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Review Article

Research Progress of PRDX3 in the Pathogenesis and Treatment of Bradyarrhythmia: A Review

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Abstract

Bradyarrhythmia, characterized by abnormally slow heart rhythms, is a common clinical cardiac arrhythmia with complex underlying mechanisms involving oxidative stress, mitochondrial dysfunction, and ion channel abnormalities. Peroxiredoxin 3 (PRDX3), a mitochondria-specific peroxide reductase, plays a crucial role in scavenging reactive oxygen species and maintaining mitochondrial functional homeostasis. This review systematically summarizes the structural and functional characteristics of PRDX3, its expression regulation in myocardial tissue, and its involvement in the molecular mechanisms underlying bradyarrhythmia. Furthermore, we discuss emerging therapeutic strategies targeting PRDX3, aiming to provide a theoretical foundation for elucidating novel pathogenic pathways and developing targeted treatments for bradyarrhythmia. By integrating current research findings, this article highlights the significance of PRDX3 in the pathophysiology of slow heart rhythms and underscores its potential as a biomarker and therapeutic target in clinical cardiology.

Keywords: PRDX3, Bradyarrhythmia, Bradycardia, Oxidative stress, Mitochondrial dysfunction, Sinoatrial node

Introduction

Slow heart rhythm disorders, collectively termed bradyarrhythmias, are characterized by a heart rate below 60 beats per minute and encompass clinical entities such as sick sinus syndrome and atrioventricular conduction block. These conditions pose significant clinical challenges as they can precipitate symptoms ranging from dizziness and syncope to life-threatening cardiac arrest and sudden cardiac death, thereby representing a critical public health issue within cardiovascular medicine. The pathophysiology underlying bradyarrhythmias is complex and multifactorial, with emerging evidence highlighting the pivotal role

of oxidative stress in the dysfunction of cardiac pacemaker cells and conduction pathways. Specifically, the Sinoatrial Node (SAN) pacemaker cells and atrioventricular conduction system exhibit heightened sensitivity to oxidative insults, wherein excessive accumulation of Reactive Oxygen Species (ROS) disrupts the electrophysiological properties of these cells, leading to diminished pacemaker activity and impaired conduction. This oxidative milieu is increasingly recognized as a key initiating factor in the development of bradycardia and conduction abnormalities. At the molecular level, mitochondrial dysfunction and redox imbalance are central to the pathogenesis of oxidative stress-related cardiac dysfunction. Mitochondria, as the primary source of cellular ROS, Particularly Hydrogen Peroxide (H2O2), require robust antioxidant defenses to maintain redox homeostasis. Peroxiredoxin 3 (PRDX3), a member of the peroxiredoxin family localized exclusively in the mitochondrial matrix, serves as a critical antioxidant enzyme responsible for the detoxification of mitochondrial H2O2. The enzymatic activity and expression levels of PRDX3 directly influence the oxidative state within cardiomyocytes, thereby modulating mitochondrial integrity and cellular function. Recent studies have elucidated that alterations in PRDX3 function contribute to the pathophysiology of various oxidative stress-related diseases, including cardiovascular disorders. For instance, PRDX3 overexpression has been shown to preserve mitochondrial membrane potential and inhibit stress-activated signaling pathways under oxidative conditions, underscoring its protective role against mitochondrial oxidative damage [1] Conversely, PRDX3 deficiency or dysfunction exacerbates oxidative injury, leading to impaired cellular bioenergetics and increased susceptibility to apoptosis.

In the context of cardiac rhythm disturbances, accumulating evidence implicates PRDX3 dysfunction as a mechanistic contributor to bradyarrhythmias. The sinoatrial node and atrioventricular conduction tissues, due to their high metabolic demand and mitochondrial density, are particularly vulnerable to oxidative damage. Excessive mitochondrial ROS can alter ion channel function and intracellular calcium handling, thereby disrupting the electrophysiological stability of pacemaker cells. PRDX3, by mitigating mitochondrial oxidative stress, plays a vital role in preserving the electrophysiological properties essential for maintaining normal heart rhythm. Experimental models have demonstrated that modulation of PRDX3 expression affects mitochondrial ROS levels and downstream signaling pathways involved in cell survival and function, suggesting that PRDX3 is a key regulator in the maintenance of cardiac pacemaker and conduction system integrity [2] Furthermore, transcriptional regulation of the PRDX3 gene under pathological conditions such as hyperglycemia involves key transcription factors including Sp1, CREB, and NF-κB, which modulate its expression and thereby influence cellular redox balance [3]. Beyond its intrinsic antioxidant function, PRDX3 has emerged as a promising therapeutic target. Pharmacological agents that enhance PRDX3 activity or expression may confer cardioprotective effects by restoring mitochondrial redox homeostasis and preventing oxidative damage to pacemaker cells. For example, natural compounds and synthetic molecules that upregulate mitochondrial antioxidant systems, including PRDX3, have demonstrated efficacy in ameliorating oxidative stress-induced cellular injury in various disease models [4] Additionally, targeted inhibition of PRDX3 in cancer cells has been explored to induce oxidative stress selectively, highlighting the enzyme's central role in redox regulation and its potential as a drug target [5] These insights underscore the dual relevance of PRDX3 in both disease pathogenesis and therapeutic intervention.

