INOSR APPLIED SCIENCES 13(2):12-16, 2025 ISSN: 2705-165X
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International Network Organization for Scientific Research
https://doi.org/10.59298/INOSRAS/2025/13.2.1216

Mitochondrial Dysfunction and Redox Imbalance in Drug-Induced Cardiotoxicity: Mechanistic Insights and Therapeutic Targets

Twesigye Davis

Department of Pharmacognosy Kampala International University Uganda
Email: twesigyedavis@studwc.kiu.ac.ug

ABSTRACT

Drug-induced cardiotoxicity represents a major challenge in modern pharmacotherapy, particularly among patients receiving long-term treatment for cancer, HIV, and chronic inflammatory conditions. While traditionally viewed as a cardiac-specific effect, cardiotoxicity is now understood as a multifaceted condition involving systemic and molecular disruptions. At the center of this pathological process lie two tightly connected phenomena: mitochondrial dysfunction and redox imbalance. The myocardium's high energy demand, continuous contractile activity, and reliance on oxidative metabolism render it especially susceptible to perturbations in mitochondrial bioenergetics and reactive oxygen species (ROS) homeostasis. This review explores the pathophysiological basis of drug-induced cardiotoxicity, focusing on mitochondrial bioenergetic failure, membrane potential collapse, impaired mitochondrial dynamics, and ROS-induced damage. The review also discusses emerging therapeutic strategies, such as mitochondrial-targeted antioxidants, modulators of mitochondrial dynamics, and novel redox-based interventions, as well as nanotechnology-enhanced drug delivery systems. A mechanistic understanding of mitochondrial and redox interactions is critical to advancing precision medicine in cardiotoxicity prevention and treatment.

Keywords: Mitochondrial dysfunction, Redox imbalance, Drug-induced cardiotoxicity, Oxidative stress, Cardioprotective therapeutics

INTRODUCTION

Cardiotoxicity, particularly that induced by therapeutic drugs, is an increasingly recognized cause of cardiac morbidity and mortality in long-term survivors of cancer and chronic infections [1]. With advancements in treatment, patients now live longer, revealing previously underestimated adverse effects, particularly cardiac injury [2]. Agents such as anthracyclines, trastuzumab, protease inhibitors, and certain tyrosine kinase inhibitors have been linked to cardiac dysfunction, ranging from asymptomatic changes in ejection fraction to overt heart failure, arrhythmias, and myocarditis [3]. Central to the emerging understanding of drug-induced cardiotoxicity are mitochondrial dysfunction and oxidative stress [4]. Mitochondria not only serve as cellular powerhouses but also regulate calcium homeostasis, apoptosis, and redox balance—functions critical to cardiomyocyte survival and function [5]. These organelles are particularly abundant in cardiac tissue, which demands constant energy production. Consequently, drugs that interfere with mitochondrial function or alter redox signaling can trigger a cascade of events culminating in cardiomyocyte death and tissue remodeling [6].

Mitochondrial Dysfunction in Cardiotoxicity

Mitochondrial Bioenergetic Failure

Mitochondria generate over 95 percent of the cardiac cell's ATP through oxidative phosphorylation [7]. Chemotherapeutic agents like doxorubicin impair complexes I and III of the electron transport chain (ETC), resulting in ATP depletion [8]. Reduced ATP availability disrupts calcium cycling, contractile protein phosphorylation, and ionic gradients—vital processes in maintaining myocardial contractility [9]. Prolonged energy insufficiency promotes cardiomyocyte apoptosis and necrosis [10].

Membrane Potential Depolarization and Permeability Transition

One of the earliest mitochondrial changes in cardiotoxicity is the loss of membrane potential, which reflects the electrochemical gradient essential for ATP synthesis [11]. Drugs that cause oxidative damage lead to the persistent opening of the mitochondrial permeability transition pore (mPTP) [12]. This event results in mitochondrial swelling, outer membrane rupture, and the release of pro-apoptotic factors such as cytochrome c into the cytoplasm, triggering caspase activation and cell death [12].

Disruption of Mitochondrial Dynamics

Mitochondria are dynamic organelles that undergo continuous fission and fusion to maintain quality control, distribution, and function [13]. Drug-induced cardiotoxicity often skews this dynamic balance toward excessive fission. Proteins like dynamin-related protein 1 (Drp1) become overactivated, leading to mitochondrial fragmentation [14]. Concurrently, fusion-related proteins such as mitofusin 1 and 2 (Mfn1/2) and optic atrophy protein 1 (OPA1) are downregulated, resulting in mitochondrial network disruption and compromised energy output [15]. These fragmented mitochondria are more prone to dysfunction and ROS overproduction.

mtDNA Damage and Replication Errors

Cardiac mitochondria contain multiple copies of mitochondrial DNA (mtDNA), which encodes essential proteins for ETC function [16]. Many drugs, particularly antiretroviral nucleoside analogues and chemotherapeutic agents, directly damage mtDNA or inhibit its replication [17]. Since mtDNA lacks protective histones and has limited repair mechanisms, such damage is cumulative and can impair ETC efficiency, exacerbating energy failure and oxidative stress [18].

Redox Imbalance and Oxidative Stress

Reactive Oxygen Species Generation

ROS, including superoxide anion, hydrogen peroxide, and hydroxyl radicals, are byproducts of aerobic metabolism [19]. Under physiological conditions, ROS are essential signaling molecules. However, when produced excessively or inadequately cleared, they cause oxidative stress [20]. In the context of mitochondrial dysfunction, impaired electron transfer increases electron leakage, particularly at complexes I and III, generating abundant ROS [21]. These molecules can oxidize mitochondrial membranes, proteins, and DNA, accelerating cardiomyocyte death [21].

