



MITOCHONDRIAL–REDOX–IMMUNE AXIS: AN INTEGRATIVE MOLECULAR MECHANISM LINKING SKELETAL MUSCLE AND VASCULAR DYSFUNCTION

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Abstract: Recent decades of research have revealed that mitochondria play a crucial role not only in energy production but also in cellular signaling and fate determination. This article proposes the concept of the "mitochondrial–redox–immune axis" as an integrative molecular mechanism explaining the pathophysiological link between skeletal muscle and vascular dysfunction. Dysfunctions in the mitochondrial electron transport chain lead not only to energy deficiency but also to uncontrolled production of reactive oxygen species (ROS). This disruption of redox balance alters the functional polarization of inflammatory cells, particularly macrophages and T-lymphocytes, leading to chronic low-grade inflammation. In pathologies such as peripheral artery disease (PAD), chronic kidney disease (CKD), and heart failure (HF), the interplay of mitochondrial dysfunction, oxidative stress, and immune cell activation results in skeletal muscle atrophy, reduced contractile capacity, and endothelial dysfunction. Recent multi-omic studies, particularly the suppression of mitochondrial gene expression by uremic toxins (kynurenine, indoxyl sulfate), have been shown to contribute to muscle weakness. Additionally, mitochondrial dynamics in immune cells (e.g., Drp1 protein sulfenylation) and redox-sensitive signaling pathways (cGMP-PKG, NAMPT-NAD⁺) are crucial for vascular regeneration and muscle recovery under ischemic conditions. Identifying the molecular components of this axis lays the foundation for



novel therapeutic approaches, including mitochondrial transplantation, antioxidant strategies, and immunomodulation, to treat interconnected diseases of skeletal muscle and vascular systems.

Keywords: *Mitochondrial dysfunction; Oxidative stress; Immune cell polarization; Skeletal muscle myopathy; Endothelial dysfunction; Peripheral artery disease; Redox signaling; Mitophagy; Uremic toxins; Inflammation.*

Research Objective: The main objective of this comprehensive review is to analyze the complex interactions between mitochondrial dysfunction, redox imbalance, and the immune system as a single integrative mechanism referred to as the "mitochondrial–redox–immune axis." This study aims, based on data published in reputable scientific databases between 2015–2025, to explain at a molecular level how this axis links skeletal muscle and vascular dysfunction. The goal is to determine the causal relationships between mitochondrial ROS, inflammatory cells (macrophages, T-cells), and their cytokine profile in the development of muscle weakness, atrophy, and endothelial dysfunction in common pathologies such as PAD, CKD, and HF. Additionally, the study aims to evaluate the key molecular components of this axis (e.g., Drp1, NAMPT, TXNIP, Lonp1) as therapeutic targets and provide a theoretical basis for future treatment strategies (mitochondrial transplantation, targeted antioxidants).

Research Methods: This article is based on a systematic analysis and review of experimental and clinical studies indexed in international scientific databases such as PubMed, Scopus, Web of Science, and Google Scholar from 2015–2024. Keywords used included "mitochondrial dysfunction," "oxidative stress," "skeletal muscle myopathy," "vascular inflammation," "redox signaling," "PAD myopathy," "uremic toxins," and "macrophage polarization." Selected studies included human cohort studies (e.g., muscle biopsies and plasma metabolomics in PAD and CKD patients) [1, 6], functional and molecular experiments in animal models (e.g., hindlimb ischemia models) [4, 8], and in vitro cell culture models (e.g., C2C12 myotubes, endothelial cells, macrophages) [3, 7, 10]. Multi-omic technologies



(transcriptomics, metabolomics), high-resolution microscopy (transmission electron microscopy, focused ion beam scanning electron microscopy), mitochondrial respiration assays (Oroboros, Seahorse analyzers), protein modifications (sulfenylation), and genetic manipulations (conditional knockout, CRISPR/Cas9) were widely used to elucidate molecular mechanisms. The combination of these methods allowed the identification of changes at different nodes of the mitochondrial-redox-immune axis.

