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REVIEW

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Targeting endoplasmic reticulum stress: an innovative therapeutic strategy for podocyte-related kidney diseases

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Abstract

The endoplasmic reticulum (ER) is a vital organelle responsible for protein quality control, including the folding, modification, and transport of proteins. When misfolded or unfolded proteins accumulate in the ER, it triggers endoplasmic reticulum stress (ERS) and activates the unfolded protein response (UPR) to restore ER homeostasis. However, prolonged or excessive ERS can lead to apoptosis. The kidneys play a crucial role in maintaining physiological functions by excreting metabolic waste, regulating blood volume, balancing electrolytes and acid-base levels, and secreting various bioactive substances. Podocytes, epithelial cells situated outside the glomerular basement membrane, are essential for maintaining the structural integrity and permeability of the glomerular filtration barrier. Previous studies have shown that ERS in podocytes can contribute to the development of diseases such as glomerulonephritis, hereditary nephropathy, and diabetic kidney disease, potentially progressing to end-stage renal disease and causing patient mortality. As such, investigating ERS in podocytes has become a key area of focus in kidney disease research. This study examines recent advancements in understanding the effects of excessive ERS on podocytes across various kidney diseases, highlights the role of podocyte ERS in disease progression, and explores the potential therapeutic benefits of targeting the UPR to manage ERS in kidney diseases, thereby providing a scientific basis for clinical interventions.

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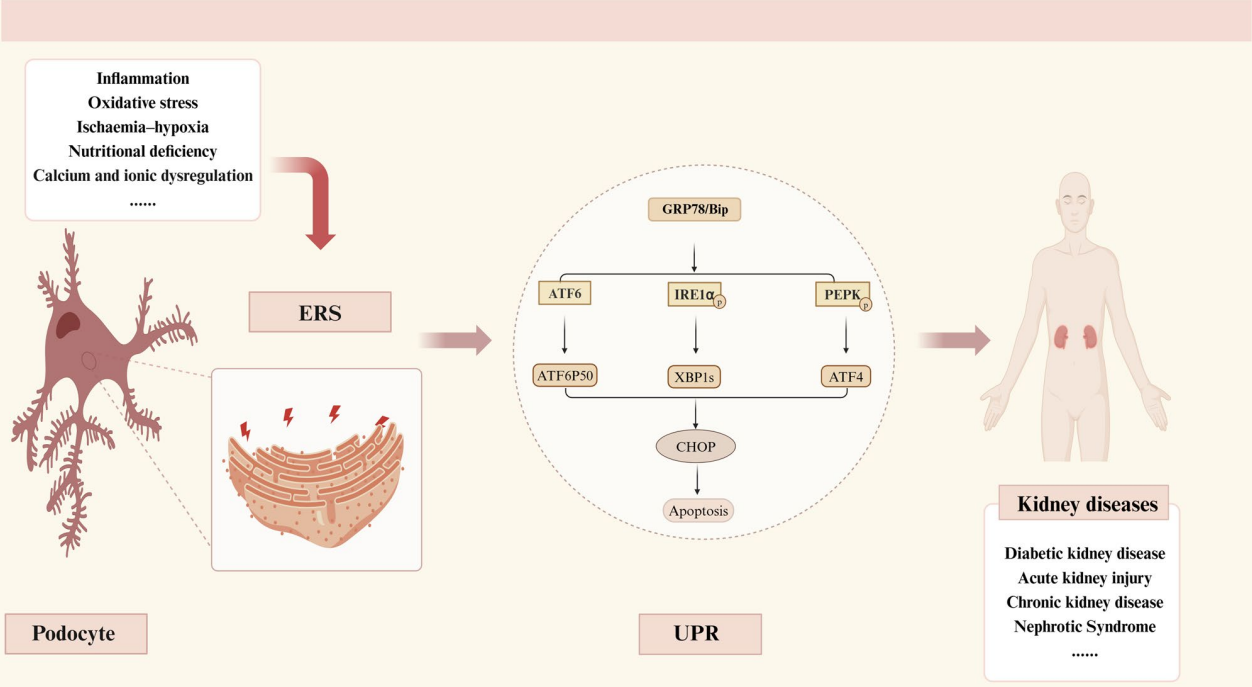
Graphical Abstract



Keywords Podocyte, Endoplasmic reticulum stress, Apoptosis, Unfolded protein response, Kidney disease

Introduction

Podocytes

The podocyte, an epithelial cell found in the visceral layer of the renal vesicle, is essential for preserving the integrity of the glomerular basement membrane (GBM) in the kidney [1]. By forming a slit membrane that connects with the basement membrane, podocytes establish a selective filtration mechanism that serves as both a charge and mechanical barrier, preventing protein passage into the urine [2]. Additionally, podocytes can also regulate the size of slit diaphragms through the contraction of myosin filaments, affecting the capillary diameter and blood flow, thereby modulating the permeability of the filtration membrane [3]. Damage to this critical barrier can lead to proteinuria and potentially progress to irreversible end-stage renal disease (ESRD), posing a significant threat to human health [4, 5].

Research has shown that podocytes are the primary site of injury in conditions such as minimal change disease, focal segmental glomerulosclerosis (FSGS), and diabetic kidney disease (DKD) [6]. Additionally, a reduction in podocyte numbers is a significant marker of glomerulosclerosis and kidney failure [7]. Therefore, protecting podocytes is crucial for the prevention and treatment of kidney diseases. The podocytes, however, possess highly efficient endoplasmic reticulum (ER) protein-folding capacities and active metabolic processes for both synthesis and degradation, making them particularly sensitive to endoplasmic reticulum stress (ERS) [8]. As a result, protecting podocytes is closely linked to maintaining ER homeostasis.

ERS

The ER is essential for protein synthesis, folding, and structural maturation, and it also functions as an intracellular transport system for organic substances [9]. However, its homeostasis can be disrupted by physiopathological factors such as nutritional deficiencies, hypoxia, lipid overload, oxidative stress, and infections. This disturbance hampers the protein quality control system of the ER, resulting in the accumulation of unfolded or misfolded proteins within the ER lumen, thereby initiating ERS [10]. ERS plays a critical role in the pathogenesis of various diseases, including diabetes, cancer, neurodegenerative, liver, lung, ocular, circulatory, skeletal muscle, and infectious diseases (Fig. 1) [11, 12]. Literature indicates that ERS is a progressive factor in kidney injury and plays a significant role in the development of kidney diseases [13].

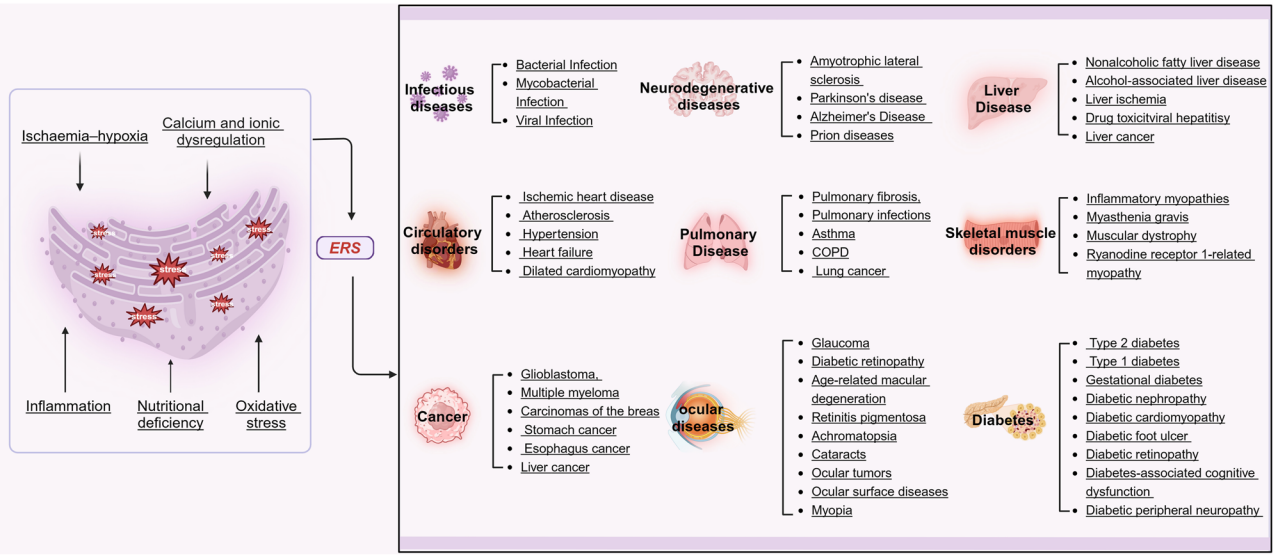


Fig. 1 Causes and diseases resulting from endoplasmic reticulum stress

Unfolded protein response (UPR)

When the buildup of misfolded proteins in the ER reaches a critical threshold, the UPR is triggered to reestablish the balance between protein folding capacity and demand [14]. This corrective response, termed the UPR, consists of three primary pathways: protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 alpha (IRE1α) [15, 16]. Glucose-Regulated Protein 78 (GRP78) is an ER chaperone and a central regulator of ER homeostasis, and it is involved in the activation of the ERS response. Under normal conditions, GRP78 binds to the ER luminal domains of the ERS sensors, including IRE1α, PERK, and ATF6, keeping them inactive [17]. During ERS, GRP78 binds to unfolded and misfolded proteins, disengaging from transmembrane sensors, which in turn activates the three branches of the UPR [18].

