

# Regulation, Pathological Role, and Therapeutic Potential of Endoplasmic Reticulum Stress in Diabetic Nephrology

## Abstract

Understanding the functions and processes of endoplasmic reticulum (ER) stress in the onset and progression of diabetic nephropathy has advanced recently (DN). Renal cells experience ER stress and apoptosis as a result of hyperglycemia. ER stress can be either cytotoxic or cytoprotective when it is induced. Animals given an experimental dose of ER stress inhibitors experienced lessened kidney damage. In light of these results, pharmacological treatments that normalise ER stress represent a promising strategy to halt or stop the course of DN. The causes, functions, and therapeutic implications of these findings are reviewed in the current article.

The cardiovascular disorders related to atherosclerosis and endoplasmic reticulum (ER) stress are intimately related (CVDs). It happens as a result of a variety of pathogenic events that disrupt ER homeostasis, generating an accumulation of unfolded or misfolded proteins in the ER lumen and culminating in ER malfunction. Here, we talk about how ER stress affects several cell types in atherosclerotic plaques. This discussion covers common atherosclerosis-related ER stressors in various lesional cells, which all contribute to the clinical progression of atherosclerosis, as well as the activation of apoptotic and inflammatory pathways induced by prolonged ER stress, particularly in advanced lesional macrophages and endothelial cells (ECs). Targeting these processes to lessen ER stress may be a novel treatment approach given the significance of ER stress and the unfolded protein response (UPR) signalling pathways in atherosclerosis and CVDs.

**Keywords:** [diabetic nephropathy](#) • [er stress](#) • [extracellular vesicle delivery](#) • [rna-based drugs](#) • [cardiovascular disorders](#)

## Introduction

One of the frequent microvascular consequences of diabetes is diabetic nephropathy (DN). Proteinuria, hyperglycemia, and decreased renal function are the primary clinical symptoms. Pathologically, it is also possible to see mesangial hyperplasia, glomerular sclerosis, extracellular matrix build-up, and tubulointerstitial fibrosis. Endoplasmic reticulum (ER) stress has been linked in numerous studies to the pathophysiology of DN. Cardiovascular diseases (CVDs), a substantial threat to human health and one of the leading causes of mortality worldwide, are influenced significantly by atherosclerosis [1]. A number of different metabolic and signalling pathways are involved in the pathogenesis of atherosclerosis, which is a complicated process. Metabolic disorders, dyslipidemia,

hyperglycemia, hypertension, and increased Homocysteine (Hcy) levels are a few established risk factors. The pathological processes of lipid accumulation in the artery wall, local inflammatory processes, and endothelial dysfunction play a role in the genesis and development of atherosclerotic lesions [2].

A growing body of research suggests that endoplasmic reticulum (ER) stress signalling pathways are crucial in the development of atherosclerosis and the associated CVDs. In eukaryotic cells, the ER is an organelle crucial for calcium homeostasis, lipid synthesis, and protein synthesis, folding, and transport. ER homeostasis may be disturbed by a number of pathogenic conditions, including hyperlipidemia, oxidative stress,

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and calcium imbalance. These perturbations manifest as an accumulation of unfolded or misfolded proteins in the ER lumen, which results in ER stress [3]. Through a number of pathways, chronic ER stress is linked to the onset of atherosclerosis. It's possible that ER stress is causing inflammation and activating apoptotic signalling pathways in this pathogenic process. This interferes with lipid metabolism, which results in cell dysfunction and interferes with the creation and stability of atherosclerotic plaques, all of which are crucial elements in the development of atherosclerosis. Targeting ER stress signalling pathways while taking into account their significant involvement in the modulation of numerous pathogenic processes [4].

Available treatment approach for atherosclerosis and CVDs may involve ER stress mechanisms. The function of ER stress in atherosclerosis and its potential as a therapeutic target are covered in this review. Upon ER stress, UPR, an evolutionarily conserved signalling cascade, is triggered to safeguard ER functional integrity and cell homeostasis. Three stress sensors on the ER membrane—protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6—are known to be involved in the primary process (ATF6) [5]. The 78 kDa glucose-regulated proteins (BiP/GRP78), which binds to the lumen domains of the three key ER transmembrane proteins discussed above, keeps the UPR inactive in the unstressed condition. BiP/GRP78 dissociates to aid in the folding process when unfolded or misfolded proteins build up in the ER lumen, starting the UPR signalling cascade. The current widely accepted theory of UPR activation is GRP78 dissociation, however other unidentified processes may potentially be at play [6].