Given the critical involvement of PRDX3 in mitochondrial oxidative stress regulation and its emerging association with bradyarrhythmia pathogenesis, a comprehensive understanding of its biological characteristics, regulatory mechanisms in cardiac tissue, and participation in pathological signaling pathways is imperative. This review aims to systematically synthesize current knowledge on PRDX3, focusing on its molecular biology, expression regulation in cardiomyocytes, mechanistic role in slow heart rhythm disorders, and potential as a diagnostic and therapeutic target. By integrating findings from diverse studies, we seek to provide an integrative perspective that may guide future research directions and clinical applications in the management of bradyarrhythmias.

Molecular Structure and Biological Function of PRDX3

Structural Characteristics and Catalytic Mechanism of PRDX3

Peroxiredoxin 3 (PRDX3) is a member of the typical 2-Cys peroxiredoxin family, characterized by its unique molecular architecture and catalytic mechanism that underpin its critical role in mitochondrial redox homeostasis. Structurally, PRDX3 comprises an N-terminal mitochondrial targeting sequence and a conserved catalytic domain. Upon translation, the precursor protein is imported into mitochondria where the targeting sequence is cleaved by mitochondrial processing peptidases, yielding the mature, functional enzyme. The fundamental functional unit of PRDX3 is a homodimer, with each monomer harboring two essential cysteine residues: the peroxidatic Cysteine (Cys47) located in the N-terminal region and the resolving Cysteine (Cys168) situated near the C-terminus. These cysteines participate in a catalytic cycle whereby the peroxidatic cysteine reacts with Hydrogen Peroxide (H_2O_2), forming a sulfenic acid intermediate. This intermediate then forms an intermolecular disulfide bond with the resolving cysteine of the adjacent subunit, completing the oxidation step. The oxidized dimer is subsequently reduced back to its active form by Mitochondrial Thioredoxin 2 (Trx2) and Thioredoxin Reductase 2 (TXN2), restoring enzymatic activity and enabling continuous detoxification of H_2O_2. Compared to other peroxiredoxin isoforms, PRDX3 exhibits a higher substrate affinity for H_2O_2, reflected in its lower Km value, which allows it to efficiently scavenge low concentrations of mitochondrial H_2O_2.

However, under conditions of elevated oxidative stress, PRDX3 can undergo hyperoxidation at the peroxidatic cysteine, converting it to sulfinic or sulfonic acid forms, leading to reversible or irreversible inactivation, respectively. This hyperoxidation serves as a regulatory mechanism, modulating PRDX3 activity and enabling it to function as a redox sensor within mitochondria. The unique catalytic features of PRDX3, including its dimeric structure, cysteine-based redox cycling, and susceptibility to hyperoxidation, confer a specialized role in maintaining mitochondrial redox signaling and protecting against oxidative damage. These properties distinguish PRDX3 from other peroxiredoxins and highlight its importance in mitochondrial oxidative stress responses, particularly in tissues with high metabolic demand such as the heart, where precise regulation of Reactive Oxygen Species (ROS) is essential for cellular function and survival [6].

