Review

The Effect of Endoplasmic Reticulum Stress on Podocyte Apoptosis in Diabetic Nephropathy

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Abstract: Diabetic nephropathy (DN) has already become the leading reason for the end-stage renal disease throughout the world. As current therapeutic strategy for progression of DN remained only moderately successful, the underlying mechanisms remain less understood. Endoplasmic reticulum (ER), mitochondria, and death receptor could activate apoptotic pathways, such as caspase-independent pathways. Accumulating evidence indicated that ER stress played a major role in the development and progression of DN. And the aberrant activation of ER stress induced both the inflammation and cellular apoptosis, and modulate the signaling of protective processes including the autophagy. In addition, a growing number of evidences suggested that glomerular podocyte was the key player in DN, and yet the mechanism how ER signaling affected the podocyte apoptosis remained to be well-understood. Because podocytes are terminally differentiated epithelial cells in lack of the capability to proliferate, thus the loss of podocytes is a significant biomarker of progressive kidney diseases, including DN. Hence, the podocyte apoptosis is to be of great significance for the DN treatment. In this review, we summarized relevant apoptotic pathways involved in excessive ER stress-induced apoptosis.

Keywords: diabetic nephropathy; endoplasmic reticulum; podocyte apoptosis

1. Introduction

Programmed cell death (PCD) is a well-recognized terminal pathway for cells of multicellular organisms, which is implicated in a wide range of biological events including morphogenesis, retention of tissue homeostasis, and elimination of harmful cells [1–3]. Among which, the apoptosis is PCD [4]. Apoptosis happened in the multicellular organisms, which was first put forward in 1972 by Kerr and his colleagues [5]. Distinct biochemical events result in the characteristic cell death and changes induced by apoptosis signaling. Excessive apoptosis can cause atrophy, while an insufficient apoptosis brings about uncontrolled cell proliferation, like cancer [6]. In mammalian cells, there are two major apoptosis pathways already have been defined as the (intrinsic) mitochondria-mediated apoptosis pathway and the (extrinsic) death receptor-mediated apoptosis pathway [7–9]. Besides these two significant pathways, ER also is found to act as a cell sensor to maintain and monitor cellular homeostasis. ER stress is a very common cellular stress response process triggered by various conditions disturbing the cellular homeostasis, not only inducing the apoptosis but also preventing cells from the apoptosis [10]. The response of cells to accumulation of unfolded proteins in the ER is termed “unfolded protein response” (UPR). UPR is a functional mechanism by which cells attempt to protect themselves against ER stress, resulting from the accumulation of the unfolded/misfolded proteins. The unfolded protein response consists of three distinct arms in mammals defined by ER transmembrane sensors, inositol-requiring enzyme-1 (IRE1), the prospective evaluation of radial keratotomy (PERK), distinct roles of activating transcription factor 6 (ATF6) [11]. ER stress has been linked to autophagy and apoptosis [12]. ER stress-induced C/EBP homologous protein (CHOP) participates in various pro-apoptotic pathways, such as IRE1-JNK and IRE1-TNXIP-NLRP3-caspase pathway [13]. Podocytes are specialized epithelial cells that play a significant role in maintaining the integrity of the glomerular filtration barrier and preventing urinary protein leakage [14]. As dynamic polarized cells settled on the surface of glomerular capillaries, they are regarded as essential components for the glomerular filtration barrier [15]. The podocyte slit diaphragm is likely to be the least understood part of the kidney filtration barrier [16]. The damage of the glomerular filtration barrier function can induce proteinuria and result in ultrastructural morphological changes on the epithelial and endothelial side as well as of the glomerular basement membrane [17]. In addition, podocyte depletion can cause glomerulosclerosis, with continuous podocyte loss as a major factor fueling the disease progression [18]. As such, podocyte dysfunction or injury is an indispensable pathogenic reason for the glomerular disease [19]. Recently, podocyte is regarded as a center stage for the development of enhanced therapeutic and preventive strategies for the chronic progressive kidney illnesses [20]. Herein, we are supposed to review the current knowledge about the effect of ER stress on the podocyte apoptosis laying a specific stress on the DN.