IRE1α pathway When activated, IRE1α facilitates the splicing of X-box binding protein 1 (XBP1) mRNA, resulting in the formation of the active transcription factor XBP1s. This activation triggers a cascade of gene expressions that improve the folding capabilities of the ER and enhance the degradation efficiency of unfolded proteins [19].

PERK pathway The PERK pathway mitigates ER load by phosphorylating eukaryotic initiation factor 2 alpha (eIF2α), which inhibits protein synthesis. It also activates activating transcription factor 4 (ATF4), which drives the transcription of the C/EBP homologous protein (CHOP) and influences cell survival and apoptosis processes [20, 21].

ATF6 pathway During ERS, ATF6 is transported to the Golgi where it is cleaved, producing the active transcription factor ATF6p50. This leads to a series of gene expressions that enhance the protein-folding capacity of the ER (Fig. 2) [22].

The UPR functions to help the cell adapt to ERS via these pathways, maintaining ER functionality and preventing cellular damage from protein accumulation [23]. However, in cases of severe or prolonged ERS, the UPR can become dysregulated, potentially leading to apoptosis [24].

Podocyte injury and ERS pose a significant threat to kidney health, and podocytes are highly sensitive to ERS [25]. ERS has been recognized as a major pathway leading to podocyte death [26]. Studies have shown that the accumulation of misfolded proteins in the ER of podocytes induces ERS, which, in turn, reduces the levels of synaptic proteins in podocytes, triggering their damage [27]. Experimental evidence supports this notion. For instance, inhibition of ATF4, a key transcription factor involved in the ERS response, significantly mitigated ERS-induced podocyte injury and improved defects in the lacunar septum [28]. Moreover, experiments with CHOP knockout mice demonstrated that deletion of the CHOP gene significantly alleviated podocyte injury [29]. Taken together, these findings provide compelling evidence for a direct causal relationship between ERS and podocyte injury.

Although the effects of ERS in podocytes on kidney disease have been extensively studied in recent years, few reviews have comprehensively summarized the progress made in this area. This paper reviews recent research advances in podocyte ERS in kidney disease. By investigating podocyte ERS and its potential regulatory

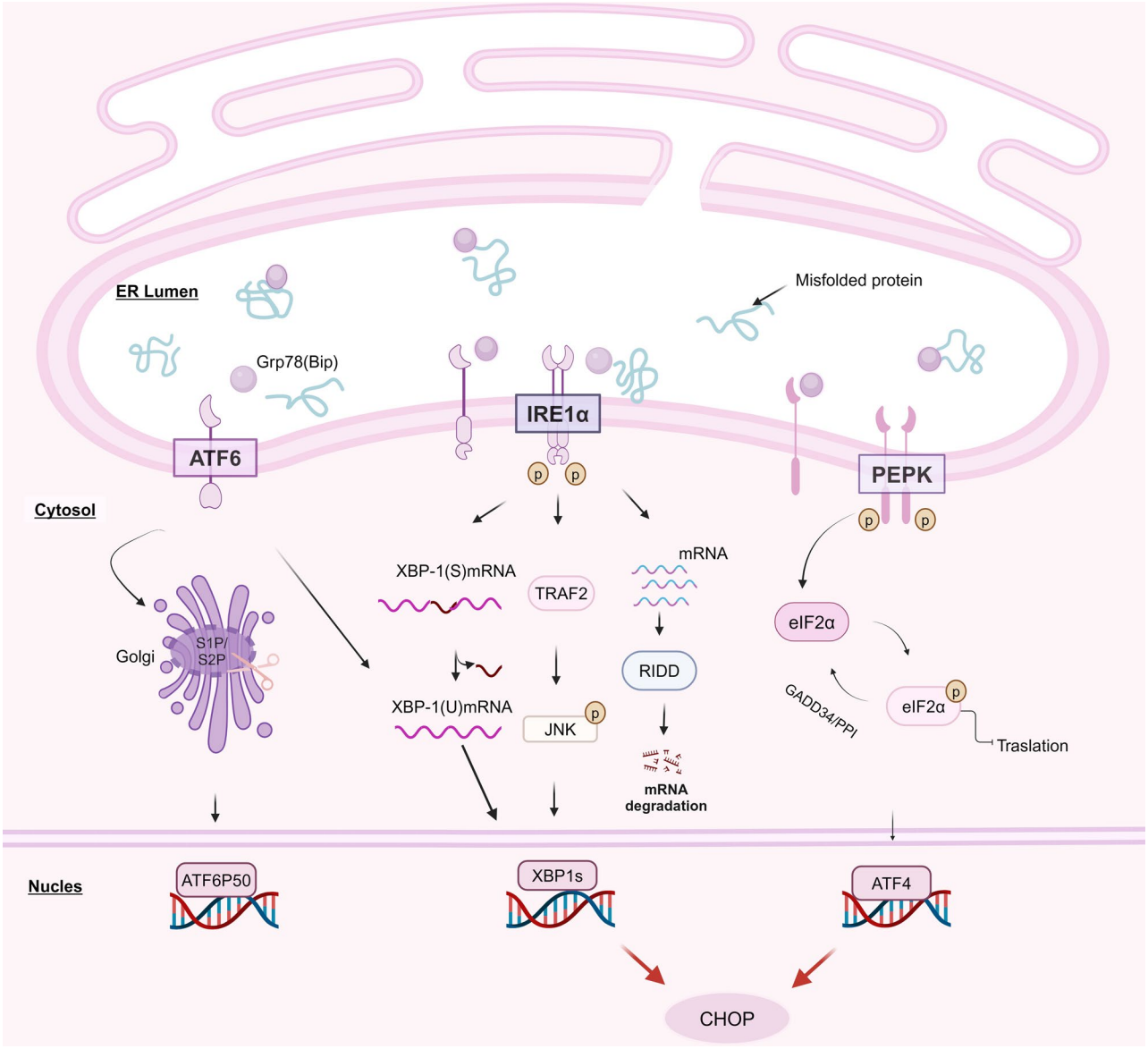


Fig. 2 Three signaling pathways of the unfolded protein response
When misfolded or unfolded proteins accumulate in the ER, the molecular chaperone GRP78/BiP is displaced from the ER lumen, triggering the activation of three ERS sensors: IRE1α, PERK, and ATF6. This activation leads to downstream signaling pathways through phosphorylation:
ATF6 Signaling Pathway: ATF6 signaling is initiated when ATF6 is cleaved by Site 1 protease and Site 2 protease in the Golgi apparatus. The cleaved subunit (p50ATF6) acts as a transcription factor, regulating the expression of genes involved in stress response and protein folding
IRE1α Pathway: Upon phosphorylation, IRE1α forms dimers. Phosphorylated IRE1α (p-IRE1α) induces the splicing of XBP1 mRNA, generating the transcription factor XBP1s. Once XBP1s enters the nucleus, it activates the transcription of CHOP. Additionally, p-IRE1α activates the JNK signaling pathway via TRAF2, which leads to the phosphorylation of JNK and the subsequent activation of Caspase-12-mediated apoptosis. Furthermore, p-IRE1α promotes the degradation of mRNA through the RIDD process
PERK Pathway: PERK undergoes autophosphorylation, resulting in dimerization. Activated PERK then phosphorylates eukaryotic initiation factor 2α (eIF2α), which in turn enhances the translation of the transcription factor ATF4. ATF4 activates the transcription of CHOP, initiating a pro-apoptotic program and promoting cell apoptosis

mechanisms comprehensively, we can gain a deeper understanding of how podocyte injury might positively impact kidney disease treatment and explore potential therapeutic options (Table 1).

