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The Role of Endoplasmic Reticulum in Pathogenesis of Congenital Anomalies

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OKU Sutro Excellence Day Project Cover Sheet

Project Title

The role of endoplasmic reticulum (ER) in pathogenesis of congenital anomalies

Full name(s) and class year(s) of all project collaborators

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Project Category

DDS/IDS/DH - Research Awards

Enter your abstract text here (max 300 words)

Objectives
This review delves into the intricate structural and functional roles of the endoplasmic reticulum (ER) in the context of congenital anomalies, encompassing conditions such as chondrodysplasias, congenital heart defects (CHD), and glycosylation mutations.

Materials and Methods
Searches within Google Scholar and PubMed databases were done using keywords " chondrodysplasias and ER stress", "maternal diabetes mellitus embryopathy and ER stress", and " UPR and birth defects". Systematic reviews, meta-analyses, and original studies were analyzed. The total of 23 articles published between the years 2012 and 2023 were reviewed.

Results
Dysregulation of protein folding in the ER, resulting in the accumulation of misfolded proteins, induces stress and has been implicated as a significant factor in the pathogenesis of congenital anomalies. In response to ER stress, cells activate the unfolded protein response (UPR), aimed at restoring ER homeostasis by reducing the amount of protein folding, enhancing the folding capacity of the ER, or degrading already misfolded proteins. Moreover, disruptions in UPR signaling pathways can also lead to structural malformations critical for embryonic development.

Conclusions
This literature review highlights the intricate relationship between the endoplasmic reticulum and congenital anomalies, shedding more light on the potential mechanisms underlying developmental abnormalities. Though many mechanisms within the endoplasmic reticulum have already been studied for a multitude of congenital anomalies, a deeper understanding of the molecular pathways is necessary to develop preventative and targeted therapies to improve the outcomes for affected individuals.

Acknowledgements
I would like to thank Dr. Tolarova and Dr. Tolar for guiding me in writing this literature review.

The role of the endoplasmic reticulum (ER) in pathogenesis of congenital anomalies

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INTRODUCTION

The endoplasmic reticulum (ER) is a network of membrane-enclosed tubules and sacs (cisternae) that extends from the nuclear membrane throughout the cytoplasm (Figure 1). The ER serves as the central orchestrator of protein synthesis, 3D protein folding, and protein quality control, pivotal for maintaining cellular homeostasis and functions. ER stress is a cellular response to adverse or very demanding conditions. It can be caused by extrinsic factors such as mechanical strain, low or high temperature, abrupt change in ion concentration, exposure to a toxin, or by intrinsic factors like overexpression of a mutated protein[1].

Accumulation of misfolded proteins and their aggregation in the ER impair normal cellular functions and can lead to cell death. Prolonged accumulation of misfolded proteins initiates a cascade of reactions called unfolded protein response (UPR). Activated UPR aims to restore ER homeostasis by reducing proteosynthesis, enhancing the folding capacity of the ER, or by degrading already misfolded proteins.

Dysregulation of protein folding in the ER resulting in the accumulation of misfolded proteins has been implicated not only in pathogenesis of many diseases but also as a significant factor in pathogenesis of some congenital anomalies. Moreover, disruptions in the UPR signaling pathways can also lead to structural malformations during embryonic development.

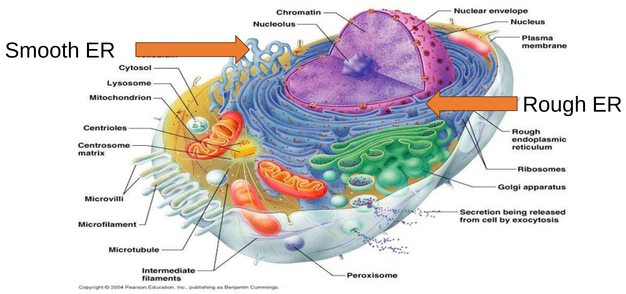

Figure 1. Diagram illustrating the cell organelles including the smooth and rough endoplasmic reticulum.

OBJECTIVES

This review will focus on roles of the ER in the context of congenital anomalies. Birth defects caused by ER dysfunction may be due to a genetic abnormality of the embryo or by an influence of environmental factors on developing embryo. To illustrate embryonal ER stress resulting from a genetic abnormality, we will examine the molecular mechanisms implicated in ER dysfunction within chondrodysplasias. Additionally, this review will explore embryopathies triggered by maternal diabetes mellitus as an instance of embryonal ER stress induced by environmental factors.

METHODS

Searches within Google Scholar and PubMed databases were done using keywords "chondrodysplasias and ER stress", "maternal diabetes mellitus embryopathy and ER stress", “UPR and birth defects”. Systematic reviews, meta-analyses, and original studies were analyzed. The total of 23 articles published between the years 2012 and 2023 were reviewed.