2. DN and Podocyte

Diabetic nephropathy (DN), as one of the most common microvascular complication among patients who suffer from diabetes, is revealed as the major reason for renal failure as compared with other kidney diseases [21]. As the most common attribution for the chronic kidney disease [22], it is a well-known risk factor for the cardiovascular events and
its mortality and often a pivotal complication of diabetes [23,24]. Many attributes of DN, including proteinuria, hyperglycemia, increased free fatty acids and advanced glycation end products, can all induce the unfolded protein response (UPR) among the kidney cells [25]. Genetic predisposition and hypertension are also the major risk factors [26]. In addition, the tubule epithelial cell apoptosis [27] and the ER stress also promote the end-stage renal failure in diabetic patients as well [28]. DN, as one the most popular chronic complication of the diabetes mellitus, affects almost one-third of the diabetic patients [29]. As the key trigger for DN, hyperglycemia can initiate various both ultramicroscopic and microscopic changes in the kidney architecture. Microscopic changes involve the thickening of the tubular basement membrane (TBM) and glomerular basement membrane (GBM), and mesangial proliferation, glomerulotubular junction abnormalities (GTJA) and arteriosclerosis. And for the ultramicroscopic changes, podocyte effacement and decrease in its density appear to be the centerpiece of DN pathogenesis [30]. Consisting of the pivotal workload of dialysis centers throughout the world, DN is often featured by glomerulosclerosis, tubulointerstitial fibrosis as well as tubular atrophy [31], which starts with albuminuria, which can progress from microalbuminuria to macroalbuminuria [32]. And it is irreversible that the progression process of DN from the proteinuria to renal failure [33]. Podocytes are critical parts of the nephron filtration barrier, depleted in various disease and kidney injury states [34]. Accumulating evidence indicates that glomerular podocyte is the key player in DN [35]. It is becoming an important focus of study efforts because of their relations to disease states of the progressive glomeruli damage [36]. Recently, accumulating evidence demonstrates that podocyte apoptosis is of pivotal importance in pathogenesis of DN [37]. And further evidence shows that excessive ER stress could lead to podocyte apoptosis, while inhibition of ER stress alleviates the podocyte apoptosis both in vivo and in vitro [38,39]. ER stress has been proved in close association with the apoptosis in DN, and yet the mechanism how ER signaling affected the podocyte apoptosis remained to be well-understood [37,40,41]. Podocytes are terminally differentiated and highly specialized glomerular epithelial cells whose dysfunction can cause defective glomerular filtration, leading to the onset of proteinuria [42]. In animal models, more than 20% podocyte loss can cause irreversible glomerular injury, aggravating from the albuminuria, glomerulosclerosis, tubulointerstitial fibrosis and finally the end-stage kidney failure [43–45]. It also showed in recent studies that, only in podocytes, the modification of key signaling pathways can ameliorate or aggravate the diabetic albuminuria development [46,47]. While both cultured primary and also immortalized podocytes cannot differentiate fully [48]. That is to say, as terminally differentiated cells, podocytes cannot proliferate and thus the apoptosis or detachment can result in the podocyte deficiency, lead to glomerulosclerosis development. Podocytes are highly sensitive to ER stress because of their high protein-folding ability in the ER as well as their great significance in the catabolic and anabonic activities [49]. And yet the effect of ER stress on the podocyte apoptosis in the DN are limited-recognized.