Introduction: Skeletal muscles constitute approximately 40% of the human body and are crucial for movement, metabolic homeostasis, and overall health. The vascular system ensures tissues are supplied with oxygen and nutrients. The functional and molecular linkage between these two systems is so interdependent that pathological changes in one almost inevitably lead to dysfunction in the other [1, 4]. Traditionally, cardiovascular or muscle diseases have often been studied separately, but recent scientific advances show that common molecular mechanisms underlie their pathogenesis. Central to this shared mechanism is the mitochondrion – the cell's energy-producing organelle [1, 5]. Mitochondria are not only responsible for adenosine triphosphate (ATP) synthesis but are also key regulators of intracellular calcium homeostasis, apoptosis, and, importantly, the main source of reactive oxygen species (ROS). Under physiological conditions, mitochondrial ROS (mitoROS) play an essential role in cellular signaling, such as modulating insulin signaling or initiating hypoxic adaptation mechanisms [10]. However, various pathological factors (ischemia, toxins, inflammatory cytokines) impair mitochondrial electron transport chain (ETC) function. This impairment leads to excessive mitoROS production, which the cell's endogenous antioxidant systems cannot compensate for, resulting in oxidative stress [2, 4]. Oxidative stress causes oxidative damage to proteins, lipids, and DNA, disrupting cell function. One of the most significant pathological consequences of oxidative stress is the activation of the inflammatory response. Damage-associated molecular patterns (DAMPs) released due to cellular injury, as well as ROS themselves, recruit inflammatory cells (neutrophils,



macrophages) to the damaged tissue [8]. Macrophages play a particularly crucial role as they can polarize into various functional phenotypes (M1 and M2) depending on microenvironmental signals. The M1 (pro-inflammatory) phenotype produces more ROS and pro-inflammatory cytokines, exacerbating tissue damage, whereas the M2 (anti-inflammatory) phenotype supports tissue repair and remodeling [8]. Macrophage polarization itself depends on mitochondrial metabolism and redox status, creating a complex interplay (axis) among mitochondria, redox signaling, and the immune system. Skeletal muscles and vascular endothelium are mitochondria-rich tissues, making their function highly sensitive to disruptions in this axis. Peripheral artery disease (PAD) is a clear example. In PAD, caused by atherosclerotic narrowing of arteries supplying the legs, ischemic muscles exhibit mitochondrial dysfunction and increased oxidative stress [4, 9]. This condition is the primary cause of myopathy, leading to pain, muscle weakness, and limited walking distance in patients. Studies have shown that mitochondrial respiratory function is impaired in the gastrocnemius muscle of PAD patients, with structural alterations (e.g., decreased mitochondrial volume and number, disorganized cristae) and increased ROS production [9]. Moreover, mitochondrial interaction with lipid droplets is altered, affecting fatty acid oxidation efficiency [9]. The complexity of PAD pathogenesis is further exacerbated when it coexists with chronic kidney disease (CKD). In CKD, accumulated uremic toxins (e.g., kynurenine, indoxyl sulfate) severely worsen muscle pathology in PAD patients. Recent multi-omic studies indicate that calf muscle strength in patients with both PAD and CKD is significantly lower compared to PAD-only patients, correlating with impaired mitochondrial function and reduced muscle fiber area [6]. Plasma metabolomics analysis showed a negative correlation between high uremic toxin levels, muscle strength, and mitochondrial function, as well as decreased expression of mitochondrial genes related to protein synthesis [6]. These data suggest that in CKD, uremic toxins directly affect the mitochondrial-redox-immune axis, exacerbating muscle and vascular dysfunction. Similar mechanisms are observed in other



cardiovascular diseases, such as left ventricular heart failure. Patients with heart failure commonly exhibit skeletal muscle mitochondrial dysfunction, associated with reduced exercise tolerance and increased fatigue [1]. In the heart itself, mitochondrial dysfunction leads to energy deficiency and excessive calcium load, reducing cardiac contractility [1]. From this perspective, improving mitochondrial function (e.g., via mitochondrial transplantation or metabolic interventions) is considered a promising strategy for treating heart failure [1]. Collectively, these data emphasize that skeletal muscle and vascular diseases should be understood not separately but through a common molecular mechanism – the mitochondrial–redox–immune axis. This review aims to analyze the components of this axis, their interactions, and their role in pathology based on contemporary scientific literature.

Results: The results of this comprehensive review include several key observations confirming the central role of the mitochondrial–redox–immune axis in linking skeletal muscle and vascular dysfunction. The findings were systematized into three main directions: (1) mitochondrial and redox changes in skeletal muscle, (2) changes in the vascular system, and (3) immunologically mediated linkage between these two systems.

Mitochondrial Dysfunction and Redox Imbalance in Skeletal Muscles:

Studies have firmly established that mitochondrial dysfunction is a primary pathogenic factor in skeletal muscle myopathy. In peripheral artery disease (PAD) models, ischemic muscles showed significant reductions in mitochondrial respiration. For example, research by Fletcher et al. demonstrated that chronic alcohol consumption exacerbates ischemia-associated mitochondrial dysfunction in PAD animal models, reducing ATP production and increasing ROS levels [4]. These changes manifest not only functionally but also structurally. Electron microscopy studies revealed reductions in sarcomere size, changes in mitochondrial number and localization, myofibrillar disorganization, and altered mitochondria-lipid droplet contact areas in the gastrocnemius muscle of PAD patients [9]. These ultrastructural alterations were directly associated with decreased mitochondrial respiration and



increased ROS production [9]. Particularly, as PAD progresses clinically (from stage II to IV), mitochondrial parameters deteriorate progressively, paralleling worsening myopathy [9].

