapoptotic UPR branches protect cells from ER stress-induced cell death. The UPR pathway is a double-edged sword for cells suffering from ER stress; normalization of the balance between the adaptive and proapoptotic UPR branches by these chemical compounds might thus be effective in promoting ER homeostasis.

Several chemical compounds have demonstrated renal protective effects against ER stress suggesting the therapeutic possibility of targeting the UPR. Trans-4,5-dihydroxy-1,2-dithiane (DTTox) protected the proximal tubular epithelium against a nephrotoxic chemical via stimulation of GRP78 (Asmellash et al, 2005), while BIX (BiP inducer X, 1-(3,4-dihydroxyphenyl)-2-thiocyanato-ethanone) ameliorated disease manifestations of renal ischemia-reperfusion injury in mice by activating the ATF6 axis with subsequent induction of GRP78 (Prachasilchai et al, 2009). Salubrinal suppresses the protein phosphatases responsible for the dephosphorylation of eIF2 α , and significantly reduces tubular injury in a rat cyclosporine nephropathy model by increasing the amounts of phosphorylated eIF2 α (Pallet et al, 2008). Methoxyflavone, a group of flavonoids, is also identified as a strong ER stress modulator. Pretreatment of mice with tangeretin, a methoxyflavone, enhanced the expression of GRP78 and HO-1 in renal tubular epithelium and prevented tunicamycin-induced cell death (Takano et al, 2007).

5.3 Others

The previous evidences regarding the crosstalk of oxidative stress, hypoxia, and ER stress emphasize that anti-oxidative stress or anti-hypoxia drugs may also hold promising in reducing pathogenic ER stress. In fact, effective attenuation of the ER stress response has also been observed in compounds which suppress oxidative stress. TM2002, an inhibitor of oxidative protein glycation, shows renoprotective effects against glomerular and tubular interstitial damage in association with a decrease in ER stress in anti-Thy1 nephritis and renal ischemic-reperfusion rats (Izuhara et al, 2008). Further, a chemical HIF stabilizer, prolyl hydroxylase inhibitor (Dimethyloxalylglycine) which attenuates ischemic cardiac injury by HIF pathway activation, selectively activates the adaptive UPR (GRP78 and ATF4 inductions), and weakens the proapoptotic UPR, suggesting that HIF stabilizer has the renoprotective effects as a UPR modulator (Natarajan et al, 2009).

One study demonstrated that treatment with mizoribine, an immunosuppressant used clinically, reduced ER stress and rescued the mislocalization of nephrin from the ER to the cytoplasm in podocytes with glucose starvation. Mizoribine is known to inhibit purine nucleotide biosynthesis, and might thereby restore the intracellular energy balance under ER stress by salvaging ATP levels. These data suggest that the effect of mizoribine in inducing the remission of proteinuria in human nephrotic syndrome might be mediated by a reduction in ER stress (Nakajo et al, 2007).

Further, similar inhibitory effects to those of mizoribine on ER stress were seen with another clinically used anti-hypertensive drugs, namely angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers. The angiotensin II type 1 receptor is thought to be an ER stress inducer, albeit that the molecular mechanisms by which angiotensin II induces ER stress remain unclear. It is therefore reasonable to consider that the increased tubular apoptosis in experimental diabetic rats is attenuated by ACE inhibitors in association with a reduction in aberrant apoptotic UPR activation and subsequent maintenance of the physiological UPR state in the tubulointerstitium (Sun et al, 2009)

5.4 ER stress preconditioning

The effects of ER stress preconditioning highlight the possibility of therapy based on ER stress. The concept of preconditioning was originally identified in ischemic diseases. Brief ischemic treatment for preconditioning prior to the subsequent insult induces a state of resistance to the loss of blood supply by initiating cellular protective responses in the tissue. These findings suggest that ER stress preconditioning may initiate the adaptive UPR and attenuate the subsequent insult. An increasing number of reports have demonstrated the beneficial effects of preconditioning in ER stress-related diseases, such as cardiac and neuronal diseases and retinopathy.

To evaluate the beneficial effect of ER stress preconditioning in kidney disease, we investigated whether a non-nephrotoxic dose of the ER stress inducers tunicamycin or thapsigargin for preconditioning ameliorate the development of anti-Thy1 nephritis, a mesangioproliferative glomerulonephritis model. As we expected, disease progression was dramatically improved by preconditioning, in association with a decrease in microaneurysm formation, adhesion of Bowman's capsule to the tuft, and proteinuria (Inagi et al, 2008). Importantly, the protective effect of preconditioning against glomerular damage was associated with modulation of the adaptive UPR. While the expression of ER chaperones (GRP78 and ORP150) was significantly increased as the disease progressed, the preconditioning slightly enhanced the basal level of this expression and significantly

suppressed the aberrant ER chaperone expression after disease induction. Similarly, preconditioning slightly enhanced the basal level of the PERK-eIF2 α axis in translation attenuation and suppressed its augmentation by disease induction. These findings demonstrate that ER preconditioning induces a robust basal (physiological) UPR state and maintains a stable UPR level in the kidney.

Other reports have also emphasized the effectiveness of ER stress preconditioning in the kidney. Preconditioning with tunicamycin or doxorubicin mitigates experimental membranous nephropathy via ER chaperone enhancement (Cybulsky et al, 2002). Kitamura and colleagues extensively investigated the role of ER stress in inflammation, and clearly showed that inflammatory cytokine-induced NF- κ B activation in mesangial cells was suppressed by preconditioning via the IRE1-XBP1 axis (Hayakawa et al, 2010).