3. ER Stress and UPR

ER is a significant organelle necessity for protein folding, synthesis, and maturation among the eukaryotic cells and disruption of ER homeostasis can result in the accumulation of misfolded or unfolded proteins, leading to ER stress as well as triggering the UPR [50]. Because ER stress is a major cause of some kidney diseases, the ER stress response and autophagy, which deal with unfolded proteins that accumulate in the ER, are promising therapeutic targets in acute and chronic kidney diseases [51]. Recently, ER stress has adapted as one of the significant mechanisms that result in diabetic complications and ER stress inhibition can improve diabetic symptoms [52]. The glucose-regulated protein 78 (GRP78/BiP), as ER chaperone protein, acts as a master regulator for the UPR signaling network. Under the ER stress, GRP78 can release from the UPR sensors and preferentially bind to unfolded and misfolded proteins [53]. Some pathophysiologically stresses lead to aberrant unfolded protein accumulation in the ER lumen, which in turn can initiate a signaling cascade named the UPR to alleviate ER stress by the mediation of those three ER-resident transducers [41,54]. All three UPR mediators regulate the ER stress by luminal domains which are connected to cytosolic effector domains, making the obvious signal transduction cascades possible [55]. In response to the ER stress, ATF6 is transported from the ER to the Golgi, where it is cleaved by site-1 and also site-2 proteases (S1P/S2P) to release the cytosolic DNA-binding protein, ATF6f, from there. ATF6f moves to the nucleus to activate gene expression [56,57]. ATF6f combines with the promoters carrying the ER stress response elements to transcriptionally exert an up-regulatory role in genes involved in ER homeostasis and ER protein folding, such as BiP/Grp78 [58–60]. GRP78 dissociation from ATF6 moves to the Golgi in which it is cleaved by site-1 and site-2 proteases (S1P/S2P). Consequently, both spliced XBP-1 (XBP-1s) and 50 kD ATF6 (p50ATF6) and translocate to the nucleus to activate a group of transcriptional factors, including ER expansion, maintenance, and ER-associated degradation (ERAD) proteins [61,62]. Unlike ATF6, PERK also contain a protein kinase domain, which undergoes activating trans-autophosphorylation by oligomerization under ER stress, and phosphorylates the eukaryotic translation can initiate the factor 2 subunit α (eIF2α). This phosphorylation globally inhibits the load of newly synthesized proteins. In addition, PERK can alleviate the protein translation [63]. GRP78 dissociation from PERK permits its transphosphorylation and homodimerization result in the activation of the activating downstream transcript factor 4 (ATF4), the UPR target genes like C/EBP homologous protein (CHOP), growth arrest and also the DNA damage inducible protein-34 (GADD34) [64,65]. Adaptive UPR phase is started to restore the homeostasis, protecting cells from injury via elevating the ER capacity and the degradation of misfolded protein in ER by ERAD. Finally, the misfolded
proteins will be deglycosylated by enzymes like ER mannosidase I (Man I) and exert their effects with ER degradation-enhancing α-mannosidase-like protein (EDEM) or other ERAD lectins. However, under excessive or prolonged ER stress, the apoptotic signaling would be induced, resulting in cell injury and even death by the mediation of some downstream molecules, including CHOP, TRB3, c-Jun N-terminal kinase (JNK), as well as caspase-12 pathways [41,54,66,67].

4. Cell Apoptosis Mediated by the ER Stress Pathway

Just as the last section, the UPR, as a signal transduction cascade, is triggered by disturbance of the ER homeostasis. UPR deals with ER stress by activating a series of cellular responses, namely, the induction of translational attenuation, molecular chaperones, ER-associated degradation, as well as other mechanisms. Nevertheless, under irremediable and prolonged ER stress, the UPR can trigger apoptosis as well [68]. Apoptosis is a highly regulated mode for cell death featured by the nuclear fragmentation, cell shrinkage and plasma membrane blebbing [69]. Several ER stress-related transcription factors are of great significance in regulating process of ER stress and related apoptosis. GRP78, as one of the members among the heat shock protein family, is taken as a key marker of ER stress and released from IRE1 to support the protein folding process, while the GRP78 can in turn be up-regulated by the ER stress [70,71]. The activating ATF6 have been regarded as a sensor of ER stress. When it was cleaved from the Golgi membrane, ATF6 promotes its place to the nucleus while the UPR target gene transcription was up-regulated, bring about apoptosis [72]. Previously, ER stress-mediated apoptosis was the dominantly led by the induction of CHOP [68]. Activated IRE1 can enhance the splicing of XBP-1 messenger RNA, and the mature XBP-1 can make contributions to the transcription of UPR target genes like CHOP, also resulting in apoptosis [73]. Recently it has been revealed that the IRE1α branch is also included in the regulation of ER stress-induced apoptosis and activated IRE1α has been demonstrated to be associated with tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF2) [68]. This complex can further recruit apoptosis signal-regulating kinase 1 (ASK1) inducing apoptosis by activation of the mitogen-activated protein (MAP) kinase c-Jun N-terminal kinase (JNK) [74]. In another study, it was showed that IRE1α can enhance activation and clustering of pro-caspase 12, which in result cleaves caspase 3 as well as induces apoptosis [75,76]. UPR also leads to intracellular calcium release, consequently bring cell death via caspase-3 and caspase-12 pathways [77]. Although ER stress has been demonstrated to play an important role in neuronal cell death, the correlative mechanism still requires further research. In the discussions below, we will be devoted to describe the effects of the ER stress pathway on the cell apoptosis in a specific way.