The UPR blocks protein translation, upregulates ER chaperone proteins, facilitates protein folding, and directs misfolded proteins into the correct degradation pathway as an initial response to ER stress. After breaking away from BiP/GRP78, auto-phosphorylation causes PERK to become active. Through activated PERK (phospho-PERK)-mediated eukaryotic initiation factor 2(eIF2) phosphorylation, the UPR first reduces protein overload in the early stages of the ER stress response. This results in translational attenuation and subsequent relief of ER stress.

IRE1's site-specific endoribonuclease function regulates the specific mRNA splicing of X-box binding protein 1 (XBP1) to form XBP1s, which are then translated into active XBP1 protein after separation from BiP/GRP78. The genes that are upregulated by activated XBP1 are related to ER chaperones like GRP78/94 and help fold proteins and break down proteins that aren't folded correctly. Misfolded protein load can be reduced by regulating the transcription of components involved in the ER-associated degradation process through activated XBP1. BiP/GRP78 releases ATF6, which is Trans located to the Golgi and activated further by proteolytic cleavage there. GRP78 and XBP1 are among the genes involved in the adaptive stress response that are induced by ATF6's translocation to the nucleus. Phosphorylation of eIF2 controls the translation of some mRNAs, including activating transcription factor 4 (ATF4), during the UPR process. C/EBP-homologous protein (CHOP), a well-studied biomarker in the ER stress-associated apoptosis signaling pathway, is expressed when ATF4, ATF6, and XBP1 are present. Long-term ER stress triggers the activation of apoptosis and inflammatory response pathways when the UPR fails to normalize ER function [7].

## Discussion

The ER is a membrane organelle that plays a number of important roles in cells. To begin, it is the location where newly formed polypeptides fold into the correct conformation and undergo any necessary posttranslational modifications like glycosylation and the formation of disulphide bonds. Protein disulphide isomerase (PDI) and other resident chaperones, foldases, and ER chaperones complete this task. Second, the ER is where phospholipid synthesis takes place, which makes it possible for the cell's lipid bilayers to grow. Thirdly, the ER is a significant storage location for calcium ions, which are necessary for the processes of cell signaling. Fourth, drug metabolism is made possible by enzymes in the ER like cytochrome p450 [8].

It is known that a variety of physiological, pharmacological, and pathological conditions can alter the ER's capacity for protein folding and disrupt its homeostasis. ER stress refers to the cell's inability to efficiently fold and secrete proteins. In order for cells to survive and maintain homeostasis, they

have developed mechanisms for adapting to adverse conditions. UPR activation in response to ER stress conditions is one such coping mechanism. Activation of the UPR ultimately results in (i) inhibition of protein translation, (ii) ER-associated protein degradation (ERAD) of misfolded proteins, and ER stress-induced cell death may occur if conditions are not resolved. Typically, caspase activation is the mechanism by which ER-stress-associated cell death occurs; however, autophagy and necrosis that are not dependent on caspase have also been observed [9].

Since about a decade ago, it has been known that hepatic steatosis and altered lipid metabolism can result from ER stress. Homocysteine-induced ER stress can alter cholesterol and TG biosynthetic pathways in both cultured cells and the livers of hyperhomocysteinemic mice, as our group found in a study. Hepatic steatosis can be reduced by decreasing SREBP-1c activity by overexpressing GRP78, which reduces ER stress and UPR activation. In order to decipher their function and role in lipid metabolism, specific arms of the UPR and their downstream signaling molecules have recently been studied in cell culture and animal models. Summarizes the interactions between various UPR signalling components and lipid metabolism, it is now well established that various UPR signaling network components play a role in the regulation of lipid metabolism [10].

### Conclusion

By activating the UPR, ER stress causes the body to respond in an adaptive and defensive manner to harmful stimuli and induces a compensatory protective mechanism. However, the UPR is unable to normalize ER function if the ER stress is prolonged or excessive, resulting in the activation of inflammatory and proapoptotic signaling pathways in various cell types in the arterial wall, affecting the formation of atherosclerotic plaques and their vulnerability. Numerous diseases, including cardiovascular disease (CVD) and atherosclerosis, are primarily caused by these factors. Targeting ER stress and the UPR signaling pathways as novel treatment options for atherosclerosis have also been confirmed by a growing number of studies. Chemical chaperones, upregulated UPR signaling

pathway inhibitors, AMPK regulation, some micro RNAs with antiatherogenic protective effects, and natural compounds that target the ER stress pathways were also discussed in this section. In conclusion, these researches on the role of ER stress in atherosclerosis may result in the creation of novel approaches and directions for the treatment and prevention of atherosclerosis.

### Conflicts of Interest

None

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