Ischemia is the most frequent cause of acute kidney injury (AKI), which is characterized by apoptosis of renal tubular cell. A common result of ischemia in AKI is dysfunction of endoplasmic reticulum (ER), which causes the protein-folding capacity to lag behind the protein-folding load. The abundance of misfolded proteins stressed the ER and results in induction of the unfolded protein response (UPR). While the UPR is an adaptive response, over time it can result in apoptosis when cells are unable to recover quickly. Recent research suggests that ER stress is a major factor in renal tubular cell apoptosis resulting from ischemic AKI. Thus, ER stress may be an important new progression factor in the pathology of ischemic AKI. In this article, we review UPR signaling, describe pathology and pathophysiology mechanisms of ischemic AKI, and highlight the dual function of ER stress on renal tubular cell apoptosis.

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Introduction

Endoplasmic reticulum (ER) stress can be triggered by many different stimulatory signals in ischemic acute kidney injury (AKI), including mutant protein aggregation, hypoxia, energy deprivation, and metabolic dysfunction. Declined protein-folding capacity in ER leads to abundance of misfolded proteins, initiating ER stress. Overwhelming ER stress causes apoptosis through the three typical signal pathways, PERK–eIF2–ATF4 pathway, IRE1–XBP1 pathway and ATF6 pathway (Figure 1). The ability of renal tubular cells to cope with ER stress is essential for maintaining normal renal function. Therefore, a deeper understanding of the pathological contribution of ER stress and its interaction with key underlying mechanisms will advance our ability to fully recognize the disease.

Endoplasmic reticulum stress

Secretory and membrane proteins are synthesized and folded in the ER, where these proteins also receive post-translational modifications such as glycosylation, disulfide bond formation and lipidation. Before proteins exit the ER and are transported to the Golgi and other destinations within the cell, they must be correctly folded into a specific final structure. Normal proteins achieve the correct structure and physiological function following the correct folding process. However, if proteins manufactured in the ER are prevented from attaining their proper tertiary structure, they become misfolded. These misfolded proteins can aggregate, and the accumulation of misfolded proteins in the ER will result in cellular stress and finally cellular damage, a process which is referred to as ER stress. The immediate response to ER stress is the activation of intracellular signal transduction pathways in ER, collectively called the unfolded protein response (UPR). ER stress can be triggered by various stimuli, such as ischemia, hypoxia, oxidative stress, glucose starvation, and elevated protein synthesis.

Three major ER stress response transmembrane proteins are primarily activated, including protein kinase-like ER kinase (PERK), inositol requiring 1 (IRE1), and activating transcription factor 6 (ATF6), which activate downstream signaling effectors.

GRP78 is a negative regulator of the UPR

Glucose-regulated protein 78 (GRP78), also called Immunoglobulin binding protein (BiP), is a molecular chaperone in cells, which can promote protein folding with hydrolysis of ATP. GRP78 binds to the unfolded or
incompletely folded proteins and prevents interactions of misfolded proteins with surrounding molecules within the ER lumen. In unstressed cells, GRP78 is bound to PERK/IRE1/ATF6 to keep them in an inactive state. When it encounters accumulated misfolded proteins in the ER, GRP78 disassociates from the three inducers of the UPR to help protein folding. Consequently, released PERK/IRE1/ATF6 undergo activation, which leads to the initiation of the UPR. In this way, GRP78 is a negative regulator of the UPR and plays a critical role in its initiation.

ATF6 signaling pathway

Upon dissociation from GRP78, Golgi localization signals on ATF6 (p90) are uncovered. ATF6 (p90) subsequently moves to the Golgi and is cleaved by Golgi-resident site-1 and site-2 proteases, releasing the cytosolic domain of ATF6 (p60). The cleaved activating transcription factor 6 (cATF6) contains a DNA-binding domain. Upon translocation to the nucleus, transcription of its target genes, including ER chaperones and enzymes such as XBP1 and CHOP/GADD153, is activated. Thus, ATF6 functions as a critical regulator of ER quality control proteins in mammalian cells.

IRE1 signaling pathway

IRE1 maintains is inactive when bound to GRP78 during homeostasis. Once ER stress occurs, GRP78 dissociates from IRE1 and triggers the activation of the endoribonuclease domain in IRE1, forming splicing X-box-binding protein-1 (sXBP1) mRNA. sXBP1 generates a functional XBP1 protein that acts as a potent transcriptional activator to amplify the ER-associated degradation (ERAD) factors, the misfolded protein degradation system, and the expression of ER resident chaperone GRP78. The IRE1–XBP1 pathway serves as an adaptive response to ER stress by degrading or refolding misfolded proteins accumulated in the ER lumen.