Subcellular Localization and Expression Distribution of PRDX3

PRDX3 is predominantly localized within the mitochondrial matrix, positioning it strategically at the primary site of Reactive Oxygen Species (ROS) generation. This subcellular localization facilitates its immediate interaction with ROS produced by the mitochondrial electron transport chain complexes embedded in the inner mitochondrial membrane. Immunohistochemical and Western blot analyses have demonstrated that PRDX3 is highly expressed in cardiac tissues, with particularly elevated levels in sinoatrial node pacemaker cells and conduction system fibers compared to ordinary working cardiomyocytes. This differential expression pattern suggests a specialized role for PRDX3 in modulating mitochondrial oxidative stress in regions critical for cardiac rhythm generation and conduction. Furthermore, PRDX3 expression in cardiomyocytes exhibits developmental regulation; its levels are relatively low during embryonic and neonatal stages but increase progressively as the heart matures, indicating its involvement in establishing and maintaining mitochondrial redox balance in mature cardiac cells. This developmental upregulation underscores the enzyme's importance in supporting the high metabolic and oxidative demands of adult myocardium. Beyond mitochondria, PRDX3 is also detected in smaller quantities associated with Mitochondria-Associated Membranes (MAMs) of the endoplasmic reticulum and within the nucleus, implicating potential roles in inter-organelle communication and nuclear redox regulation. However, the physiological significance of these non-mitochondrial pools remains to be fully elucidated. The mitochondrial confinement of PRDX3, combined with its enriched expression in cardiac pacemaker and conduction tissues, highlights its critical function in safeguarding mitochondrial integrity and redox homeostasis in cells that are essential for maintaining cardiac electrophysiological stability. This spatial and temporal expression pattern aligns with the enzyme's role in mitigating oxidative stress-related damage and preserving mitochondrial function, which are vital for normal cardiac rhythm and function [6].

Post-Translational Modifications and Activity Regulation of PRDX3

The enzymatic activity of PRDX3 is intricately regulated by multiple Post-Translational Modifications (PTMs) that fine-tune its function in response to cellular redox states. Central to its catalytic mechanism is the peroxidatic Cysteine (Cys47), whose oxidation state dictates enzyme activity. Under oxidative stress, Cys47 can be hyperoxidized to sulfinic or sulfonic acid forms, resulting in irreversible inactivation of PRDX3. This hyperoxidation serves as a biomarker of oxidative damage and reflects mitochondrial redox imbalance. Additionally, phosphorylation and acetylation modulate PRDX3 activity and stability. For instance, phosphorylation mediated by PTEN-Induced Kinase 1 (PINK1) enhances PRDX3's capacity to scavenge H_2O_2, thereby bolstering mitochondrial antioxidant defenses. Conversely, deacetylation by the mitochondrial sirtuin Sirt3 stabilizes PRDX3's conformation and maintains a higher proportion of the enzyme in its reduced, active state. These modifications collectively regulate the dynamic balance between PRDX3 activation and inactivation, enabling adaptive responses to fluctuating oxidative conditions. In pathological contexts such as myocardial ischemia-reperfusion injury, excessive oxidative stress leads to pronounced hyperoxidation of PRDX3, correlating with mitochondrial ROS overflow and increased cardiomyocyte apoptosis. This observation underscores the critical role of PTM-mediated regulation of PRDX3 in cardiac oxidative injury and suggests that therapeutic strategies aimed at preserving PRDX3 activity through modulation of its PTMs could mitigate mitochondrial oxidative damage and improve cardiac outcomes. Thus, the complex interplay of phosphorylation, acetylation, S-nitrosylation, and hyperoxidation governs PRDX3's enzymatic function, highlighting the enzyme's pivotal role as a redox sensor and protector within mitochondria, especially in the oxidative stress-prone environment of cardiac tissue [6].

Pathophysiological Basis and Oxidative Stress Mechanisms in Bradyarrhythmias

Molecular Basis of Sinoatrial Node Pacemaking Function

The Sinoatrial Node (SAN) serves as the primary pacemaker of the heart, orchestrating rhythmic cardiac contractions through the spontaneous generation of action potentials. This intrinsic pacemaking activity is fundamentally dependent on the coordinated function of multiple ion channels embedded in the membranes of specialized pacemaker cells. Among these, the Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) channels, particularly HCN4, mediate the If ("funny") current, which contributes to the slow diastolic depolarization phase that initiates each heartbeat. Additionally, T-type (Cav3.1) and L-type (Cav1.3) calcium channels facilitate Ca^{2+} influx, which is critical for the upstroke of the pacemaker action potential, while delayed rectifier potassium channels regulate repolarization, ensuring proper cycle timing. Notably, the resting membrane potential of SAN pacemaker cells is

