

MITOCHONDRIAL DYSFUNCTION AND REDOX REMODELING IN THE NOX-UNCOUPLED ENOS AXIS: IMPLICATIONS FOR ATHEROSCLEROSIS AND VASCULAR STIFFNESS

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RESUMO

Introduction: Cardiovascular diseases remain the leading cause of mortality worldwide, with atherosclerosis and vascular stiffness representing key pathological processes driven by complex molecular mechanisms. Among these, redox imbalance and mitochondrial dysfunction play central roles in the initiation and progression of vascular damage. **Objective:** This review aims to explore the interplay between mitochondrial dysfunction and redox remodeling within the NADPH oxidase (NOX)-endothelial nitric oxide synthase (eNOS) axis, with particular emphasis on eNOS uncoupling as a critical event in endothelial dysfunction. **Methods:** This narrative review employed a systematic search strategy in PubMed/MEDLINE, Scopus, and Web of Science, including studies published between 2015 and 2026. Keywords such as “mitochondrial dysfunction,” “oxidative stress,” “NOX,” and “eNOS uncoupling” were combined using Boolean operators. Original articles and reviews addressing molecular mechanisms of endothelial dysfunction were included, while duplicates and unrelated studies were excluded. **Results:** A comprehensive analysis of recent evidence highlights that excessive reactive oxygen species (ROS) production, primarily mediated by NOX enzymes, contributes to the oxidation of tetrahydrobiopterin (BH₄), leading to eNOS uncoupling and reduced nitric oxide (NO) bioavailability. This shift promotes a vicious cycle of oxidative stress, inflammation, and vascular remodeling. In parallel, mitochondrial dysfunction exacerbates ROS generation, impairs ATP production, and activates pro-inflammatory signaling pathways, further aggravating endothelial injury. These interconnected processes contribute to the progression of atherosclerotic plaque formation, increased arterial stiffness, and impaired vascular homeostasis. Additionally, emerging evidence suggests that targeting mitochondrial function and restoring redox balance may represent promising therapeutic strategies to mitigate cardiovascular risk. **Conclusion:** The NOX-uncoupled eNOS axis, closely linked to mitochondrial dysfunction, represents a pivotal mechanism underlying vascular pathology and offers novel insights into potential molecular targets for the prevention and treatment of cardiovascular diseases.

Palavras-chave: Redox Signaling Endothelial Dysfunction NOX-eNOS Axis Reactive Oxygen Species (ROS) Vascular Remodeling.