Modality	Site (disease) and enhanced UPR	Reference
Tunicamycin or Doxorubicin		
	Podocytes (Heymann nephritis) GRP78 \uparrow , PERK-eIF2α axis	Cybursky AV, et al, J Biol Chem 2002
Tunicamycin or thapsigargin		
	Mesangial cells (anti-Thy1 nephritis) GRP78 \uparrow , PERK-eIF2α axis	Inagi R, et al, Am J Soc Nephrol 2008
	(NF-κB-related Inflammation) IRE1, PERK-eIF2α axis	Hayakawa K, et al, Am J Soc Nephrol 2010
Tunicamycin, thapsigargin, or trans-4,5-dihydroxy-1,2-dithiane,		
	Tubular epithelial cells (oxidative stress) GRP78 \uparrow	Hung CC, et al, J Biol Chem 2003
BIX (GRP78 inducer)		
	Tubular epithelial cells (ischemia-reperfusion) ATF6 axis	Prachasilchai W et al., J Pharmacol Sci, 2009

Table 4. ER stress preconditioning in kidney disease

Preconditioning with an ER stress inducer such as tunicamycin and thapsigargin confers a protective effect against kidney disease. BIX is a GRP78 inducer, 1-(3,4-dihydroxyphenyl)-2-thiocyanate-ethanone which markedly induces GRP78 production and is preferentially mediated by the ATF6 pathway.

6. Conclusion

The physiological state of the UPR pathway is important to the maintenance of ER homeostasis. Under pathogenic conditions, however, ER stress and the subsequent overwhelming UPR activation are significantly induced in various kidney cells and

contribute to kidney disease progression rather than regulating ER homeostasis. Enhancement of the basal level of the UPR, particularly the adaptive UPR axis, might support appropriate ER homeostasis and a robust cell state. Cells might accordingly become resistant to pathogenic factors, and an aberrant UPR might be suppressed (Fig. 2).

It is now established that ER stress is involved in cardiac, vascular, and metabolic diseases, which in turn affect kidney disease development. UPR is intricately linked to two other important stress pathways, HIF and Nrf2, which also contribute to disease progression. Keeping intact the balance of these stress signal networks via regulation of the UPR will allow us to maintain cellular homeostasis and disease prevention.

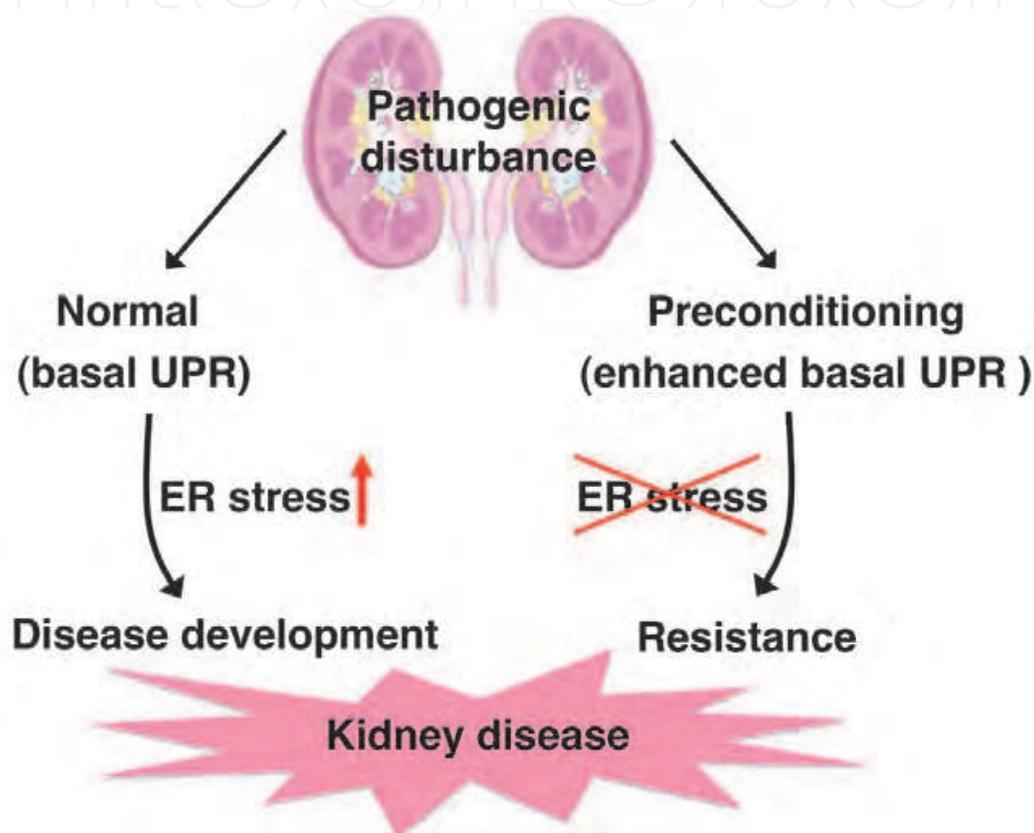


Fig. 2. ER stress preconditioning in the kidney.

Under pathogenic conditions, the basal UPR for ER homeostasis transformed to the pathogenic state, and thereby leads to the features of ER stress-related kidney diseases. In contrast, preconditioning with ER stress enhances the basal UPR level and induces kidney cells to develop resistance to pathogens.

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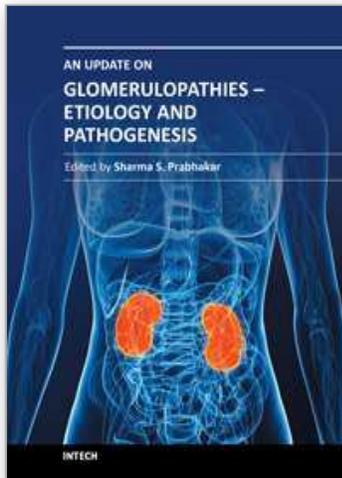
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Phone: +86-21-62489820
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