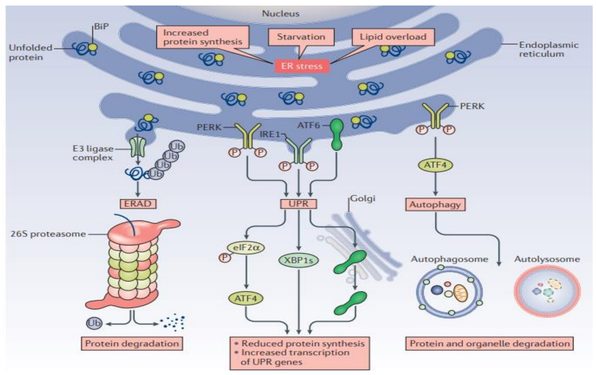

Figure 2. ER stress and UPR pathways. To restore cellular homeostasis in the cell exposed to ER stress the cell activates ER-associated degradation (ERAD), which guides misfolded proteins towards the cytosol where they are degraded by proteasomes. If the misfolded protein load is too high, the UPR activates PERK, IRE1, and ATF6 pathways. They can either facilitate the reduction of protein synthesis or induce the expression of more UPR genes. During long-term ER stress, however, PERK can activate ATF4 which increases protein and organelle degradation (autophagy)[2]. Altogether, they reduce the amount of ER stress. If not successful, the cell undergoes apoptosis.

RESULTS

The endoplasmic reticulum (ER) serves as a central hub in cellular physiology, orchestrating vital processes such as protein synthesis and folding, lipid synthesis, and calcium ion storage. It consists of rough ER, studded with ribosomes for protein synthesis, and smooth ER, which plays a role in lipid metabolism and detoxification of harmful chemicals[1]. Insights into mechanisms of pathogenesis of ER stress-related diseases and congenital anomalies may lead to development of novel therapeutic strategies to mitigate the impact of ER stress by pharmacological targeting of ER stress and UPR signaling pathways.

CHONDRODYSPLASIA

Chondrodysplasias are genetic disorders affecting skeletal development due to malfunction of chondrocytes. Accumulation of mutant collagen II or X proteins in ER causes ER stress and UPR signaling may lead to apoptosis of chondrocytes[3,4]. In addition, modulating genes and proteins associated with the UPR enables the mechanisms causing chondrodysplasias to be mapped and targeted for future therapies[5].

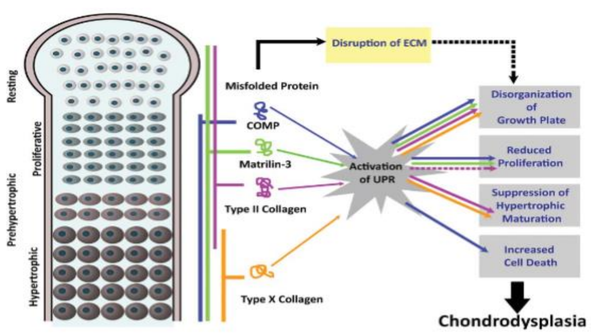

Figure 3. Mechanisms in the pathogenesis of chondrodysplasias. Mutations in COMP, Matrilin-3, type II and X collagen can result in protein misfolding and retention in the ER, causing ER stress and UPR activation. Accumulation of misfolded extracellular matrix proteins during development and disorganized growth of the growth plate leads to metaphyseal chondrodysplasia phenotypes like short stature, short limbs, coxa vara, and lumbar lordosis[3].

EMBRYOPATHY CAUSED BY MATERNAL DIABETES MELLITUS

Maternal diabetes mellitus increases the risk of abnormal development of the embryo such as neural tube defects or congenital heart defects (CHD)[6]. Increased oxidative stress and ER stress caused by gestational diabetes has also been linked with neural cell apoptosis and the formation of neural tube defects [7].

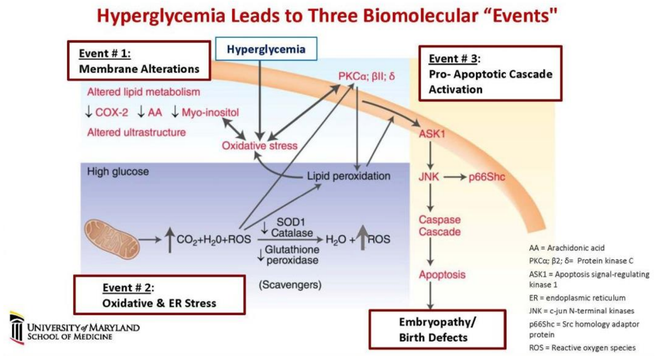

Figure 4. Molecular mechanisms causing maternal diabetes mellitus embryopathies. Hyperglycemia-induced apoptosis of embryonic cells is a primary causal mechanism of diabetic embryopathy. Hyperglycemia induces cell membrane disruption, increased production of reactive oxygen species (ROS) and a weakening of antioxidant systems. In addition, a buildup of misfolded and unfolded proteins triggers ER stress which in turn can lead to activation of apoptosis. Excessive cell death in the neural crest or developing heart can eventually lead to birth defects such as neural tube defects or congenital heart defects[7].

CONCLUSION

ER stress and UPR have important roles in disease pathogenesis and in the development of congenital anomalies. Targeting ER stress and UPR pathways holds promise for the development of novel therapeutic strategies to mitigate the impact of ER stress-related diseases. Continued research into these pathways and their modulation is essential for improving patient outcomes and advancing precision and personalized medicine approaches in the treatment of these disorders.

ACKNOWLEDGEMENTS

I would like to thank Dr. Tolarova and Dr. Tolar for guiding me in writing this literature review.

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