The impact of ERS in podocytes on the development of kidney disease

Primary glomerular disease

FSGS

Data indicates that FSGS constitutes 7% of primary glomerulonephritis cases in China [30]. The primary clinical

Table 1 The role of endoplasmic reticulum stress in kidney disease in podocytes

Reference	Disease	Model	Changes in ERS	Conclusions	Treatment
[33]	FSGS	**Animal model**: Atg5 mutant mice	GRP78, PERK, ATF4, CHOP, p-eIF2α↑	ERS due to impaired autophagic organelle turnover in podocytes is sufficient to cause many of the manifestations of FSGS in mice.	\
[34]	FSGS	**Animal model**: single injection ADR of iPLA2γ KO mice	Treatment with clindamycin: UPR↑	ERS-induced autophagy is facilitated by iPLA2γ.	\
[35]	FSGS	**Cell model**: cultured rat GECs in the presence of ECM and integrin engagement **Animal model**: in male CD mice injections of sheep anti-rabbit glomerular antiserum	GRP78, p-eIF2α, CHOP↑	FSGS is associated with induction of ERS.	\
[36]	FSGS	**Cell model**: ANLNR431C overexpression in podocytes	CHOP↑	*ANLNR431C* induces ERS and apoptosis in podocytes.	\
[37]	FSGS	**Animal model**: podocyte-specific Sall1-deficient mice with ADR	GRP78↑	The loss of Sall1 in podocytes increases ERS and apoptosis.	\
[38]	FSGS	**Cell model**: transfection of podocytes with podocin^{R168H}	GRP78, p-PERK ↑	R168H mutant pod cytosine leads to podocyte apoptosis through ERS.	\
[39]	FSGS	**Animal model**: FSGS transgenic mouse model	Treatment with 4-PBA: CHOP, GRP78↓	4-PBA could have reduced cytotoxic ERS independently.	4-PBA
[41]	MN	**Animal model**: Injected SD rats with rabbit anti-Fx1A IgG antibody **Cell model**: podocytes with Tunicamycin	GRP78↑	ERS plays an important role in podocyte damage. Autophagy can repair the cytoskeleton damage caused by ERS as a protective mechanism.	\
[44]	IgAN	**Animal model**: ddY mice **Cell model**: podocyte with recombinant FABP4 and PA	p-eIF2α, p-IRE1α, GRP78, XBP1s, CHOP↑	Secreted FABP4 derived from the glomerulus increases ERS in podocytes, leading to proteinuria in IgAN.	\
[48]	DKD	**Animal models**: podocyte-specific Atg5-deficient mice witn TM and fed HFD and STZ	Treatment with TUDCA: CHOP ↓	Insufficient autophagy leads to severe podocyte injury by activation of ERS in DKD.	TUDCA
[49]	DKD	**Animal model**: C57BL/6 mice injected with STZ	Treatment with puerarin: PERK, eIF2α, ATF4↓	The activation of ERS-mediated PERK pathway mediated by puerarin promotes autophagy to protect from kidney damage in DKD.	Puerarin
[50]	DKD	**Cell model**: mouse podocytes with HG	GRP78, CHOP, p-JNK↑	Cyclin-dependent kinase 5 contributes to ERS induced podocyte apoptosis via promoting MEKK1 phosphorylation at Ser280 in diabetic nephropathy.	\
[51]	DKD	**Cell model**: mouse podocytes with HG	GRP78, CHOP ↑	Hyperglycemia induced apoptosis partly through ERS in the podocytes, which possibly contributes to the pathogenesis of DKD.	\
[52]	DKD	**Cell model**: GRP78 siRNA specifically podocytes with HG	Treatment with HQH: GRP78, CHOP↓	Beneficial effects of HQH on HGinduced MPC5 podocyte dysfunction were observed, and occurred through the ERS.	HQH
[53]	DKD	**Cell model**: podocytes with PA	GRP78, CHOP↑	ERS is involved in podocyte apoptosis induced by saturated fatty acid palmitate.	\
[54]	DKD	**Cell model**: podocytes with PA	Treatment with AS-IV: GRP78, CHOP ↓	AS-IV inhibited PA-induced ERS and podocyte apoptosis.	AS-IV
[55]	DKD	**Animal model**: Podocyte-Specific NOX4 transgenic mice	GRP78, CHOP↑	Upregulation of NOX4 leads to podocyte apoptosis via ERS.	\
[56]	DKD	**Animal model**: mice with Tsc1-deficient podocytes	Treatment with 4-PBA or rapamycin: GRP78↓	ERS induced by mTORC1 activation may contribute to podocyte damage.	4-PBA, Rapamycin
[57]	DKD	**Cell model**: podocytes with AGEs	Treatment with TUDCA: GRP78↓	TUDCA protects podocytes by inhibiting AGEs-mediated ERS.	TUDCA

Table 1 (continued)

Reference	Disease	Model	Changes in ERS	Conclusions	Treatment
[58]	DKD	**Cell model**: podocytes with PA	GRP78, CHOP, XBP1s, p-PERK↑	Palmitate causes podocyte apoptosis through ERS.	\
[59]	DKD	**Cell model**: podocytes with PA and CHOP knockdown podocytes by lentiviral infection using a CHOP-specific shRNA	Treatment with Palmitoleic or oleic acid: GRP78, CHOP↓	Palmitic acid causes apoptosis in podocytes through ERS, whereas palmitoleic or oleic acid and CHOP gene silencing attenuate palmitic acid-induced podocyte cell death.	Palmitoleic acid
[60]	DKD	**Cell model**: podocytes with PA	Treatment with TO901317: CHOP↓	TO901317 induce Scd-1 and Ameliorate Palmitic Acid–Induced Podocyte Death.	TO901317
[61]	DKD	**Cell model**: podocytes with PA	Treatment with rapamycin: p-PERK, CHOP↓	Palmitate induced ERS-triggered apoptosis via mTORC1 in podocytes.	Rapamycin
[62]	DKD	**Cell model**: podocytes with HG	Treatment with overexpression of AM251: PERK, p-eIF2α↓	CB1R is an upstream regulator of high glucose-induced B1R and B2R expression, and that it regulates the high glucose to induce ERS and the eventual apoptosis of rat podocytes.	AM251
[63]	DKD	**Cell model**: podocytes with HG and apelin **Animal model**: kk-Ay mice with apelin	p-eIF2α, CHOP↑	Apelin aggravated podocyte injuries by ERS.	\
[64]	DKD	**Animal model**: COX-2 deletion mice were injected with STZ	CHOP↑	Deficiency of macrophage cyclooxygenase-2 leads to podocyte apoptosis via ERS.	\
[29]	DKD	**Cell model**: human podocytes were transfected with RTN1A **Animal model**: db/db mice with early unilateral nephrectomy	Treatment with TUDCA: GRP78, p-PERK, CHOP↓	ERS plays a major role in podocyte injury in DN and RTN1A might be a key regulator of ERS in podocytes.	TUDCA
[65]	DKD	**Cell model**: podocytes with the supernatant of MCs and HG	CHOP, p-IRE1α↑	Suppressed ER-associated degradation by intraglomerular cross talk between mesangial cells and podocytes causes podocyte injury.	\
[66]	DKD	**Cell model**: podocytes with HG and PA	Treatment with IR over-expression: GRP78, CHOP, p-PERK↓	Insulin receptor over-expression protects podocytes from ERS and apoptosis.	IR over-expression
[67]	DKD	**Cell model**: podocytes with HG **Animal model**: SD rats were injected with STZ	Treatment with overexpression of Mfn2: PERK, CHOP↓	Mfn2 inhibits high glucose-induced podocyte apoptosis through the PERK pathway.	Mfn2
[68]	DKD	**Cell model**: E11 podocytes lines with Shp2 knockdown with HG **Animal models**: Mice with podocyte-specific disruption of Shp2 and with HFD and Injected with STZ	Treatment with the Shp2-defcient: PERK, eIF2α, IRE1α↓	Deficiency of the Src homology phosphatase 2 protects podocytes by inhibiting ERS.	Deficiency of the Shp2
[69]	DKD	**Animal model**: Mice with podocyte-specific sEH disruption and LPS	Treatment with sEH deficiency: PERK, eIF2α, p-IREα, XBP1s ↓	Podocyte sEH deficiency attenuates LPS-induced ERS.	sEH
[70]	DKD	**Cell model**: podocytes with HG **Animal model**: kk-Ay mice	Treatment with the Emodin: GRP78, p-PERK, p-eIF2α, ATF4, CHOP↓	Emodin mitigates podocytes apoptosis induced by ERS through the inhibition of the PERK pathway.	Emodin
[71]	DKD	**Cell model**: podocytes with HG **Animal model**: SD rats were injected with STZ	Treatment with IMD: GRP78, ATF4, CHOP↓	Intermedin by inhibiting kidney ERS and ERS-induced podocyte injury and apoptosis.	IMD
[72]	DKD	**Cell model**: podocytes with HG **Animal model**: rats were injected with STZ	Treatment with AS-IV: p-eIF2α, p-PERK, JNK, GRP78, CHOP↓	AS-IV protects podocytes by inhibiting ERS.	AS-IV

