Endoplasmic reticulum stress and metabolic dysfunction: A cellular perspective.

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Introduction

The endoplasmic reticulum (ER) is a vital organelle responsible for protein folding, lipid synthesis, and calcium storage. It ensures cellular homeostasis by managing the quality control of newly synthesized proteins and coordinating their proper folding and trafficking. However, when the ER's capacity to fold proteins is overwhelmed—due to factors such as nutrient excess, oxidative stress, or genetic mutations—misfolded or unfolded proteins accumulate, triggering a condition known as ER stress. This activates an adaptive response known as the unfolded protein response (UPR), which aims to restore ER function and maintain cellular balance. Persistent or unresolved ER stress, however, contributes to metabolic dysfunction and plays a central role in the pathogenesis of numerous chronic diseases [1, 2].

The UPR is mediated through three primary ER membrane sensors: inositol-requiring enzyme 1 (IRE1), protein kinase R-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Upon activation, these sensors initiate a cascade of transcriptional and translational events designed to reduce the load of unfolded proteins, increase the expression of molecular chaperones, and enhance ER-associated degradation (ERAD). While this response is initially protective, prolonged ER stress can lead to inflammation, apoptosis, and metabolic disturbances [3, 4].

One of the key links between ER stress and metabolic dysfunction is its impact on insulin signaling. In metabolic tissues such as the liver, adipose tissue, and skeletal muscle, chronic ER stress impairs insulin action through multiple mechanisms, including the activation of stress kinases like JNK and IKKβ. These kinases interfere with insulin receptor signaling pathways, promoting insulin resistance—a hallmark of type 2 diabetes. Additionally, ER stress influences lipid metabolism by altering the expression of genes involved in lipogenesis and lipid storage, contributing to hepatic steatosis and dyslipidemia [5, 6].

In obesity, nutrient overload and excess free fatty acids contribute to sustained ER stress in adipocytes and hepatocytes. This stress disrupts adipokine secretion, promotes inflammation, and exacerbates metabolic imbalance. In pancreatic β-cells, which have a high demand for protein synthesis to produce insulin, ER stress can lead to β-cell dysfunction and apoptosis, reducing insulin secretion and further worsening glycemic control [7].

Beyond diabetes and obesity, ER stress is implicated in a variety of metabolic diseases, including cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and neurodegenerative disorders. In the cardiovascular system, ER stress contributes to endothelial dysfunction and promotes the progression of atherosclerosis. In the brain, disrupted ER homeostasis is linked to neuronal degeneration and cognitive decline, with metabolic stress serving as a common trigger [8, 9].

Efforts to mitigate ER stress have shown promise in restoring metabolic function. Chemical chaperones such as 4-phenylbutyrate (4-PBA) and tauroursodeoxycholic acid (TUDCA) help enhance protein folding capacity and reduce ER stress in experimental models. Lifestyle interventions like caloric restriction, physical exercise, and certain dietary compounds (e.g., polyphenols) have also been shown to alleviate ER stress and improve metabolic outcomes [10].

Conclusion

In conclusion, endoplasmic reticulum stress represents a critical node connecting cellular stress responses to metabolic dysfunction. While the UPR is essential for maintaining ER and cellular health, its chronic activation disrupts metabolic pathways and contributes to the development of insulin resistance, lipid imbalance, and cell death. Targeting ER stress and enhancing its resolution offer promising strategies for treating metabolic diseases and preserving cellular homeostasis in the face of metabolic challenges.

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***Received:** 03-Apr-2025, Manuscript No. AACBM-25-164640; **Editor assigned:** 04-Apr-2025, PreQC No. AACBM-25-1646405(PQ); **Reviewed:** 18-Apr-2025, QC No AACBM-25-1646405; **Revised:** 21-Apr-2025, Manuscript No. AACBM-25-1646405(R); **Published:** 28-Apr-2025, DOI:10.35841/aacbm-7.2.261*

***Citation:** De J. Endoplasmic reticulum stress and metabolic dysfunction: A cellular perspective. J Cell Biol Metab. 2025;7(2):261.*

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Citation: *De J. Endoplasmic reticulum stress and metabolic dysfunction: A cellular perspective. J Cell Biol Metab. 2025;7(2):261.*