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EDITORIAL

Mitochondrial dysfunction in type 2 diabetes: A neglected path to skeletal muscle atrophy

Jian-Jun Wu, Hui-Min Xian, Da-Wei Yang, Fan Yang

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Abstract

Over the course of several decades, robust research has firmly established the significance of mitochondrial pathology as a central contributor to the onset of skeletal muscle atrophy in individuals with diabetes. However, the specific intricacies governing this process remain elusive. Extensive evidence highlights that individuals with diabetes regularly confront the severe consequences of skeletal muscle degradation. Deciphering the sophisticated mechanisms at the core of this pathology requires a thorough and meticulous exploration into the nuanced factors intricately associated with mitochondrial dysfunction.

Key Words: Mfn-2; Oxidative stress; Mitochondria metabolism; Skeletal muscle atrophy; Diabetes

Core Tip: Type 2 diabetes mellitus (T2DM) poses a substantial global health challenge. Attaining optimal glycemic control is crucial for mitigating complications and mortality associated with T2DM. However, recent research has unveiled a frequently overlooked complication: The progressive atrophy of skeletal muscle. Mitochondria, pivotal for cellular energy production, uphold a delicate equilibrium in their fusion and fission processes. Investigating the interplay between mitochondrial dysfunction and skeletal muscle atrophy in T2DM is imperative for advancing our comprehension of diabetes. Findings from cellular and animal models suggest that targeting mitochondrial dynamics, particularly through the modulation of Mfn-2, holds promise as a therapeutic strategy to counteract muscle atrophy induced by diabetes. This approach underscores a novel intersection in the management of diabetic complications, forging a connection between metabolic control and muscular health.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a relentless and chronic hyperglycemic disorder that has emerged as a grave global public health concern, imposing a substantial burden on both afflicted individuals and healthcare systems[1]. The immense financial toll, surpassing £800 billion annually, covering expenses for T2DM diagnosis, treatment, and care, highlights the urgent need to address this swiftly escalating epidemic[2]. Recent studies indicate that among the numerous factors linked to T2DM, age, place of residence, education level, social status, family income, smoking, body mass index, family history, and physical exercise exert the most significant adverse effects on quality of life (QoL)[3]. Beyond the immediate metabolic disturbances, the insidious nature of T2DM engenders a spectrum of incapacitating complications, marked by their gradual onset and often inconspicuous progression, that exert a significant detrimental impact on both the life expectancy and QoL of individuals grappling with diabetes.

SKELETAL MUSCLE ATROPHY AND MITOCHONDRIA IN T2DM

Glycemic control is pivotal for reducing complications and mortality in T2DM. Emerging research in diabetes highlights skeletal muscle atrophy as a critical aspect of diabetic pathophysiology[4,5]. Skeletal muscle, characterized by high metabolic activity and dense mitochondrial networks, is integral for movement and health, efficiently generating ATP for muscle contraction and metabolic regulation. Diabetes-induced impairment in muscle cell energy production can lead to muscle atrophy and reduced physical function, making mitochondrial function preservation vital for both athletic performance enhancement and QoL improvement in chronic disease management.

Mitochondrial dynamics play a crucial role. Mitochondrial fusion, regulated by GTPases such as (mitofusins (Mfns) and optic atrophy protein 1 (Opa1), and fission, mediated by dynamin-related protein 1 and fission protein 1 (Fis1), undergo significant changes in T2DM[6]. Notably, T2DM patients exhibit downregulation of Mfn2 and Opa1 in skeletal muscles, correlating with reduced mitochondrial mass and density, suggesting aberrant mitochondrial dynamics as an early biomarker for metabolic diseases. Animal models with Mfn2 dysfunction show decreased substrate metabolism, whereas Mfn2 and Opa1 overexpression improves mitochondrial respiratory efficiency and glucose oxidation[7]. This paradoxical interplay between mitochondrial adaptation and dysfunction in diabetic muscles highlights the dual role of mitochondria in energy production and oxidative stress, contributing to muscle atrophy. This balance with reactive oxygen species underscores the complex nature of mitochondrial functions in metabolic regulation.