Table 1 (continued)

Reference	Disease	Model	Changes in ERS	Conclusions	Treatment
[73]	DKD	**Cell model**: podocytes with HG **Animal model**: SD rats were injected with STZ	Treatment with AS-IV: GRP78, p-PERK, p-eIF2α, CHOP, ATF4↓	The protective effect of AS-IV on ERS-induced podocyte apoptosis is associated with inhibition of PERK-ATF4-CHOP pathway.	AS-IV
[74]	DKD	**Cell model**: podocytes with HG	Treatment with EGCG: GRP78, p-PERK↓	Epigallocatechin-3gallate protects from high glucose induced podocyte apoptosis via suppressing ERS.	EGCG
[75]	DKD	**Animal model**: C57BL/6J mice were fed HFD	Treatment with dapagliflozin: GRP78, p-PERK, p- IRE1α, ATF4↓	Dagliflozin protects podocytes by inhibiting ERS.	Dapagliflozin
[76]	DKD	**Animal model**: Mice specifically lacking XBP1 in podocytes	ATF6, CHOP ↑	Podocyte-specific deletion of XBP1 promotes ERS in DN.	\
[77]	DKD	**Animal model**: a podocyte-specific OST48 knock-in mouse model	GRP78, XBP1s↑	Podocyte OST48-mediated AGE accumulation resulted in ERS.	\
[78]	DKD	**Cell model**: podocytes with HG	Treatment with EW-7197: ATF6α↓	EW-7197 protects podocytes through ERS.	EW-7197
[79]	DKD	**Cell model**: podocytes with PA	Treatment with paclitaxel: CHOP, ATF6α, XBP1s, GRP78↓	Paclitaxel ameliorates palmitate-induced injury in mouse podocytes via ERS.	Paclitaxel
[80]	DKD	**Animal models**: DBA/2J mice with HFD and Injected with STZ	Treatment with Aliskiren or valsartan: CHOP, XBP1↓	Aliskiren or valsartan protects podocytes through ERS.	Aliskiren or valsartan
[81]	DKD	**Animal models**: aPC^{high} mice with HFD and injected with STZ and db/db mice **Cell model**: podocytes with aPC	Treatment with aPC: XBP1s, ATF6, CHOP↓	Insulin signaling is defective, but aPC still protects podocytes by maintaining endoplasmic reticulum homeostasis.	aPC
[82]	DKD	**Cell model**: podocytes with HG and AOPP	GRP78, CHOP, PERK, ATF6, IREα↑	The PERK, ATF6, and IRE1 pathways, mediate AOPP induced podocyte apoptosis.	\
[83]	DKD	**Cell model**: podocytes with PA **Animal model**: db/db mice	Treatment with AS-IV: ATF6, PERK, IREα, eIF2α, ATF4, XBP1, CHOP, p-JNK↓	AS-IV Restored SERCA2 Expression and Inhibited ERS-Induced Apoptosis in Podocytes.	AS-IV
[84]	DKD	**Cell model**: podocytes with HG **Animal model**: Mice were injected with STZ	Treatment with AS-IV: GRP78, ATF6, p-PERK, p-IREα, CHOP, p-JNK↓	AS-IV ameliorated HG-induced podocytes apoptosis partially through mitigating ERS-mediated apoptotic pathway.	AS-IV
[85]	DKD	**Animal model**: db/db mice	Treatment with DL-3-NBP: GRP78, p-PERK, p-IRE1α, ATF6, p-PERK, CHOP↓	DL-3-N-Butylphthalide protects podocytes by inhibiting ERS.	DL-3-NBP
[86]	DKD	**Cell model**: podocytes with HG **Animal model**: db/db mice	Treatment with UDCA: GRP78, p-IRE1α, ATF6, p-PERK, CHOP↓	UDCA protects podocytes by inhibiting ERS.	UDCA
[87]	DKD	**Cell model**: podocytes with HG **Animal model**: db/db mice	Treatment with UDCA and 4-PBA: GRP78, p-PERK, p-IRE1α, ATF6, CHOP, XBP1s↓	Ursodeoxycholic acid and 4-phenylbutyrate prevent ERS-induced podocyte apoptosis in diabetic nephropathy.	UDCA and 4-PBA
[90]	OKD	**Cell model**: podocytes with PA	CHOP, GRP78↑	Palmitate-induced lipid excess leads to podocyte apoptosis through ERS.	\
[91]	OKD	**Animal model**: C57BL/6-CCR2 knockout mice were fed HFD	Treatment with CCR2 knockout: XBP1, GRP78↓,	CCR2 knockout ameliorates obesity-induced podocyte injury through inhibiting ERS.	CCR2 knockout

Table 1 (continued)

Reference	Disease	Model	Changes in ERS	Conclusions	Treatment
[95]	Type IV collagen nephropathy	**Cell model**: human podocytes overexpressed APOL1 G0, G1, or G2	Treatment with PBA and salubrina: GRP78, p-eIF2α↓	APOL1 risk variants cause podocytes injury through enhancing ERS.	PBA and salubrinal
[96]	Type IV collagen nephropathy	**Cell model**: knockdown of OSGEP, TP53RK, or TPRKB in human podocytes	p-IRE1α, XBP1s, p-eIF2α, ATF4↑	Mutations in the KEOPS complex gene lead to podocyte apoptosis through ERS.	\
[94]	Type IV collagen nephropathy	**Cell model**: podocytes with COL4A3 overexpression **Animal model**: COL4A3 knockout mouse	Treatment with COL4A3 downregulation: CHOP, PERK, p- eIF2α↓	COL4A3 overexpression leads to podocyte apoptosis, whereas COL4A3 downregulation leads to the activation of ERS to exert podocyte protective effects.	COL4A3 down-regulation
[97]	Type IV collagen nephropathy	**Cell model**: podocytes were transfected with siRNA COL4A3	Treatment with MG132: GRP78, CHOP↓	MG132 inhibits ERS and reduces podocyte apoptosis by significantly elevating COL4A3 expression.	MG132
[28]	Type IV collagen nephropathy	**Cell model**: the human podocyte line with doxycycline	ATF4, CHOP↑	The transcription factor ATF4 mediates ERS-related podocyte injury and slit diaphragm defects.	\
[99]	AKI	**Cell model**: E11 murine kidney podocytes treated with LPS **Animal model**: podocyte-specific sEH-deficient mice	PERK, eIF2α, p-IRE1α, XBP1s↓	Podocyte sEH deficiency attenuates LPS-induced ERS to protect podocytes.	sEH deficiency
[102]	CKD	**Cell model**: mouse podocytes with BSA	GRP78, p-IRE1α↑	Intracellular albumin overload elicits ERS to induce podocyte apoptosis.	\
[104]	CKD	**Cell model**: Podocytes were transiently transfected with TRPC6 siRNA and treated with BSA	Treatment with TRPC6: GRP78↓	TRPC6 mediates albumin overload-induced ERS and apoptosis in podocytes.	TRPC6
[103]	CKD	**Cell model**: CD2AP siRNA was transfected into podocytes before exposed to BSA	Treatment with CD2AP: GRP78↓	CD2AP reduce podocyte damage by inhibiting ERS.	CD2AP
[105]	CKD	**Animal model**: C57BL/6 mice infused with aldosterone **Cell model**: podocytes with aldosterone	Treatment with PBA and Spi: GRP78, CHOP↓	Aldosterone/MR induced ERS and podocyte injury.	PBA and Spi
[106]	CKD	**Cell model**: podocytes with Ang II	Treatment with Curcumin: GRP78, ATF4, p-eIF2α, CHOP↓	Curcumin attenuates angiotensin II-induced podocyte injury and apoptosis by inhibiting ERS.	Curcumin
[107]	CKD	**Cell model**: podocytes with PA	Treatment with Berberine: PERK, ATF4, CHOP, IRE1α, ATF6↓	BBR may protect against PA-induced podocyte apoptosis by ERS.	Berberine
[108]	CKD	**Cell model**: podocytes with AOPP	Treatment with Arctiin: GRP78, CHOP↓	Arctiin reduce podocyte damage by inhibiting ERS.	Arctiin
[110]	Other	**Cell model**: podocytes with PAN	GRP78, ATF6α↑	Puromycin amino nucleoside triggers apoptosis in podocytes by inducing ERS.	\
[111]	Other	**Animal model**: SD rats injection of PAN **Cell model**: podocytes with PAN	eIF2α, GRP78↑	mTORC1 activation triggers the unfolded protein response in podocytes and leads to nephrotic syndrome.	\
[112]	Other	**Animal model**: C321R-LAMB2 Transgenic Mice	GRP78, CHOP↑	Laminin β2 gene missense mutation produces ERS in podocytes.	\
[113]	Other	**Cell model**: Use of puromycin on transfected podocytes **Animal model**: Crb2 knockout mice	GRP78↑	Increasing ERS are pivotal factors for onset and progression of CRB2-related SRNS.	\
[114]	Other	**Animal model**: mouse model of NS caused by LAMB2 C321R **Cell model**: Tg-C321R podocytes	Treatment with K201and MANF: IRE1α, XBP1s, p-eIF2α, ATF4↓	ER calcium stabilizers to rescue ER-Stressed Podocytes in Nephrotic Syndrome.	K201 and MANF

manifestation in FSGS patients is nephrotic syndrome (NS), predominantly characterized by significant proteinuria in most cases [31]. Research shows that FSGS causes significant fusion of podocyte foot processes and associated capillary damage, which ultimately leads to glomerulosclerosis [32].