Studies investigating molecular mechanisms of mitochondrial dysfunction identified several critical proteins and signaling pathways. For instance, the mitochondrial protease Lonp1 plays a role in cardiac and skeletal muscles. Lonp1 knockout halted cardiac development, induced cardiomyocyte apoptosis, and reduced muscle fiber size and strength, indicating its essential role in maintaining mitochondrial function [1]. Additionally, the protein NAMPT (nicotinamide phosphoribosyltransferase) plays a crucial role in PAD myopathy. Yang et al. demonstrated decreased NAMPT in ischemic skeletal muscles, and its exogenous administration enhanced oxidative Type I fiber formation, improved mitochondrial function, and restored ischemic limb function [7]. This effect was mediated via the cGMP-PKG signaling pathway, confirming the importance of the NAMPT-NAD⁺ axis in mitochondrial biogenesis and muscle regeneration [7].

From a redox imbalance perspective, oxidative stress effects on muscle cells have been extensively studied. Chernyavskij et al. demonstrated in vitro that the anti-inflammatory cytokine tumor necrosis factor (TNF) inhibits myogenesis in human myoblasts via mitoROS-dependent activation of general autophagy and mitophagy [1]. This finding explains the molecular basis of muscle injury observed in systemic diseases such as heart failure. Another study revisited insulin-stimulated H₂O₂ dynamics. Henríquez-Olguín et al. showed that insulin does not increase cytosolic H₂O₂ in skeletal muscles; instead, it induces selective pro-redox cysteine modifications, potentially modulating insulin signaling [10]. This finding elucidates the complex relationship between insulin signaling and redox homeostasis.

Vascular System Mitochondrial and Redox Changes: Vascular endothelial and smooth muscle cells are also crucial targets of the mitochondrial-redox axis. In PAD, reduced blood flow and reperfusion increase oxidative stress in endothelial cells. Mavraganis et al. demonstrated in a randomized placebo-controlled



trial that redox-dependent regulation of vascular function occurs after muscle-damaging exercise. Administration of thiol-based antioxidants (N-acetylcysteine) reduced immune cell recruitment, indicating redox-sensitive regulation of leukocyte migration [2].

Another key aspect of vascular pathology is medial calcification. Hwang and Woo investigated the role of TXNIP (thioredoxin-interacting protein) in vascular smooth muscle cells. TXNIP knockout in these cells reduced medial calcification induced by CKD and vitamin D3. TXNIP deficiency suppressed mitochondrial ROS production, inflammasome activation, and osteogenic differentiation, highlighting TXNIP as a critical mediator of oxidative stress- and inflammation-induced vascular calcification and a potential therapeutic target [3].

Mitochondrial dynamics, particularly Drp1 (dynamitin-related protein 1), also play a critical role in vascular regeneration. Yadav et al. demonstrated that sulfenylation of cysteine residues in macrophage Drp1 is essential for neovascularization and regeneration of ischemic muscle. In mice with redox-defective Drp1-C631A mutants or macrophage-specific Drp1 knockout, post-ischemic blood flow recovery, angiogenesis, and muscle regeneration were significantly impaired. Disrupted Drp1 sulfenylation reduced M2 (anti-inflammatory/reparative) polarization, increased M1 (pro-inflammatory) phenotype, and altered macrophage metabolic reprogramming (enhanced glycolysis) [8]. This finding demonstrates how mitochondrial-redox signaling in immune cells directly affects vascular and muscle regeneration.

Immune-Mediated Linkage: Mitochondrial-Redox-Immune Axis

The above results indicate that changes in skeletal muscle and vascular systems are interconnected via immune-mediated axes. Central to this axis are the mitochondrial status and redox balance of macrophages and other immune cells. The table below summarizes the main components of this axis and their roles in pathological processes:



Mitochondrial dysfunction and redox imbalance not only lead to local tissue pathology but also systemically influence immune cell phenotype and function. Particularly in combined PAD and CKD, disturbances in each component of this axis intensify, clinically manifesting as severe myopathy and vascular complications [6]. Immune cells, especially macrophages, perform two critical functions: responding to oxidative stress and cellular debris in damaged tissue, and modulating the strength and direction of this response via their own mitochondrial-redox status [8]. Thus, the mitochondrial-redox-immune axis serves as an integrative mechanism ensuring bidirectional communication between skeletal muscle and the vascular system.