Activation of ATF6 precedes the activation of IRE1 during ER stress. In the initial stages of the UPR, ATF6 signaling pathway leads to accumulation of unspliced XBP1 mRNA. In parallel with ATF6, activated IRE1 is then available for splicing XBP1 mRNA. In addition, the cytosolic domain of IRE1 binds tumor necrosis factor receptor-associated factor 2 (TRAF2), which then activates the c-Jun N-terminal Kinase (JNK)-mediated apoptotic pathway via apoptosis signal regulating kinase-1 (ASK1) phosphorylation. This pathway, which is independent of XBP1, ultimately leads to apoptosis upon ER stress.

PERK signaling pathway

During ER stress, activation of PERK occurs by dimerization and trans-autophosphorylation, leading to the recruitment and phosphorylation of its substrate, eIF2a. Phosphorylation of eIF2a is inhibitory and reduces overall translation in cells, thereby decreasing the ER protein load. The attendant decrease in eIF2a activity
Ischemic acute kidney injury

Acute kidney injury is characterized by a rapid decline of renal function, leading to the accumulation of metabolic waste and toxins and, even worse, resulting in failure of other organs. According to the Kidney Disease Improving Global Outcomes (KDIGO) working Group, AKI is defined as any of the following three criteria: (1) increase in serum creatinine (sCr) by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or (2) an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the preceding 7 days; or (3) a urine volume <0.5 mL/kg/h for 6 h.18,19 AKI is a common problem among hospitalized patients, affecting around one in five patients admitted to hospital, with mortality rates ~25–40% in severe cases.20,21 This is of critical importance to the elderly population, as the number of AKI patients’ increases with age.

AKI is a multifactorial renal disease, encompassing a wide spectrum of injury to the kidneys such as ischemia-reperfusion (IR) injury, sepsis, drugs, obstruction and various endogenous or exogenous injuries. AKI can be divided into pre-renal, intrinsic, and post-renal (obstructive) AKI. Intrinsic AKI can be further divided into tubulo-interstitial, glomerular, and vascular lesion.22 Most tubulo-interstitial disease, and indeed most AKI, is caused by ischemia, which causes a generalized or localized impairment of both oxygen and nutrient delivery to cells and waste product removal from cells in the kidney.19 In animal models, mice undergo unilateral clamping of the renal pedicle for a certain time and simultaneous contralateral nephrectomy to develop ischemic AKI.23 In humans, renal surgery or transplantation, cardiac surgery, blood loss, blockages in kidney blood vessels, hypoperfusion, hypotension, and various other factors can all initiate ischemic AKI.24–26

Changes of tubular epithelial cells in ischemic AKI

Pathologically, AKI is characterized by sublethal and lethal damage of renal tubular epithelial cells, endothelial cell injury, inflammation, and hemodynamic dysfunction.27,28 Injury and death of tubular cells are especially recognized as the characteristic pathological change in AKI. Furthermore, tubular repair and regeneration are considered as major events in kidney recovery from AKI. In ischemic AKI, there is an imbalance of local tissue oxygen supply and demand as well as accumulation of waste products of metabolism. As a consequence of this mismatch, the tubular epithelial cells undergo injury and with increasing time or severity of ischemia, there is cell death by either necrosis or apoptosis, resulting in impairment of water and electrolyte homeostasis and reduced excretion of waste products of metabolism.29 Although sublethal injury is reversible, the death of tubular cells is accompanied by the inevitable loss of the function of the affected cells. Epithelial cell injury associated with ischemia is most apparent in the S3 segment of the proximal tubule.30 Characteristic histological changes of renal tubular cells include effacement and loss of the tubular brush border, sloughing of tubular epithelial cells or the necrotic cell debris into the tubular lumen, the dilatation of the tubular lumen, and the formation of tubular casts due to necrosis and apoptosis.29,31,32 Rather than necrosis, apoptosis may be the dominant mode of injury.24 In the last two decades, tubular apoptosis has been demonstrated in various animal models and some clinical samples from patients with AKI. Experimentally, apoptosis can be observed by cell