Research has shown that autophagy-related gene 5 (Atg5) mutant mice exhibit impaired autophagic organelle conversion in podocytes, leading to ERS [33]. In a related study, mice deficient in calcium-independent phospholipase $A_2\gamma$ ($iPLA_2\gamma$) were treated with adriamycin (ADR), which triggered the UPR and increased the expression of LC3. These findings suggest that ERS, induced by the absence of $iPLA_2\gamma$, initiates an autophagic process in podocytes, providing a protective autophagic response in these cells [34].

To investigate whether mitigating ERS can protect podocytes, a study was conducted involving the induction of glomerulonephritis in male CD-1 mice through intraperitoneal injections of anti-glomerular serum. This scenario was compared with cultured rat podocytes lacking extracellular matrix (ECM) and integrins. The findings showed a disruption in the podocyte-ECM interaction, with significant increases in GRP78 and phosphorylated eIF2α (p-eIF2α) levels, while CHOP levels remained unchanged. However, following clindamycin administration, there was an increase in CHOP levels and subsequent podocyte apoptosis, highlighting a significant relationship between the intensity of ERS and podocyte apoptosis [35].

The increase in CHOP levels in podocytes overexpressing ANLNR431C, coupled with elevated GRP78 expression in podocyte-specific Sall1-deficient mice treated with ADR, demonstrates that both ANLNR431C overexpression and Sall1 deletion exacerbate ERS. This intensification contributes to the induction of apoptosis in podocytes [36, 37].

In related research, scholars constructed podocytes to express podocin R168H by transfecting them with podomycin R168H. This modification resulted in a significant increase in the expression of GRP78, phosphorylated PERK (p-PERK), and caspase-12, leading to the loss of actin filaments in podocytes and subsequent podocyte damage, indicating that the podocin-R168H mutation induces podocyte damage via ERS [38]. Additionally, in a separate study that developed a FSGS transgenic mouse model, an upsurge in GRP78 and CHOP expression was observed. Notably, this expression diminished following treatment with 4-Phenylbutyric Acid (4-PBA), indicating that 4-PBA may alleviate ERS-induced podocyte toxicity and ameliorate albuminuria [39].

Membranous nephropathy (MN)

In China, MN accounts for 9.89% of primary glomerulonephritis cases [30]. MN is a prevalent cause of NS in adults, characterized by numerous immune complex deposits located on the epithelial side of glomerular capillary walls in affected individuals [40]. In one particular study, SD rats were injected with rabbit anti-Fx1A IgG antibody to induce MN, and podocytes were treated with tunicamycin (TM). The findings revealed an increase in GRP78 and LC3 levels, coupled with a decrease in the cytoskeletal protein microtubulin-β, underscoring the pivotal role of ERS in the development of MN due to podocyte damage [41].

Immunoglobulin A nephropathy (IgAN)

The primary clinical feature of IgAN is diffuse deposition of IgA in the mesangial zone, and it is accompanied by podocytopathies in some cases [42]. As the most prevalent type of primary glomerulonephritis, IgAN is a major factor in chronic kidney disease (CKD) and kidney failure [43]. Research with spontaneously hypertensive ddY mice and palmitate-treated podocytes shows activation of p-eIF2α and phosphorylated IRE1α(p-IRE1α). Subsequent treatment of these podocytes with recombinant fatty acid-binding protein 4 (FABP4) led to elevated gene expression levels of GRP78, XBP1s, and CHOP. These findings suggest that FABP4, secreted by glomeruli, triggers ERS in podocytes, potentially initiating the development of IgAN [44].

DKD

DKD is a major complication of both type 1 and type 2 diabetes and is a leading cause of ESRD, representing a significant threat to human health [45, 46].

Podocytes ERS and autophagy

In DKD, ERS in podocytes is closely intertwined with autophagy. Initially, impaired autophagy triggers ERS, leading to podocyte damage [47]. This relationship was demonstrated in a study using tamoxifen-inducible podocyte-specific Atg5-deficient (iPodo-Atg5) mice on a high-fat diet (HFD) combined with streptozotocin (STZ) injection, which revealed a significant increase in CHOP levels, highlighting its role in the apoptosis of autophagy-deficient podocytes. Additionally, treatment with tauro ursodeoxycholic acid (TUDCA) improved podocyte foot process effacement and podocin expression, while also reducing ERS [48]. Additionally, in STZ-induced C57BL/6 mice treated with puerarin, there was an upregulation in PERK, eIF2α, ATF4, Beclin-1, LC3II, and Atg5 expression, coupled with a downregulation in p62. This was accompanied by an enhancement in the functional protein expression of the peduncle, indicating that puerarin promotes mitochondrial autophagy, thereby

safeguarding podocytes by modulating the PERK/ eIF2α/ ATF4 pathway in DKD [49].

Activation of GRP78

Research on mouse podocytes exposed to high glucose (HG) conditions demonstrated elevated levels of GRP78, CHOP, and caspase-12, establishing a clear association with podocyte apoptosis. In a related study, cyclin-dependent kinase 5 (Cdk5) was found to play a role in the upregulation of GRP78, cleaved caspase-12, and CHOP in podocytes exposed to HG. Further investigation revealed that TM treatment escalated Cdk5's kinase activity and protein expression, particularly at the Ser280 site of phosphorylated MEKK1 (p-MEKK1). The interaction between Cdk5 and p-MEKK1 led to the activation of phosphorylated c-Jun amino (N)-terminal kinases (p-JNK), contributing to podocyte apoptosis. These findings suggest that HG may induce podocyte apoptosis via ERS, and that Cdk5 exacerbates this process by enhancing p-MEKK1 phosphorylation at the Ser280 site in DKD [50, 51]. Conversely, GRP78 siRNA-transfected podocytes under HG conditions showed improved function upon GRP78 inhibition, indicating its potential detrimental role. Additionally, treatment with Huaiqihuang (HQH) demonstrated that reducing GRP78 and CHOP expression could mitigate podocyte apoptosis, indicating that HQH exerts its protective effect on podocytes mainly by inhibiting the activation of GRP78 in the ERS [52].

Treatment of podocytes with palmitic acid (PA) has been shown to increase GRP78 and CHOP protein levels while reducing B-cell lymphoma-2 (Bcl-2) protein levels, culminating in podocyte apoptosis [53]. However, treatment with Astragaloside IV (AS-IV) mitigated the PA-induced ERS in podocytes. AS-IV decreased GRP78 and CHOP expressions and significantly lowered the Bcl-2-associated X protein (Bax)/Bcl-2 ratio, thus reducing podocyte apoptosis [54]. Additionally, podocyte-specific NADPH oxidase 4 (Nox4) transgenic mice exhibited increased levels of both CHOP and GRP78, along with elevated gene expression of Bax and the Bax/Bcl-2 ratio, contributing to podocyte apoptosis [55]. The foregoing had demonstrated that PA and NOX4 genes had induced ERS by up-regulating GRP78, resulting in apoptosis of podocytes. AS-IV had been capable of inhibiting ERS induced by PA and alleviating podocyte injury and apoptosis, thus possessing potential therapeutic value. In mice with tuberous sclerosis complex 1 (Tsc1) deficient podocytes, heightened GRP78 expression was observed, but treatments with rapamycin and 4-PBA significantly decreased GRP78 levels and curbed the reduction in podocyte numbers, indicating that activation of mechanistic target of mechanistic target of rapamycin complex 1 (mTORC1) intensifies ERS and subsequent podocyte damage [56]. Lastly, different doses of advanced glycation end products (AGEs) induced podocyte apoptosis in a dose- and time-dependent manner, elevating GRP78 expression. Conversely, treatment with TUDCA counteracted podocyte apoptosis by inhibiting the ERS-mediated apoptotic pathway [57].

