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Endoplasmic Reticulum Stress: Unfolding the Impact on Cellular Environment, Anaerobic Respiration, Tumor Activity and the Pre-Glucolipotoxicity Stage

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Letter to Editor

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Abbreviation: ER: Endoplasmic Reticulum.

Letter to Editor

This letter explores the intricate relationship between endoplasmic reticulum (ER) stress and its effects on cellular environment, specifically focusing on anaerobic respiration and its role in tumor activity and the pre-glucolipotoxicity stage. ER stress disrupts protein homeostasis, leading to the accumulation of misfolded proteins within the ER [1]. To restore proteostasis, cells activate an adaptive unfolded protein response involving various signaling pathways. However, ER stress extends beyond protein processing and transcription, exerting epigenetic effects [2]. Immune responses occurring during cellular stresses often rely on the unfolded protein response to maintain ER homeostasis. Dysregulated ER stress responses can contribute to the development of autoimmune disorders, making the unfolded protein response a potential therapeutic target [3]. Additionally, ER stress alters cellular metabolism, shifting energy utilization from aerobic to anaerobic pathways, such as fermentation [4]. This metabolic adaptation enables cells to meet energy demands under stressful conditions. Notably, ER stress also impacts the activity of the P53 protein, a critical regulator of cell growth and tumor suppression. Inhibition of P53 alters gene expression, favoring the development of tumor-promoting genes. Hence, understanding the complex interplay between ER stress and cellular processes provides insights into tumor growth regulation [5].

Recent perspective proposes the existence of a pre-glucolipotoxicity stage preceding glucolipotoxicity, which contributes to the development of specific pathological conditions [6]. Glucolipotoxicity refers to the detrimental effects of elevated levels of glucose and lipids on cellular function, primarily observed in pancreatic beta cells, adipocytes, and hepatocytes. Elevated nutrient availability, insulin resistance, and dysregulated lipid metabolism during the pre- glucolipotoxicity stage contribute to ER stress [7]. This disruption initiates a cascade of events eventually leading to the development of diseases. The interplay between ER stress and glucolipotoxicity profoundly impairs the functions of various cell types. In pancreatic beta cells, ER stress disrupts insulin signaling pathways and impairs insulin secretion, contributing to type 2 diabetes mellitus [8]. Adipocytes experience disrupted adipokine secretion and increased release of pro-inflammatory cytokines, contributing to obesity-related metabolic disorders. Hepatocytes, on the other hand, face dysregulated lipid metabolism resulting in hepatic steatosis and non-alcoholic fatty liver disease [9]. Elucidating the molecular events and signaling pathways involved in the transition from the pre-glucolipotoxicity stage to glucolipotoxicity is crucial for understanding and intervening in the progression of these specific pathological conditions associated with ER stress-induced deterioration [10]. Future investigations are needed to identify potential therapeutic targets for preventing or ameliorating the progression of these diseases.

Statements and Declarations

The authors declare that there are no conflicts of interest.

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