Antioxidant System Exhaustion

The heart possesses a robust antioxidant defense network, including enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase [22]. However, during chronic drug exposure, these systems are overwhelmed. Studies have shown downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), the master regulator of antioxidant gene expression, in hearts exposed to doxorubicin [23]. This leads to impaired antioxidant regeneration and susceptibility to cumulative oxidative damage.

Inflammation and Immune Modulation

ROS also act as second messengers in inflammatory pathways [24]. They activate redox-sensitive transcription factors such as NF-kappa B, leading to the upregulation of pro-inflammatory cytokines including interleukin-6 and tumor necrosis factor-alpha [25]. This inflammatory milieu worsens endothelial dysfunction, promotes fibrosis, and perpetuates the cycle of cardiotoxicity.

Interconnectivity of Mitochondrial and Redox Pathways

Mitochondrial dysfunction and redox imbalance are not parallel events but are tightly interwoven in a self-perpetuating cycle. Mitochondrial damage increases ROS production, while excessive ROS exacerbate mitochondrial damage [26]. Moreover, impaired mitophagy—the process by which damaged mitochondria are selectively degraded—leads to the accumulation of dysfunctional mitochondria, further fueling oxidative stress [27]. These feedback loops underscore the need for therapeutic strategies that target both mitochondrial function and redox homeostasis simultaneously.

Drug Classes Implicated in Mitochondrial Redox Disruption

A broad range of pharmacological agents contributes to mitochondrial and redox dysregulation:
Anthracyclines (e.g., doxorubicin) interfere with ETC and stimulate iron-dependent ROS production [28].
Tyrosine kinase inhibitors (e.g., sunitinib) impair mitochondrial morphology and induce vascular oxidative stress [29]. Protease inhibitors (e.g., ritonavir) impair mitochondrial enzymes involved in fatty acid oxidation, increasing ROS generation [30]. Antiepileptics and antipsychotics have been linked to decreased mitochondrial enzyme activity and increased oxidative markers [31].

Therapeutic Strategies Targeting Mitochondrial and Redox Pathways

Mitochondrial-Targeted Antioxidants

Novel agents such as MitoQ, SS-31 (elamipretide), and SkQ1 are engineered to accumulate in the mitochondrial matrix, where they neutralize ROS directly at the site of production [32]. These compounds preserve mitochondrial integrity, reduce apoptosis, and improve cardiac performance in preclinical models of drug-induced cardiotoxicity.

Nrf2 Pathway Activation

Activators of the Nrf2 pathway, such as sulforaphane and bardoxolone methyl, upregulate antioxidant enzyme expression and enhance mitochondrial function [33]. These agents counteract oxidative stress and reduce inflammation, offering cardioprotection without interfering with primary drug efficacy [33].

Modulators of Mitochondrial Dynamics

Pharmacological inhibitors of Drp1, such as mdivi-1, restore the fission-fusion balance and reduce mitochondrial fragmentation [34]. Enhancing fusion through gene therapy or small molecules targeting Mfn2 may preserve mitochondrial networks and ATP production [35].

Nanocarrier-Based Delivery Systems

Nanotechnology offers the potential for precise delivery of cardioprotective agents to the mitochondria. Lipid nanoparticles, polymeric micelles, and dendrimers can encapsulate antioxidants, peptides, or gene modulators and release them selectively into cardiac tissues, minimizing systemic toxicity [36].

Lifestyle and Nutraceutical Approaches

Regular aerobic exercise and dietary restriction enhance mitochondrial biogenesis and antioxidant capacity [37]. Nutraceuticals such as resveratrol, quercetin, and coenzyme Q10 exhibit mitochondrial protective effects by activating sirtuins, AMPK, and PGC-1α pathways [38]. These interventions offer accessible and adjunctive options in mitigating cardiotoxic risk.

Future Perspectives and Research Gaps

There is a pressing need to identify reliable biomarkers of early mitochondrial dysfunction in cardiotoxicity. Circulating levels of mitochondrial DNA, cardiolipin oxidation products, or ETC enzyme activity could serve as diagnostic tools. Personalized risk assessment through mitochondrial genomics may allow clinicians to predict susceptibility and tailor therapies. Furthermore, clinical trials evaluating the long-term cardioprotective effects of mitochondrial-targeted therapies are urgently needed to translate preclinical success into practice.

CONCLUSION

Mitochondrial dysfunction and redox imbalance represent central, interconnected drivers of drug-induced cardiotoxicity. These processes initiate and sustain cardiac injury through energy deprivation, oxidative damage, and apoptosis. As our mechanistic understanding deepens, targeted interventions that preserve mitochondrial function and redox balance offer promising avenues for preventing or reversing cardiotoxicity. Future research must focus on integrating molecular biomarkers, personalized interventions, and novel delivery systems into clinical practice to safeguard the cardiovascular health of patients undergoing long-term pharmacotherapy.

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CITE AS: Twesigye Davis (2025). Mitochondrial Dysfunction and Redox Imbalance in Drug-Induced Cardiotoxicity: Mechanistic Insights and Therapeutic Targets. INOSR APPLIED SCIENCES 13(2):12-16. https://doi.org/10.59298/INOSRAS/2025/13.2.1216