5. CHOP as a Key Mediator in ER Stress Pathway for Cell Apoptosis

The gene encoding CHOP (also called C/EBPζ), also well-known as the growth arrest as well as DNA-damage-inducible gene 153 (GADD153), can be activated by bio-agents which adversely influence the ER function [78]. It could regulate chronic kidney disease-induced vascular calcification [79] and can also, as one of the C/EBP family transcription factors, involve in ER stress-induced apoptosis by modulation of various anti-apoptotic and apoptotic factors. Stress responses in specific organelles, like ER and mitochondria, are effective inducers of CHOP expression [80]. In a more specific way, it can also play an important role in ER stress-related organ diseases, involved kidney diseases [81]. CHOP is properly induced in differentiation process of the 1.29 μm B lymphoma cells [82]. Even if ER stress is the strongest inducer for CHOP, it is mostly deemed as a pro-apoptotic factor and it is involved in numerous physiological adaptive processes, including amino-acid starvation, mitochondrial and oxidative stress, as well as the differentiation of keratinocytes, adipocytes, and osteoblasts [60,82–86]. Importantly, whether stressed cells die or not is significantly controlled by the interplay between anti-apoptotic and pro-apoptotic members among the Bcl-2 protein family [87]. CHOP/GADD153, namely a bZIP transcription factor, is induced by the PERK and ATF6 UPR pathways [88,89]. One of the commonly cited effects of CHOP-induced apoptosis is the inhibition of the pro-survival protein Bcl-2 [90]. In addition, both PUMA and BIM were implicated as key starters of the apoptotic regulators reacting to the prolonged ER stress and ER stress increased BIM levels via decreased CHOP C/EBPα-mediated gene induction and proteasomal degradation [91]. ER stress was also revealed to activate BIM by two novel pathways, including the protein phosphatase 2A-mediated dephosphorylation that prevented its ubiquitination as well as CHOP-mediated direct transcriptional induction. In turn, CHOP was found to bind with PUMA promoter during the ER stress process and CHOP knockdown could alleviate neuronal apoptosis and PUMA induction [92]. Other CHOP-induced molecules which have already been implicated in apoptosis involving death Tribbles-related protein 3 (TRB3) and receptor-5 (DR5; TRAIL-R2). All those apoptotic factors were of great importance in the cell death and apoptosis, and the CHOP were found to exert its indispensable significance in their expression regulation processes, indicating that CHOP was the key mediator for the ER stress pathway. What’s more, PERK/eIF2α signaling pathway was more effective than the ATF6 and IRE1/XB1-pathway, and the p38 MAPK/CHOP pathway was able to enhance the cellular death related to ER stress-induced apoptosis [93]. Altogether, the CHOP was risen as a central point in UPR-related pathway in the ER stress.
6. IRE1-ASK1-JNK Signaling Pathway as a Mediator in ER Stress Pathway for Cell Apoptosis

The IRE1α/XBP-1 pathway is deemed as the most conserved one among the ER stress pathways [94]. IRE1α is commonly adapted as a membrane-bound threonine/serine kinase with endonuclease activity [95,96]. And ER stress is sensed when GRP78/BiP was dissociated from IRE1α [97] or IRE1α spliced a 26 bp intron from XBP-1. XBP-1 can induce the gene transcription involved in the ER expansion, ER maintenance, and ER associated degradation as well [98,99]. Studies indicate that XBP1 may regulate the UPR by excluding and binding spliced XBP-1 (sXBP) from the nucleus in a negative way [100]. In addition, IRE1α can also activate apoptosis signal-regulating kinase (ASK1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) as well as JNK and [101], which are all involved in inflammatory and apoptotic pathways [102–104]. The IRE1-ASK1-JNK signaling pathway was also regarded as one of the cell death pathways, because JNK-mediated phosphorylation was found to be capable of activating the pro-apoptotic Bcl-2 family member such as BIM, while at the same time suppressing the antiapoptotic protein like Bcl-2 [105–108]. IRE-1 can produce the spliced mRNA of the XBP-1 via its RNase activity and after that XBP-1 protein can upregulate the GRP78 expression [109,110]. Importantly, it has recently demonstrated that variances in ER stress kinetics by inducers was able to lead to the prolonged and transient JNK activation, and subsequently affect the cell apoptosis and survival [111]. Thus, from all studies above, it is convincing to reach a conclusion that IRE1-ASK1-JNK signaling pathway can be adapted as a mediator in ER stress pathway for cell apoptosis.