Prosurvival or proapoptotic effects of ER stress

The activation of the UPR induces an adaptive response in which the cell attempts to overcome the accumulation of misfolded proteins and ER stress. However, prolonged UPR activation has been demonstrated to have toxic effects, ultimately leading to cell death.12 UPR involves factors that may lead to either cell survival or apoptosis, depending on the degree of ER stress. Prosurvival effects include eIF2α phosphorylation, GRP78 induction, and XBP splicing. Proapoptotic factors include JNK phosphorylation, CHOP/GADD153 induction, and caspase-12 activation. Caspase 12 is an ER-specific caspase, which helps initiate ER stress-mediated apoptosis through a caspase-9/caspase-3 cascade reaction upon activation.17

paradoxically activates the translation of the ATF4 mRNA,13 which can be preferentially translated. After ATF4 enters the nucleus, it activates the transcription of CHOP (C/EBP homologous protein), which can downregulate bcl-2 and cause cell apoptosis.14 CHOP→→ mice and cells exhibited significantly less programmed cell death,15 and deregulated CHOP activity compromises cell viability.14 On the other hand, ATF4 and CHOP can also activate GADD34 (growth arrest and DNA-damage inducible protein-34), promoting eIF2α dephosphorylation by the Protein Phosphatase 1 (PP1) complex thereby exerting negative feedback on the PERK pathway.16
morphology, caspase activation, and terminal deoxy- 
nucleotidyl transferase-mediated digoxigenin-deoxyuri- 
dine nick-end labeling (TUNEL) assay of DNA damage 
as well as the activation of other pro-apoptotic pro-
teins, for example, CHOP and Bcl-2 family.

**ER stress interacts with the extrinsic and 
intrinsic apoptosis signaling pathways**

In tubular epithelial cells, stimulation of ischemia trig-
gers the accumulation of unfolded proteins in the ER 
lumen, leading to the UPR. Early adaptive responses of 
UPR involve expansion of ER membranes, accelerated 
degradation of unfolded proteins, increased translation 
of folding chaperones, and inhibition of general protein 
synthesis. However, if the damage is severe irrevers-
ible damage will occur and cells will inevitably undergo 
apoptosis.

Mechanistically, there are three main ways for induc-
ing cell apoptosis: extrinsic pathways, intrinsic pathways, 
and ER stress. The intrinsic pathway is derived from 
nuclear DNA damage, ischemia, oxidative stress and so 
on, which leads to the oligomerization of Bax and Bak. 
This results in mitochondrial outer membrane perme-
ability (MOMP), and the resulting release of Cytochrome 
C (Cyt C) causes activation of caspase 9 and caspase 
3. The extrinsic pathway of apoptosis is initiated by 
death ligand binding to the death receptor (e.g. FasL 
binding to Fas), leading to formation of the Death 
inducing signaling complex (DISC) and activation of cas-
pase 8. Activated caspase 8 amplifies the apoptotic cas-
cade through cleaving Bid to its truncated form tBid, 
which can increase the release of the apoptogenic fac-
tor Cyt C from mitochondria, eventually resulting in 
apoptosis.

In the ER stress pathway, JNK phosphorylation, 
CHOP/GADD153 induction, and caspase-12 activation 
can all lead to apoptosis. Activation of caspase-12 or 
JNK can activate the caspase-9/caspase-3 or caspase-
3 cascades, respectively, which are important mem-
bers in the intrinsic death pathway. CHOP promotes 
hyperoxidation of the ER and promotes IP3-induced 
Ca2+ release from the ER lumen. Ca2+ leaked from the 
ER lumen enters the mitochondria and generates 
mitochondrial reactive oxygen species (ROS), trigger-
ing a vicious cycle of oxidative stress both in the ER 
and mitochondria. In addition, CHOP decreases the 
expression of pro-survival protein BCL-2. BCL-2 can 
inhibit the release of Cyt C from mitochondria, and 
therefore CHOP indirectly abolishes this protective 
effect.

**Double effects of ER stress on renal tubular 
cells apoptosis in ischemic AKI**

**The early protective effects of ER stress**

The increased amount of GRP78 protein after ischemia-
reperfusion was mainly localized in the proximal tubule 
cells. GRP78 elevates earlier than blood urea nitrogen (BUN) and creatinine, which reached their peaks 
24–48 h after ischemia. The UPR was activated soon 
after renal ischemia, and this activation may have had a 
protective effect. For example, pretreatment with tunica-
mycin or thapsigargin, two ER stress inducers, protected 
tubule cells from renal ischemia-reperfusion injury 
through enhancement of GRP78 protein expression, and 
ameliorated renal dysfunction and injury. In a culture 
system of simulated ischemia, proteomic analysis of 
renal tubule epithelial LLC-PK1 cells showed upregula-
tion of GRP78 and heat shock protein 70(HSP70), which 
confers cytoprotection by suppressing JNK activation 
and inhibiting apoptotic cell death.