Activation of the PERK-ATF4-CHOP signaling pathway

Following PA treatment, podocytes exhibited upregulation in the mRNA levels of GRP78, CHOP, PERK, and XBP1s [58]. Conversely, treating podocytes with palmitoleic acid significantly suppressed CHOP and GRP78 protein expression, subsequently reducing podocyte apoptosis. To better understand the role of CHOP in PA-induced podocyte death, CHOP expression was specifically reduced using CHOP-specific shRNA. The findings demonstrated notable suppression of CHOP and GRP78 protein levels, which subsequently decreased podocyte apoptosis [59]. Furthermore, treatment of PA-induced podocytes with TO901317, a liver X receptor agonist and Scd-1 inducer, led to decreased CHOP expression and a reduction in podocyte apoptosis [60]. Moreover, mTORC1 down-regulation by rapamycin significantly curbed PA-induced nuclear overexpression of p-PERK and CHOP in podocytes, and CHOP knockdown notably enhanced the reduction of cleaved caspase-3 [61]. In summary, studies have shown that PA treatment can activate the PERK-ATF4-CHOP pathway, leading to podocyte apoptosis. In contrast, liver X receptor agonists and rapamycin can reduce podocyte apoptosis by inhibiting this pathway.

Activation of PERK and p- eIF2α followed HG treatment of rat podocytes. Subsequent treatment with AM251 (a CB1R inhibitor) improved HG-induced expression of Bradykinin receptor B1 (B1R) and Bradykinin receptor B2 (B2R), inhibited activation of PERK and eIF2α, and slowed down cleavage of caspase-3 [62]. Another study treated podocytes with HG and in kk-Ay mice, and the addition of apelin treatment led to a rise in the expression of CHOP and eIF2α, triggering podocyte apoptosis [63]. Meanwhile, induction of macrophage cyclooxygenase-2 (COX-2) deficient mice by STZ revealed increased CHOP expression in the kidneys, leading to podocyte apoptosis [64]. Furthermore, using db/db mice with early unilateral nephrectomy and transfecting human podocytes with reticulon-1 A (RTN1A), then treating with TUDCA, showed that TUDCA-treated diabetic mice exhibited a partial restoration of podocyte numbers, along with decreased expressions of RTN1A, p-PERK, GRP78, and CHOP. This suggested that RTN1A is a key regulator of ERS in podocytes [29]. In addition, podocytes stimulated with the supernatant of mesangial cells (MCs) cultured in HG conditions showed increased protein expression of CHOP, p-IRE1α, and

elevated Bax/Bcl-2 ratios, leading to podocyte apoptosis [65].

Simultaneous treatment of podocytes with HG and PA under insulin overexpression conditions resulted in the complete inhibition of GRP78, CHOP, and p-PERK expressions [66]. In STZ-induced SD rats and HG-treated podocytes, PERK activation led to increased CHOP expression and podocyte apoptosis, which was countered by mitofusin-2 (Mfn2) overexpression [67]. Additionally, the Src homology phosphatase 2 (Shp2) deficiency in podocytes and mice, under combined STZ and HFD conditions, resulted in reduced expressions of PERK, eIF2α, and IRE1α [68]. Furthermore, in lipopolysaccharide (LPS)-induced podocyte-specific soluble epoxide hydrolase (sEH) knockout mice, there was a decrease in PERK, eIF2α, p-IRE1α, XBP1s, and caspase-3 cleavage in podocytes, leading to increased apoptosis [69]. Similarly, in HG-treated mouse podocytes as well as in kk-Ay mice, Emodin treatment inhibited the up-regulation of GRP78, p-PERK, p- eIF2α, ATF4, and CHOP [70]. Additionally, intermedin treatment in STZ-induced SD rats and HG-treated human podocytes lowered the expressions of GRP78, ATF4, and CHOP, thereby reducing podocyte apoptosis and Bax induction while increasing Bcl-2 expression [71]. Studies have also found that AS-IV not only reduces the protein expression of GRP78, ATF4, p-PERK, and CHOP in podocytes cultured under HG stimulation but also significantly inhibits the expression of p- eIF2α, GRP78, and cleaved caspase-3 in TM-induced human podocytes and STZ-injected SD rats, thereby alleviating podocyte apoptosis [72, 73]. Moreover, Epigallocatechin-3-gallate drastically lowered GRP78, p-PERK, and caspase-12 protein levels in HG-induced mouse podocytes, lessening podocyte apoptosis [74]. Lastly, in a DKD mouse model induced by HFD feeding, dagliflozin treatment significantly reduced GRP78, p-PERK, p-IRE1α, and ATF4 expressions, effectively restoring expressions of podocin and nephrin. Dagliflozin also countered the reduction in podocyte numbers and ameliorated the severe distortion and loss of peduncles [75]. Overall, in the experiment treating podocytes with HG and PA, therapies such as insulin, overexpression of Mfn2, inhibition of Shp2 and SHE, as well as the use of intermedin, emodin, AS-IV, and dapagliflozin, significantly inhibited ERS and effectively protected podocytes.

Activation of ATF6 and IRE1-XBP1s pathways

The knockdown of the XBP1 gene in mouse podocytes led to increased nuclear ATF6 and CHOP levels, resulting in proteinuria and expanded GBM [76]. Furthermore, an oligosaccharyltransferase-48 kDa subunit (OST48) knock-in model demonstrated a rise in GRP78 and XBP1s, underscoring the importance of XBP1 in ERS [77]. Additionally, mRNA expression levels of ATF6α, GRP78, CHOP, and XBP1s decreased in podocytes induced with PA and treated with paclitaxel, as well as in HG-induced podocytes treated with EW-7197 (a TGF-β inhibitor). These treatments also reduced Bax and caspase-3 expression while increasing Bcl-2 expression [78, 79]. On the other hand, aliskiren and valsartan significantly reduced CHOP and XBP1 expression, mitigating podocyte damage in STZ and HFD-induced DBA/2J mice [80]. Lastly, treatment of podocytes with activated protein C (aPC) downregulated ATF6 and CHOP levels and restored XBP1s levels in the nucleus. In a db/db mouse model, despite defective insulin signaling, aPC treatment protects podocytes by maintaining ER homeostasis, thus avoiding ATF6-CHOP-dependent adverse ER responses [81]. Overall, various interventions such as paclitaxel, EW-7197, aliskiren, valsartan and aPC were able to attenuate the ERS response and inhibit the expression of ATF6, CHOP and xBP1, thus protecting podocytes and ameliorating the pathological changes in diabetic kidney disease.

UPR three pathways activated

To determine whether the simultaneous activation of the three UPR pathways mediates podocyte apoptosis, a study demonstrated that after inducing podocytes with advanced oxidation protein products (AOPPs), the activation of GRP78, PERK, ATF6, and IRE1α significantly increased the expression levels of CHOP, Bcl-2, caspase-12, and cleaved caspase-3, leading to podocyte apoptosis [82]. Additionally, in db/db mice, STZ-induced mice, or PA/HG-treated mouse podocytes, AS-IV inhibited the three UPR pathways by restoring sarcoplasmic reticulum Ca^{2+}ATPase 2a expression and reducing CHOP, p-JNK, and cleaved caspase levels, thereby diminishing podocyte apoptosis [83, 84]. Moreover, treatment with Dl-3-n-Butylphthalide in db/db mice significantly decreased the expressions of GRP78, p-PERK, p-IRE1α, ATF6, CHOP, and cleaved caspase-3 [85]. Finally, treatment with UDCA and 4-PBA in db/db mice and HG-induced podocytes altered the expressions of GRP78, p-IRE1α, ATF6, p-PERK, and CHOP. UDCA rebalanced Bax and Bcl-2 expressions, while 4-PBA reduced caspase-3 and caspase-12 expressions [86, 87]. These findings show that Dl-3-n-butylphthalide, UDCA, and 4-PBA attenuated podocyte apoptosis and ameliorated the pathological changes in diabetic kidney disease by inhibiting the activation of the three UPR signaling pathways.

Obesity-related kidney disease (OKD)

As living standards improve, obesity rates are rising, marking it as a major risk factor for CKD, affecting 20–25% of the global population [88]. Obesity is recognized as an independent detriment to kidney health, and

its link to nephropathy is increasingly acknowledged [89]. Studies have shown that treating podocytes with PA leads to lipid accumulation and a significant increase in CHOP and GRP78 mRNA expression, coupled with a decrease in Bcl-2 expression. This suggests that PA-induced lipid overload might instigate podocyte apoptosis through ERS [90]. Moreover, in C57BL/6 C-C chemokine receptor 2 (CCR2) knockout mice fed an HFD, XBP1 and GRP78 levels significantly decreased, yet the CCR2 knockout managed to reduce podocyte loss, enhancing GBM thickness and podocyte structure. These findings suggest that CCR2 knockdown could mitigate obesity-related podocyte damage by suppressing ERS [91].