7. Caspase 12 and CASPASE 4 in ER Stress Pathway for Cell Apoptosis

The family member of cysteine proteases, namely caspases involved in apoptotic pathways, are pivotal modulators of PCD, and 14 family members have already been demonstrated, which play significant roles in different processes such as, inflammation and apoptosis. Caspase-12 located at the ER, can also be activated by excess ER stress, leading to cell death without the presence of the cytochrome c-dependent pathway. It is generally regarded as a negative modulator of the inflammatory response resulted from infections, for it can inhibit the caspase-1 activation in the inflammasome complexes, as well as the production of the pro-inflammatory cytokines involved in IL-18 and IL-1β. Caspase-12, as one of a proapoptotic genes induced by ER stress, reveals as the key molecule for the ER-related apoptosis [112]. And its inhibition decreases stretch-induced apoptosis, and it can activate caspase-3 and induce apoptosis, indicating that caspase-12 can exert significance in stretch-induced apoptosis through activating caspase-3 [113]. On the contrary, caspase-4, the humankind paralog of caspase-12, regulates a positive modulatory action to the infectious agents [114]. In addition, it showed in a study that caspase-4 played a significant role in the neural cell death by ER stress [115]. ER stress, involving the translational and transcriptional machinery to regulate the post-transcriptional modifications and expressions of many factors included in the ER stress response induced cell death. And in this scenario, these two apoptotic players, namely caspase 4 or caspase 12, begin to control cell fate through downstream cell death proteins [116]. The caspase-4 in humans and the caspase-12 in rodents activate the caspase-9 and caspase-3 mediated apoptotic pathways [117–119]. All findings demonstrated that Caspase 12 and Caspase 4 could exert great importance in ER stress pathway for cell apoptosis.

8. PERK/Nrf2 Pathway in ER Stress Pathway for Cell Apoptosis

PERK, as a transmembrane protein in the UPR signaling, cane be activated by the ERS [63,120,121]. And it is generally demonstrated as an activated first reacting the ER stress, which was followed by ATF6 and then IRE1α [68,122]. The phosphorylation of PERK along with its downstream factor eIF2α can alleviate the protein synthesis and maintain the ER homeostasis [123]. The Nrf2 is also well-known as a fundamental substrate of PERK [123,124]. In addition, PERK phosphorylation can result in a change of Nrf2 protein by inducing the Keap1-Nrf2 complex dissociation, and dissociation of Nrf2 becoming nucleus can elevate antioxidant gene expression [125]. It is also proposed that autophagy led by the PERK pathway is an important factor in the cell fate by PERK [126]. Therefore, ER stress has some specific relevance via PERK/Nrf2 pathway and PERK interfering with Nrf2 response resulted in accumulation of injured proteins, bringing about PERK-dependent apoptosis [127].

9. Bak and Bax in ER Stress Pathway for Cell Apoptosis

Besides signaling strategy mentioned above, the Bak and Bax were also involved in the ER stress pathway for cell apoptosis. As we all know, the irreversible ER stress can result in the apoptosis, which demand the expressions of BAX or/and BAK at the area of mitochondria [128]. The Bcl-2 family of proteins are a group of upstream modulators for the caspase cascade, which are made up of both anti- and pro-apoptotic components [129,130]. BAK and BAX are fundamental parts of the major apoptosis pathway on which multiple death signals collect through upregulation or activation of specific BH3-only proteins to induce the cytochrome c release [129,131–133]. Double deficiency of BAK and BAX in mice is an embryonic lethal event because of the failure of developmental programs which rely on apoptosis. In a recent study, the context observed the activation of BAK/BAX-independent apoptosis if the cells were deprived of glucose [134]. Many forms of apoptosis demand, at the mitochondria, the BAK and BAX are directly activated by the PUMA, BID, or BIM family of proteins [135]. Once activated, those initiator caspases then directly target the downstream
ER stress can trigger signals which accumulates on the mitochondria through the regulation of Bcl-2 family proteins, destroying the balance by the proapoptotic members [122,137]. This process can facilitate the BAX-BAK1 oligomerization, insertion into the outer membrane of the mitochondria, as well as the depolarization of the mitochondria [138]. The effect of the Bcl-2 family in the ER stress-induced apoptosis is highlighted by concurrent suppression of Bcl-2 and promotion of BIM via the transcription factors. Bcl-2 family members are well-known to localize either to the mitochondria or the ER, where they may be able to regulate the signaling pathways which enhance the opening of the permeability transition pore [139].