Moreover, ischemic preconditioning (PC), defined as 
brief intermittent cycles of ischemia alternating with 
reperfusion applied after the ischemic event, may 
increase the tolerance of the ischemic kidneys against 
sustained injury. The use of ischemic PC protects 
kidney from ischemia-induced injury by suppressing ER 
stress, as indicated by downregulation of GRP78, ATF4, 
PERK, XBP-1 and the caspase12 protein levels. 
Additional research reported that early ischemic PC atte-
nuted ER stress in ischemic kidneys via increasing the 
relative amounts of GRP78 and decreasing PERK, ATF4 
and TNF-receptor associated factor 2 (TRAF2) levels. 
The beneficial impact of early ischemic PC was dependent 
on nitric oxide (NO) levels, as the protective effect was 
abolished when NO production was inhibited before 
early ischemic PC application. The early protective 
effects on ER stress could possibly be because ischemic 
PC leads to a pro-survival phenotype in different cells. In 
renal epithelial cells suffering from oxidative injury, pre-
conditioning with ER stress caused activation of ERK1/2 
signaling, accompanied by a reduction in JNK activation. 
Thus, the ER stress response modulates the balance 
between ERK and JNK signaling pathways to prevent 
cell death after oxidative injury. Consistent with this, 
in the post-ischemic kidney, cells were protected from 
the following ischemia injury for up to 15 days and this 
was associated with reduction of JNK signaling by 
remote ischemic pretreatment. Also of note, benefits 
related to ischemic PC have been documented in 
laboratory studies. However, the relevance to human 
AKI remains to be determined in a large number of clin-
cial trials.
Apoptosis promoting effect of ER stress and interventions

Upregulation of mRNAs encoding the ER localized proteins GRP78, GRP94, and ERP72 were observed 30 min following acute renal ischemia.47 In ischemia induced AKI mouse models, renal tubular necrosis score and cell apoptosis index reached their peak 24 hr after IR. GRP78, CHOP expression, and Caspase 12 activation were enhanced, reaching their peaks at 4 and 12 h, respectively.48 A 20-fold increase in phospho-eIF2a accompanied by activation of the PERK pathway was observed in kidney homogenates following 10 min of cardiac arrest-induced ischemia and 10 min reperfusion.25

In parallel, two ER stress hallmarks, GRP78 and CHOP, showed increased protein levels after hypoxia and ER stress, and participated in hypoxia/reoxygenation induced apoptosis in human renal proximal tubular epithelial cell line (HK-2 cells).49 However, those parameters were significantly suppressed by berberine pretreatment.49 It was also demonstrated that tauroursodeoxycholic acid (TUDCA) pretreatment had a nephroprotective effect on ischemia-induced AKI by inhibiting ER stress and by blocking GRP78 and CHOP expression, reducing Caspase 12 activation, and inhibiting cell apoptosis.48

There are other interventions being explored. 1-(3,4-dihydroxyphenyl)-2-thiocyanate-ethanone, referred to as BiP inducer X (BIX), selectively upregulates GRP78/BiP mRNA and protein in cultured cells via the ATF6 pathway,50 without inducing the XBP-1 and CHOP mRNAs, to protect against ischemic AKI.51 Bax inhibitor-1 also has been shown to have a cytoprotective effect against renal ischemic injury by modulating ER stress. After ischemia, marked increases in sXBP-1, CHOP, ATF6, and phospho-JNK were found in kidneys in Bax inhibitor-1 knockout mice in comparison to wild type animals, indicating that injury and renal dysfunction was greater.52 Moreover, the 150 kDa oxygen-regulated protein (ORP150) is an inducible ER chaperone protein with cytoprotective properties related to cell stresses such as ischemia. Renal tubular epithelial cells transfected with ORP150 were protected against hypoxic injury, and transgenic mice overexpressing ORP150 subjected to renal I/R displayed a blunted kidney injury.53

Conclusion

The ER has many important roles in the induction of renal tubular epithelial cell apoptosis in ischemic AKI. Double effects of ER stress suggest that modulation of ER stress through pharmacologic intervention to amplify the cytoprotective aspects of the UPR, such as GRP78 and sXBP-1 upregulation, while down regulating the apoptosis promoting effects of UPR induction, such as CHOP and JNK upregulation, may benefit ischemic-related renal injury. Further explorations of the underlying mechanisms between ER stress and ischemic AKI are still needed.

Actually, the intrinsic, extrinsic and ER stress associated apoptotic pathways have all been implicated in ischemic AKI and have a lot of interrelation and interaction. For example, mitochondria is one of the converging points in cell apoptosis. In this regard, combination therapies that block multiple upstream pathways of cell apoptosis simultaneously or at different time points to ensure cell survival and renal function may be one of the future research focuses.

Disclosure statement

The authors declare that they have no competing interests. M.G. designed and drafted manuscript; J.Z. edited and revised manuscript; Y.X., W.J., H.D., Y.H. and X.-F. An approved final version of manuscript. This article does not contain any studies with human participants or animals performed by any of the authors.

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