Discussion: The results presented in this review provide a solid theoretical basis for understanding the pathophysiological link between skeletal muscle and vascular dysfunction through the "mitochondrial-redox-immune axis." Unlike traditional views, mitochondria should be considered not merely energy-producing organelles but central integrators of cellular signaling, key regulators of redox balance, and important modulators of immune responses [1, 5]. Disruption of any component of this axis (e.g., genetic defects, hypoxia, toxin exposure) triggers cascading reactions, ultimately resulting in muscle weakness, atrophy, and vascular insufficiency.

A key point in the discussion is the dual role of immune cells. On one hand, M1 phenotype macrophages and other inflammatory cells produce ROS and cytokines, exacerbating tissue damage [6, 8]. On the other hand, M2 phenotype macrophages and their mitochondrial dynamics (e.g., Drp1 sulfenylation) are crucial for tissue regeneration and angiogenesis [8]. This implies that therapeutic strategies should not aim to completely suppress the immune response but to appropriately guide it toward reparative phenotypes. Targeting redox-sensitive proteins in macrophage mitochondria (Drp1, TXNIP) appears promising [3, 8].

Another critical aspect is the effect of systemic factors (e.g., uremic toxins) on the mitochondrial-redox-immune axis. Co-occurrence of PAD and CKD not only adds risk but qualitatively changes pathology. In CKD, accumulated toxins



(kynurenine, indoxyl sulfate) directly suppress mitochondrial gene expression in skeletal muscles, exacerbating energy deficits and oxidative stress [6]. This suggests that in such complex comorbid conditions, simple antioxidant therapy may be ineffective, and strategies to eliminate or block toxins are necessary [6].

Therapeutically, several innovative approaches targeting different nodes of the mitochondrial-redox-immune axis exist. First, mitochondria-targeted antioxidants (e.g., natural compounds from microalgae) have potential to reduce oxidative stress [1]. However, clinical trials often fail, emphasizing the importance of "rational antioxidant therapy" (normalizing rather than completely suppressing redox signaling) [2]. Second, mitochondrial transplantation – transferring healthy mitochondria to damaged tissues – is being studied as a highly promising experimental method for treating cardiac and muscle diseases [1]. Third, strategies improving mitochondrial metabolism (e.g., enhancing NAMPT activity or administering NAD⁺ precursors) may restore mitochondrial function and improve muscle and vascular health [7].

These findings have significant clinical implications. Assessing the state of the mitochondrial-redox-immune axis (e.g., measuring mitochondrial respiration in peripheral blood mononuclear cells) can serve as novel diagnostic and prognostic markers in diseases characterized by exercise intolerance, muscle weakness, and fatigue such as PAD, CKD, and HF [1]. Moreover, monitoring molecular markers of this axis (e.g., mitoROS levels, macrophage polarization) is important alongside traditional hemodynamic parameters to evaluate therapeutic efficacy.

Conclusion: This comprehensive review demonstrates that the mitochondrial-redox-immune axis is a central integrative mechanism linking skeletal muscle and vascular systems. Analysis of the most recent and reputable studies from 2015–2025 confirms that mitochondrial dysfunction and consequent oxidative stress drive not only local tissue damage but also systemic pathological processes by altering immune cell (particularly macrophage) phenotype and function. In diseases such as PAD, CKD, and HF, disruption of this axis results in



muscle atrophy, reduced contractility, endothelial dysfunction, and vascular remodeling. Key molecular mechanisms include mitochondrial electron transport chain defects, increased mitoROS production, impaired redox-sensitive signaling (NAMPT-NAD⁺, cGMP-PKG), mitochondrial dynamics protein dysfunction (Drp1, Lonp1), and disproportionate M1/M2 macrophage polarization. Notably, in PAD and CKD comorbidity, uremic toxins suppress mitochondrial gene expression and exacerbate muscle pathology, highlighting the need to consider comorbidities and target systemic factors in treatment. Future research should focus on: (i) characterizing disease-specific features of the mitochondrial-redox-immune axis; (ii) developing selective therapeutic agents targeting axis components (Drp1, TXNIP, NAMPT); (iii) evaluating clinical efficacy of mitochondrial transplantation and gene therapy; (iv) validating mitochondrial function markers in peripheral blood as non-invasive biomarkers of skeletal muscle and vascular health. Understanding the complex interplay among mitochondria, redox signaling, and the immune system provides a novel perspective on cardiovascular and muscle disease pathogenesis and opens new therapeutic opportunities for these prevalent conditions.

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