10. ER Stress and Podocyte

Altogether, ER stress can be taken as a protective mechanism for the injury factors and an impairing mechanism led to the cell apoptosis and cell death. Recently, lots of studies demonstrated that ER stress could participate in the apoptosis process of various cells. ERS is commonly present under pathological and physiological conditions, and is a very pivotal inducer of cell apoptosis [140]. A growing series of researches have revealed that ERS played a key role during the pathogenesis process of several various renal diseases, including DN [141]. Recent evidence has demonstrated that ER stress consists of a key secondary modulator in the melanoma development, making contributions to the resistance to apoptosis by the persistent expression of pro-survival replacing of the pro-apoptotic proteins [142]. In addition, one study demonstrated in its context that, UPR induction response to ER stress can also lead to the tumor growth, basal autophagy enhancement, as well as resistance to chemotherapy [143,144]. Enhancement of ER stress markers and also aberrant over-accumulated proteins have been demonstrated in dying neurons among the animal models of ischemia [145], Huntington disease [146], Alzheimer disease [147] as well as Parkinson disease [148]. Emerging evidence has also indicated that the ER stress-induced apoptosis was presented in several chronic diseases, such as diabetes, ischemia, and neurodegenerative diseases as well [145,149,150].

Podocytes, a kind of glomerular epithelial cell, are highly specialized, unique, and terminally differentiated cells [42]. The absence of podocytes brings about the stripping of regions in the glomerular basement membrane, to contribute to the impaired renal function, just as is clear by the development of glomerulosclerosis and proteinuria [140]. Moreover, the podocyte apoptosis was in close correlation with the albuminuria onset and preceded podocytopenia in the DN. However, there is a short of effective therapeutic strategy to protect podocytes against apoptosis [151]. For understanding the role of podocyte apoptosis in DR with regard of the ER stress, the relation of podocyte and ER stress was urgently needed to clarify. High glucose concentrations can induce ER stress and apoptosis in podocytes [152,140]. And the advanced sympathetic activation, elevated endothelin system, intrarenal renin-angiotensin system (RAS) activity, as well as oxidative stress and reduced nitric oxide (NO)-availability can damage podocytes [153]. What is important for study the podocyte apoptosis that is Podocytes are considered be highly sensitive to ER stress because of their high levels of catabolic or anabolic activities and their high protein-folding ability in the ER [49]. In addition, persistent proteinuria makes great contributions to the glomerular dysfunction mediated by ER stress in DN and is regarded as one of the key mechanisms during the process of albumin-induced podocyte damage [154]. It is generally received that apoptosis is a pivotal cause of podocyte loss, taking place early stage of the development of DN and closely relating to its progression [155,156]. It was once implicated in a study that TGF-β1 was related to the close balance of apoptotic and survival responses in podocytes [157]. Previous study also showed that the activation of CHOP (p-ERK/CHOP) or MAPK may also result in the injury of podocytes [79]. Zhang et al. demonstrated that the ERK activation could result in apoptosis of the angiotensin II-induced podocyte. Fujita et al. revealed that ERK could mediate the high-glucose-induced hypertrophy in the renal tubular cells [158,159]. GRP78 along with its two sensors and CHOP and cleaved caspase-12 as well were also induced in high glucose treated podocytes can exert their effects through JNK pathway in DN [40]. Those signaling and biomarkers were regulated by the ER stress pathway and related data were in line with the studies presented as above, thus this review could bring insights for the DR treatment from the effects of ER stress on the podocyte apoptosis.

The pathological changes in the early stage of DN mainly involved in podocyte detachment, injury, and apoptosis as well [160]. Multiple studies have proved that podocyte apoptosis coincides with albuminuria onset and precedes podocytopenia in different mouse models of diabetes [161,162]. At present, the treatment selections for patients with the clinical DN are quite limited, and mainly include strict regulation of low-protein diet, blood glucose, the usage of angiotensin II-converting enzyme inhibitors and angiotensin II type 1 (AT1) receptor antagonists, and also other drugs [163]. These results indicated that previously unknown mechanisms related to the DN might be targeted by new therapeutic interventions. In this review, a new angle for the DN diagnosis and treatment was provided.

11. Conclusions

Growing evidence indicates that ER stress plays a pivotal role in the progression and development of kidney disease, such as DN, and that can reduce the ER stress and may thwart the kidney disease progression. And the evidence further proves that the focus on the maladaptive ER stress response declines the apoptosis of renal cells and also alleviates the kidney injury, serving as a novel therapeutic method in the kidney diseases, including DN. Hyperglycemia mediated apoptosis partly by ERS among differentiated mouse podocytes, which may make contributions to the pathogenesis of
DN. However, the podocytes underwent the ERS, which often possibly was regarded as a protective and adaptive UPR reaction for cell survival, while this protective influence was short-lived. Further investigations are required to develop novel treatment strategies targeting apoptosis pathway in DN.

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