MFN-2: REGULATING MITOCHONDRIAL DYNAMICS AND POTENTIAL THERAPEUTIC TARGET

Deficiency in Mfn-2 exacerbates the division of mitochondria in cardiomyocytes, impairing cardiac and mitochondrial health, while its overexpression in vascular smooth muscle cells induces apoptosis. These observations underscore the complex and varied roles of Mfn-2 in cellular processes. Maintaining a balance between mitochondrial fusion and fission is essential for cellular homeostasis; disruptions leading to increased fragmentation are linked to various cellular dysfunctions, including a heightened propensity for mitochondrial-related apoptosis.

Innovative research avenues are exploring interventions targeting Mfn-2 and mitochondrial dysfunction. Notably, antioxidative treatments and exogenous hydrogen sulfide have shown potential in counteracting high glucose-induced injuries, mediated through Mfn-2 facilitated endoplasmic reticulum-mitochondria contacts[8]. These advancements present hopeful therapeutic avenues, especially for addressing mitochondrial dysfunction in skeletal muscle injuries related to diabetes.

Additionally, the diterpenoid derivative 15-oxospiramilactone (S3) emerges as a significant player in enhancing mitochondrial dynamics. It targets the mitochondrial enzyme USP30, integral for modulating MFN1 and MFN2, thereby boosting their activity and fostering mitochondrial fusion. Importantly, the ability of S3 to restore mitochondrial function in cells deficient in Mfn1 or Mfn2 underscores its therapeutic potential in treating insulin resistance-related diseases[9].

TOWARD THERAPEUTIC STRATEGIES FOR MODULATING MFN-2 AND MITOCHONDRIAL DYNAMICS

In the realm of diabetes research, a significant focus lies in understanding the correlation between cellular metabolism and the pathophysiology of the disease, emphasizing the role of mitochondria in skeletal muscle atrophy. The mitochondrion, vital for cellular energy, is central to this research, especially regarding Mfn-2-mediated mitochondrial fusion in skeletal muscle. This is particularly relevant in T2DM, where studying skeletal muscle tissues from affected individuals can shed light on the downregulation of Mfn-2 in diabetic conditions. Moreover, exploring type 1 diabetes, specifically the impact of high-fat diets on Mfn-2 in skeletal muscle, is crucial for a comprehensive understanding of diabetes and its effects on skeletal muscle health.

CONCLUSION

The intricate interplay between T2DM and skeletal muscle atrophy, with a focus on the pivotal role of mitochondrial dynamics and Mfn-2, underscores the urgency of developing targeted therapeutic strategies to address these complex metabolic challenges.

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FOOTNOTES

Co-first authors: Jian-Jun Wu and Hui-Min Xian.

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Author contributions: Wu JJ, Xian HM, Yang DW, and Yang F drafted the manuscript; all authors contributed to the critical review of the manuscript, and have read and approved the final manuscript; Wu JJ and Xian HM contributed equally to this work as co-first authors. Yang DW and Yang F contributed equally to this work as co-corresponding authors. The decision to designate Wu JJ and Xian HM as co-first authors as well as Yang DW and Yang F as co-corresponding authors is based on multiple factors. First, this research was conducted as a collaborative endeavor, and the designation of co-first/co-corresponding authorship accurately reflects the distribution of responsibilities and the considerable effort required to complete the paper. This ensures effective communication and management of post-submission matters, thereby enhancing the paper's quality and reliability. Second, the research team comprises individuals with diverse expertise and skills from various fields, and appointing co-authors best represents this diversity. This approach fosters a more comprehensive and profound examination of the research topic, enriching readers' understanding by presenting multiple expert perspectives. Third, Wu JJ and Xian HM as well as Yang DW and Yang F made equally substantial contributions throughout the research process. Designating them as co-first/co-corresponding authors acknowledges their equal involvement, while also honoring the collaborative spirit and teamwork that characterized this study.

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