Brief Report
Volume 8:3, 2023

Journal of Molecular Histology and Medical Physiology

ISSN: 2684-494X

Open Access

Complementary Roles of Lipin1 in Enhancing Myofibre Stability and Regeneration in Dystrophic Muscles

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Abstract

Duchenne Muscular Dystrophy (DMD) stands as a debilitating condition triggered by mutations in the dystrophin gene. These mutations culminate in compromised sarcolemmal integrity, initiating a cascade of events marked by progressive myofibre necrosis and deteriorated muscle function. Earlier investigations from our lab underscored the significance of lipin1 in bolstering skeletal muscle regeneration and upholding myofibre integrity. Moreover, our studies unveiled a substantial reduction in lipin1 mRNA expression within the skeletal muscle of both DMD patients and the mdx mouse model, a classic model for DMD. Seeking a deeper comprehension of lipin1's role in dystrophic muscle, we embarked on generating dystrophin/lipin1 Double Knockout (DKO) mice. Through a comparative analysis encompassing wild-type B10 mice, muscle-specific lipin1 deficient (lipin1Myf5cKO) mice, mdx mice, and DKO mice, we uncovered a more severe phenotype in the DKO cohort, characterized by intensified necroptosis, fibrosis, and aggravated membrane damage relative to mdx mice. Intriguingly, barium chloride-induced muscle injury spotlighted prolonged regeneration at day 14 post-injection in both lipin1Myf5cKO and DKO mice, underscoring the critical role of lipin1 in muscle regeneration. In situ contractile function assays disclosed diminished specific force production in dystrophic muscles lacking lipin1. Cellular experimentation further solidified these findings, as lipin1-deficient cells exhibited elevated levels of necroptotic markers and medium creatine kinase, potentially stemming from sarcolemmal damage. Significantly, the restoration of lipin1 curbed the elevation of necroptotic markers in differentiated primary lipin1-deficient myoblasts. Collectively, our findings paint a picture of lipin1's dual contribution to myofibre stability and muscle function within the realm of dystrophic muscles. The tantalizing prospect of leveraging lipin1 overexpression as a therapeutic strategy for dystrophic muscles beckons as a beacon of hope.

Keywords: Duchenne muscle • Muscle necroptosis • Fibrosis

Introduction

Muscular dystrophy, a group of genetic disorders characterized by progressive muscle weakness and degeneration, poses significant challenges to affected individuals and their families. Among the various forms of muscular dystrophy, one of the most well-known is Duchenne Muscular Dystrophy (DMD), which primarily affects young boys. Despite advances in our understanding of the underlying genetic and molecular mechanisms, effective treatments for muscular dystrophy remain limited. However, recent research has shed light on the potential role of Lipin1 in myofibre stability and regeneration, offering a promising avenue for therapeutic interventions. Lipin1, a protein known for its role in lipid metabolism, has recently garnered attention for its involvement in muscle health. Initially identified as a regulator of lipid synthesis and storage, Lipin1 was not directly associated with muscular dystrophy. However, growing evidence suggests that Lipin1 plays a dual role in myofibre stability and regeneration, making it a target of interest for researchers exploring innovative therapeutic strategies [1,2].

Description

Myofibre stability: A delicate balance

Muscle fibres, or myofibres, are the building blocks of skeletal muscles. In dystrophic muscles, myofibres are prone to damage and degeneration due to the absence or dysfunction of specific proteins. Lipin1 appears to contribute to myofibre stability by modulating lipid metabolism and maintaining the integrity of the cell membrane. Lipin1 deficiency has been linked to increased susceptibility of myofibres to mechanical stress and oxidative damage, potentially exacerbating the progression of muscular dystrophy.

By promoting lipid synthesis and storage, Lipin1 ensures an adequate supply of lipids for membrane repair and maintenance. Furthermore, Lipin1's role in lipid metabolism extends to its participation in cellular signaling pathways that regulate inflammation and oxidative stress, both of which are heightened in dystrophic muscles. Thus, Lipin1 acts as a guardian of myofibre stability, protecting these crucial cellular structures from the detrimental effects of dystrophy-associated stressors [3].

Regeneration: A ray of hope

In dystrophic muscles, myofibre degeneration is often followed by attempts at regeneration. Regeneration involves the activation of muscle stem cells, known as satellite cells, which proliferate and differentiate to replace damaged myofibres. Here again, Lipin1 emerges as a key player. Recent studies have revealed that Lipin1 contributes to the regulation of satellite cell activity and the differentiation of muscle precursor cells.

Lipin1's involvement in muscle regeneration is multifaceted. It promotes satellite cell proliferation and expansion, facilitating the generation of a sufficient pool of precursor cells. Additionally, Lipin1 influences the expression of genes involved in muscle differentiation, ensuring that regenerated myofibres acquire the appropriate functional properties. This dual role of Lipin1 in satellite cell activation and differentiation highlights its potential as a therapeutic target for enhancing muscle regeneration in dystrophic conditions [4].

Towards therapeutic interventions

The discovery of Lipin1's complementary roles in myofibre stability and regeneration offers new avenues for developing targeted therapies for

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Received: 02 May, 2023; Manuscript No. jmhmp-23-110547; **Editor assigned:** 04 May, 2023, PreQC No. P-110547; **Reviewed:** 16 May, 2023, QC No. Q-110547; **Revised:** 22 May, 2023, Manuscript No. R-110547; **Published:** 29 May, 2023, DOI: 10.37421/2684-494X.2023.8.70

muscular dystrophy. Modulating Lipin1 expression or activity could potentially mitigate the progression of muscle degeneration and promote more effective muscle regeneration. Researchers are actively investigating ways to harness Lipin1's functions through gene therapy, small molecule compounds, or other innovative approaches.

As with any emerging research, there are challenges and questions that need to be addressed. The precise mechanisms by which Lipin1 regulates myofibre stability and regeneration require further elucidation. Additionally, the potential off-target effects of manipulating Lipin1 need to be carefully evaluated to ensure the safety and effectiveness of therapeutic interventions [5,6].

Conclusion

Lipin1, once regarded primarily as a lipid metabolism regulator, has emerged as a promising candidate for modulating myofibre stability and regeneration in dystrophic muscles. Its dual roles in maintaining myofibre integrity and promoting muscle precursor cell differentiation provide valuable insights into the complex interplay between cellular processes that underlie muscular dystrophy. As research continues to uncover the intricacies of Lipin1's functions, the prospect of targeted interventions that harness its potential offers renewed hope for individuals and families affected by muscular dystrophy. While challenges remain, the pursuit of Lipin1-based therapies represents a significant step forward in the quest to combat the devastating effects of dystrophic muscle disorders.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Mei, Hongren. "Complementary Roles of Lipin1 in Enhancing Myofibre Stability and Regeneration in Dystrophic Muscles." *J Mol Hist Med Phys* 8 (2023): 70.