Hereditary and congenital kidney diseases

Type IV collagen nephropathy is one of the most common inherited glomerular diseases, including Alport syndrome (AS) and thin basement membrane nephropathy [92]. Genetic mutations in these conditions compromise the mechanical integrity of the GBM, disrupt interactions between podocytes and ECM receptors, and ultimately lead to podocyte damage [93]. Normally, collagen type IV (COL4) undergoes glycosylation and folding within the ER, but ERS can induce mutations in COL4 [94]. These observations highlight a significant connection between podocyte ERS and the pathogenesis of inherited and congenital kidney diseases.

To assess if COL4-associated nephropathy gene variants trigger podocyte injury via ERS, a study established stable human podocytes overexpressing APOL1 risk variants G0, G1, or G2. In these podocytes, the expression of GRP78 protein and the levels of p-IRE1αsignificantly increased. Subsequently, treatment with PBA (an ERS inhibitor) and salubrinal (an eIF2α inhibitor) demonstrated that reducing ERS lessened podocyte injury induced by the APOL1 risk variant [95]. In another research effort, employing shRNA to knock down OSGEP, TP53RK, and TPRKB gene expressions in human podocytes resulted in increased levels of XBP1s, p-IRE1α, p- eIF2α, ATF4 proteins, and activated caspase-3, leading to podocyte apoptosis [96]. Furthermore, introducing the G1334E mutation in mice upregulated CHOP, while downregulating COL4A3 did not change CHOP levels but increased PERK and p-eIF2α levels, suggesting that overexpression of COL4A3 may induce podocyte apoptosis in type IV collagen nephropathy [94]. Conversely, downregulation of COL4A3 might inhibit ERS activation, protecting podocytes. Furthermore, overexpression of COL4A3 in human podocytes, along with the administration of MG132 (a proteasome inhibitor), led to a significant decrease in GRP78, CHOP, and cleaved caspase-3 levels, while simultaneously increasing Bcl-2 levels. This ultimately reduced podocyte apoptosis, suggesting that ERS-induced apoptosis plays a role in the podocyte damage caused by the NC1-truncated COL4A3 mutation [97]. Lastly, a study induced ATF4 overexpression in podocytes using doxycycline, which raised ATF4 and CHOP levels, associated with podocyte damage and slit diaphragm defects. However, the use of an ATF4 inhibitor significantly alleviated these issues and preserved podocyte integrity, suggesting that ATF4 plays a crucial role in ERS-induced podocyte damage [28].

Acute kidney injury (AKI)

Podocyte injury plays a crucial role in the onset and progression of AKI [98]. In a study, podocyte-specific SHE-deficient mice were developed, and human podocytes were treated with LPS. This treatment led to decreased expression of PERK, eIF2α, p-IRE1α, and XBP1 proteins, along with reduced caspase-3 cleavage. These findings suggest that a deficiency in podocyte SHE mitigates LPS-triggered ERS, ultimately contributing to the protection of podocytes [99].

CKD

ERS in podocytes leads to their dysfunction and apoptosis, significantly contributing to the progression of CKD [100, 101]. Research has shown that bovine serum albumin (BSA) induces albumin overload in mouse podocytes, elevating levels of GRP78, p-IRE1α, and cleaved caspase-12, which instigate apoptosis [102]. Further research showed that podocyte intervention through transient Receptor Protein 6 (TRPC6) and CD2-associated protein (CD2AP) transfection reduced BSA-induced GRP78 protein and caspase-12 mRNA expression, mitigating apoptosis [103, 104]. Additionally, studies have shown that aldosterone induction in male C57BL/6 mice and mouse podocytes upregulates GRP78 and CHOP. However, treatment with the mineralocorticoid receptor (MR) antagonist Spi and PBA decreased GRP78 and CHOP mRNA/protein levels, restored glomerular structure, and reduced podocyte apoptosis [105]. Moreover, curcumin treatment of angiotensin II-induced mouse podocytes lowered GRP78, ATF4, p-eIF2α, CHOP, Bax, and caspase-3 levels while enhancing Bcl-2, thereby reducing podocyte damage and apoptosis [106]. Furthermore, berberine treatment of PA-induced mouse podocytes decreased PERK, ATF4, CHOP, IRE1α, and ATF6 protein levels, significantly reducing caspase-12 and cleaved-caspase-3 expression and podocyte apoptosis [107]. Finally, stimulation of mouse podocytes with AOPPs escalated GRP78, CHOP, and α-SMA protein expression. However, arctiin intervention reversed these effects, safeguarding the podocytes [108]. In conclusion, podocyte ERS plays a crucial role in the progression of CKD. Factors such as albumin overload, aldosterone, angiotensin II, and PA can activate ERS, leading to podocyte apoptosis. However, interventions like ER inhibitors

(e.g., PBA, Spi), MR antagonists, and antioxidants (e.g., berberine, arctiin) effectively attenuate the ERS response, thereby protecting podocytes from damage.

Others

NS is a common manifestation of glomerular diseases, arising from a variety of underlying conditions. It is important to note that NS is not a distinct disease but a clinical syndrome with multiple potential etiologies [109]. In section of primary glomerular disease, we discussed the common pathological types of NS associated with primary glomerulonephritis, such as GN and FSGS. The following sections will focus on cases of NS that do not fit neatly into these specific pathological categories.

Studies using puromycin aminonucleoside (PAN) induction in mouse podocytes have shown that GRP78 activation occurs 12 h after PAN exposure. Subsequently, ATF6α activation *at* 48 h triggers caspase-12 activation, ultimately leading to podocyte apoptosis [110]. Further investigations in SD rats following intravenous PAN injection and in podocytes treated with PAN revealed activation of the mTORC1 pathway, which upregulated GRP78 and eIF2α while downregulating nephrin levels, resulting in podocyte damage [111]. Moreover, the creation of C321R-lamininβ2 gene (LAMB2) transgenic rats showed that the C321R mutation increased GRP78 expression, triggering ERS in podocytes. This change caused a significant enlargement of the rough ER and elevated CHOP protein levels, leading to podocyte injury [112]. Elevated GRP78 expression was also observed in conditional Crumbs2 (Crb2) knockout mice and puromycin-treated human podocytes, highlighting the role of ERS in the progression of Crb2-associated NS [113]. Notably, treatment of C321R-LAMB2 mutant podocytes with K201 (an RyR2 inhibitor) and MANF (*a* calcium channel stabilizer) mitigated activation of the IRE1α and PERK pathways, reducing CHOP and caspase-12 levels, thus protecting podocytes [114]. Taken together, these findings suggest that PAN treatment activates ERS, leading to podocyte apoptosis and dysfunction, while interventions such as mTORC1 pathway inhibition, RyR2 inhibitors, and MANF calcium channel stabilizers can attenuate ERS and protect podocytes from damage.

Discussion

Podocytes are highly specialized epithelial cells essential for selective glomerular filtration. Growing evidence suggests that podocyte dysfunction is a key driver in the progression of glomerular diseases [115]. Growing evidence indicates that podocyte dysfunction is a key driver in the progression of glomerular diseases, with increasing damage to podocytes closely linked to the advancement of kidney disease and its eventual progression to kidney failure [116, 117].

ERS activates a cytoprotective mechanism designed to restore cellular function, which includes upregulating molecular chaperones, reducing protein synthesis, and initiating the degradation of misfolded proteins [118]. However, sustained or excessive stress may trigger a cell death program, potentially impairing tissue and organ function [12]. Current research suggests that ERS plays a role in the onset and progression of various kidney diseases [119].

This paper explores how ERS in podocytes influences primary glomerular diseases, metabolism-associated kidney disease, hereditary and congenital kidney diseases, AKI, CKD, and NS. It establishes that the initiation of ERS in podocytes correlates with the activation of the UPR. The UPR functions through the activation of the GRP78, PERK, ATF6α, and IRE1α pathways, which are vital for regulating podocyte ERS [120]. Our study reveals varied activation patterns of ERS in podocytes, which may involve isolated GRP78 activation, activation of any of the aforementioned pathways, or simultaneous activation of all three pathways. Additionally, CHOP plays a crucial role in ERS-induced apoptosis of podocytes. We also discovered that activation of autophagy effectively alleviates or reverses kidney injury in podocytes caused by ERS. However, podocyte apoptosis is not a transient event but requires prolonged and intense ERS to initiate [121]. When ERS is mild, autophagy activation can effectively mitigate or even reverse the kidney damage caused by ERS in podocytes. However, when ERS becomes more severe, it may induce both autophagy and podocyte apoptosis simultaneously. Despite its importance, assessing the severity and duration of ERS in podocytes remains an underexplored area in kidney disease research. Furthermore, managing the extent of this stress response presents an ongoing challenge. Our research also identifies various gene expressions or defects (e.g., Atg5, Sall1, Crumbs2 deficiency, ANLNR431C, COL4A3 overexpression, C321R, Cdk5, TRPC6, RTN1A, OST48, APOL1 risk variants, OSGEP, TP53RK, and TPRKB), pathological states, *and* biological processes (e.g., glomerular secretion of FABP4, cross-talk between MCs and podocytes in the glomerulus, lipid accumulation), as well as molecules and chemicals (e.g., HG, PA, NADPH oxidase 4, AGEs, Apelin, iPLA2γ, AOPPs, BSA, aldosterone, angiotensin II) that can induce ERS, leading to podocyte apoptosis and potentially advancing the progression of various kidney diseases.

