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Proteostasis and Metabolism Dysregulated in the Skeletal Muscle of a Pompe Mouse Model before Symptoms

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Introduction

Pompe disease, also known as Glycogen Storage Disease type II (GSD II), is a rare genetic disorder caused by the deficiency of the enzyme acid alpha-glucosidase (GAA). This enzyme plays a critical role in breaking down glycogen within lysosomes. In the absence of functional GAA, glycogen accumulates in lysosomes, leading to progressive organ damage, particularly in skeletal muscles, the heart, and the respiratory system. The onset of symptoms can vary, with infantile-onset Pompe disease presenting in the first few months of life and late-onset forms becoming apparent later in childhood or adulthood [1]. Despite the known pathophysiological effects of Pompe disease, recent studies have focused on understanding the early molecular events that precede the overt clinical symptoms of the disease. This is particularly significant because by the time symptoms become evident, irreversible damage to tissues, especially skeletal muscle, has often already occurred. One such study has focused on the dysregulation of proteostasis and metabolism in the skeletal muscle of a Pompe mouse model, identifying disruptions in these cellular processes before any clinical symptoms manifest. This early dysregulation provides insight into the pathophysiology of Pompe disease and offers potential targets for early intervention [2].

Description

Proteostasis refers to the regulation and maintenance of the proper folding, function, and degradation of proteins within a cell. It is a dynamic process that involves molecular chaperones, the ubiquitin-proteasome system, and the autophagy-lysosomal pathway. In the context of Pompe disease, proteostasis is significantly impaired due to the accumulation of glycogen in lysosomes, which disrupts normal cellular processes. The glycogen buildup not only impedes normal cellular functions but also alters protein folding and function. Lysosomes, which are involved in both glycogen degradation and protein turnover, become overwhelmed by the excessive storage material. This leads to a series of downstream effects that compromise proteostasis in skeletal muscle cells [3].

In the Pompe mouse model, a genetic knock-out of the GAA enzyme leads to glycogen accumulation in tissues, which has been shown to disrupt several cellular processes before any noticeable symptoms appear. Studies have demonstrated that even in the absence of overt muscle weakness or histopathological damage, skeletal muscle cells in these models exhibit altered protein homeostasis. Proteins that would normally be degraded accumulate within cells, and the chaperone proteins responsible for maintaining proper folding are overwhelmed. This leads to the buildup of misfolded proteins, triggering the Unfolded Protein Response (UPR). The UPR is a cellular stress response aimed at restoring proteostasis by enhancing the capacity of the protein-folding machinery, slowing down protein translation, and promoting the degradation of misfolded proteins. However, in the Pompe mouse model, this response is often insufficient to cope with the increased protein burden. As a result, skeletal muscle cells experience a buildup of dysfunctional proteins that can interfere with cellular function, leading to muscle dysfunction in the long run [4].

The dysregulation of proteostasis in Pompe disease is intricately linked with metabolic disruptions, particularly in energy homeostasis. Skeletal muscle cells, which rely heavily on mitochondrial function for ATP production, are especially vulnerable to changes in metabolism. In Pompe disease, the impaired ability to degrade glycogen leads to an imbalance in energy metabolism. The excess glycogen within lysosomes is not readily accessible for energy production, and this disruption in glycogen metabolism impedes the normal flow of energy substrates within muscle cells. Moreover, mitochondria, the primary energy producers in muscle cells, are affected by the changes in proteostasis and metabolism. Mitochondrial dysfunction in Pompe disease has been observed before the onset of clinical symptoms, suggesting that it is an early event in disease progression [5].

Conclusion

In addition to these molecular insights, the findings also underscore the importance of understanding the pathophysiological mechanisms underlying Pompe disease at the cellular level. By identifying the early disruptions in proteostasis and metabolism, researchers can develop targeted therapeutic strategies that address the root causes of the disease. Potential treatments could focus on enhancing the cellular machinery responsible for protein folding, improving mitochondrial function, or restoring normal glycogen metabolism. Such approaches could delay or even prevent the onset of symptoms, improving the quality of life for individuals with Pompe disease.

In conclusion, the dysregulation of proteostasis and metabolism in the skeletal muscle of Pompe mouse models occurs before the manifestation of clinical symptoms. This early disruption in cellular homeostasis provides valuable insights into the pathophysiology of Pompe disease and highlights the importance of early detection and intervention. Understanding these early molecular events could lead to the development of novel therapeutic strategies aimed at preventing the progression of the disease before irreversible damage occurs. Further research into the molecular mechanisms underlying these early alterations will be crucial for advancing our understanding of Pompe disease and improving outcomes for affected individuals.

Acknowledgement

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Conflict of Interest

None.

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