We also found that various therapeutic agents play a crucial role in inhibiting ERS to protect podocytes, including western medicines (e.g., Rapamycin, Dapagliflozin, Aliskiren, Valsartan), Chinese medicines (e.g., Huaiqihuang), Chinese medicine compounds (e.g., Emodin, Paclitaxel, Arctiin, Curcumin, Berberine, Puerarin, AS-IV), chemical compounds (e.g.,

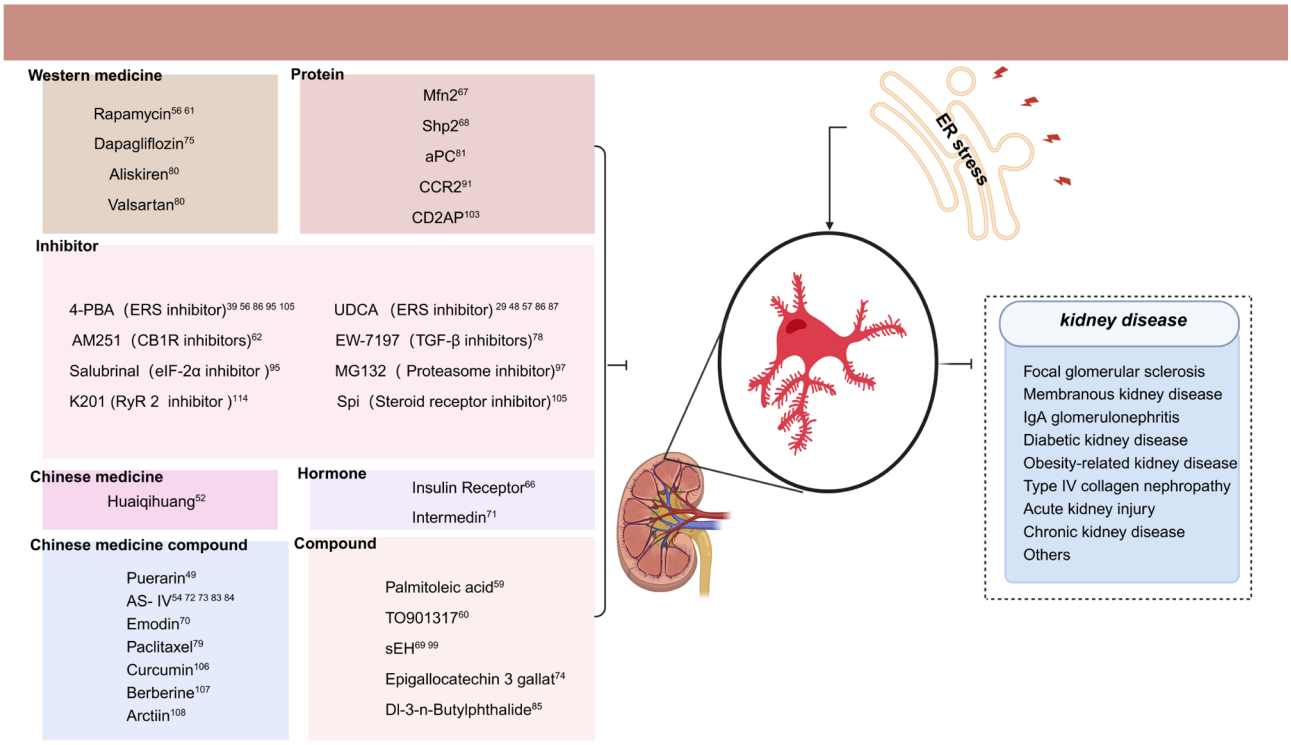


Fig. 3 Treatment of kidney disease caused by excessive endoplasmic reticulum stress in podocytes

Dl-3-n-Butylphthalide, Palmitoleic acid, Epigallocatechin 3 gallat, TO90131771, SEH), hormones (e.g., Intermedin, Insulin receptor), protein expressions (e.g., aPC, Mfn2, Shp2, CCR2, CD2AP), and inhibitors (e.g., EW-7197, MG132, AM251, TUDCA and 4-PBA, salubrinal, spironolactone, K201) (Fig. 3).

Targeting ERS in podocytes may substantially decelerate or even prevent the progression of kidney diseases. These findings significantly improve our understanding of ERS mechanisms in podocytes and provide a crucial theoretical basis for developing new therapeutic strategies. However, the current knowledge of ERS in podocytes is mainly based on fundamental experiments, revealing a significant gap in clinical research. This review aims to summarize the existing research on ERS in podocytes in kidney diseases, hoping to contribute to future clinical research efforts.

Conclusion

ERS triggers the UPR, which results in podocyte apoptosis and subsequently initiates kidney diseases. Thus, ERS in podocytes is a critical mechanism in the development and progression of kidney disease. Targeting ERS in podocytes could be a strategic method for treating kidney diseases.

Abbreviations

GBM	Glomerular basement membrane
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
DKD	Diabetic kidney disease
ER	Endoplasmic reticulum
ERS	Endoplasmic reticulum stress
UPR	Unfolded protein response
PERK	Protein kinase R-like ER kinase
ATF6	activating transcription factor 6
IRE1α	Inositol-Requiring Enzyme 1 alpha
GRP78	Glucose-Regulated Protein 78
XBP1	X-box binding protein 1
eIF2α	Eukaryotic initiation factor 2 alpha
ATF4	Activating transcription factor 4
CHOP	CHOPC/EBP-homologous protein
NS	Nephrotic syndrome
Atg5	Autophagy-related gene 5
iPLA2γ	Calcium-independent phospholipase A2γ
ADR	Adriamycin
ECM	Extracellular matrix
p-eIF2α	Phosphorylated eIF2α
p-PERK	Phosphorylated eIF2α
4-PBA	4-Phenylbutyric acid
MN	Membranous nephropathy
TM	Tunicamycin
IgAN	Immunoglobulin A nephropathy
CKD	Chronic kidney disease
p-IRE1α	phosphorylated IRE1α
FABP4	fatty acid binding protein 4
HFD	High fat diet
STZ	Streptozotocin
TUDCA	Tauro ursodeoxycholic acid
HG	High glucose
Cdk5	Cyclin-dependent kinase 5
p-JNK	Phosphorylated c-Jun amino (N)-terminal kinases
HQH	Huaiqihuang
PA	Palmitic acid
Bcl-2	B-cell lymphoma-2
AS-IV	Astragaloside IV
Bax	Bcl-2-associated X protein

Nox4	NADPH oxidase 4
Tsc1	Tuberous sclerosis complex 1
mTORC1	Mechanistic target of rapamycin complex 1
AGEs	Advanced glycation end products
B1R	Bradykinin receptor B1
B2R	Bradykinin receptor B2
COX-2	Cyclooxygenase-2
RTN1A	Reticulon-1A
MCs	Mesangial cells
Mfn2	Mitofusin2
Shp2	Src homology phosphatase 2
LPS	Lipopolysaccharide
sEH	Soluble epoxide hydrolase
OST48	Oligosaccharyltransferase-48 kDa subunit
aPC	Activated protein C
AOPPs	Advanced oxidation protein products
OKD	Obesity-related kidney disease
CCR2	C-C chemokine receptor 2
AS	Alport syndrome
COL4	Collagen type IV
AKI	Acute kidney injury
BSA	Bovine serum albumin
TRPC6	Transient Receptor Protein 6
CD2AP	CD2-associated protein
MR	Mineralocorticoid receptor
PAN	Puromycin aminonucleoside
LAMB2	Laminin β2 gene
Crb2	Crumbs2

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Author contributions
J.L. and W.Q. were conceived the idea of this review. J.L. was performed literature searching, drafted the manuscript, created the figures and finished the tables. P.X. and H.Y. were responsible for manuscript revision. S.D. was provided writing assistance for this article. Y. Z. was performed the literature search. X.W. and W.Q. designed and supervised the final version of the manuscript as co-corresponding authors. All authors reviewed and accepted the final version of the manuscript.

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