relatively depolarized, approximately -50 to -60mV, which results in the majority of voltage-gated sodium channels being inactivated under resting conditions. Consequently, the generation of action potentials in these cells relies predominantly on calcium rather than sodium influx, a distinctive electrophysiological feature that renders SAN function highly sensitive to alterations in cellular energy metabolism and redox state. Mitochondria, abundant in SAN cells and strategically positioned near the plasma membrane, supply ATP necessary for ion channel function and simultaneously generate Reactive Oxygen Species (ROS) as metabolic byproducts. This close "membrane-mitochondria" coupling forms a functional unit whereby mitochondrial output directly modulates ion channel activity, thereby maintaining normal pacemaker frequency. Furthermore, autonomic nervous system inputs finely tune SAN automaticity: sympathetic stimulation enhances If and Ca^{2+} currents via the cAMP-PKA signaling pathway, accelerating heart rate, whereas parasympathetic (vagal) activation slows pacemaking by activating G protein-coupled inwardly rectifying potassium channels through acetylcholine release. This complex interplay of ion channel dynamics, mitochondrial energetics, and autonomic regulation underpins the molecular basis of SAN pacemaking and highlights potential vulnerabilities to pathological insults such as oxidative stress that can disrupt this delicate balance [7,8].

Role of Oxidative Stress in Sinoatrial Node Dysfunction

Oxidative stress arises when the production of Reactive Oxygen Species (ROS) within cardiomyocytes exceeds the capacity of endogenous antioxidant defenses, leading to cellular damage. The Sinoatrial Node (SAN), characterized by high metabolic activity and relatively low baseline expression of antioxidant enzymes, is particularly susceptible to oxidative injury. Excess ROS can directly modify critical cysteine residues on HCN4 channel proteins, altering their voltage-dependent gating properties and resulting in diminished If current density. This reduction in If impairs the diastolic depolarization phase, thereby slowing the intrinsic pacemaker rate and contributing to bradyarrhythmias. Moreover, oxidative stress induces mitochondrial DNA damage and compromises the activity of electron transport chain complexes, exacerbating mitochondrial ROS generation in a self-amplifying "ROS-induced ROS release" cycle. This vicious feedback loop accelerates SAN cell dysfunction and death. Experimental models have demonstrated that exogenous administration of hydrogen peroxide or mitochondrial complex I inhibitors such as rotenone dose-dependently reduce heart rate, effects that can be partially reversed by antioxidants like N-acetylcysteine, providing direct evidence of oxidative stress involvement in SAN impairment. These findings underscore the critical role of mitochondrial ROS in modulating SAN electrophysiology and suggest that therapeutic strategies aimed at enhancing antioxidant capacity or preserving mitochondrial function may mitigate SAN dysfunction and associated bradyarrhythmias [8,9].

Mitochondrial Dysfunction and Atrioventricular Conduction Abnormalities

The Atrioventricular (AV) node and His-Purkinje system, integral components of the cardiac conduction pathway, share the sinoatrial node's high metabolic demand and mitochondrial density. Mitochondrial dysfunction within these conduction cells can lead to insufficient ATP production, impairing the activity of energy-dependent ion pumps such as Na^+/K^+-ATPase, which are essential for maintaining membrane potential and action potential propagation. One pivotal event in oxidative stress-induced conduction impairment is the aberrant opening of the Mitochondrial Permeability Transition Pore (mPTP), which disrupts mitochondrial membrane potential, halts ATP synthesis, and triggers the release of pro-apoptotic factors. Concurrently, defective mitophagy-the selective autophagic removal of damaged mitochondria-results in the accumulation of dysfunctional mitochondria that release excessive ROS and cytochrome c, activating caspase cascades and inducing programmed cell death in conduction system cells. Clinically, ultrastructural analyses of aged patients with degenerative bradyarrhythmias reveal mitochondrial swelling, cristae fragmentation, and lipofuscin deposition within atrial and conduction tissues, correlating with impaired conduction function. These mitochondrial alterations contribute to atrioventricular block and other conduction disorders by compromising cellular viability and electrophysiological integrity. Understanding these mitochondrial pathomechanisms offers insights into potential interventions targeting mitochondrial preservation and mitophagy enhancement to prevent or treat conduction abnormalities [9,10].

Molecular Mechanisms of PRDX3 Involvement in Bradyarrhythmia

PRDX3 and the Regulatory Relationship with HCN4 Channel Function

The Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel 4 (HCN4) is the molecular basis of the If current in Sinoatrial Node (SAN) pacemaker cells, playing a critical role in generating and regulating cardiac pacemaking activity. The function of HCN4 channels is highly sensitive to the cellular redox state, as multiple cysteine residues within the HCN4 protein are susceptible to oxidative modifications by Reactive Oxygen Species (ROS). These oxidative modifications can alter channel gating properties, thereby impacting the If current density and ultimately the heart rate. PRDX3, a mitochondrial peroxiredoxin, is pivotal in maintaining mitochondrial Hydrogen Peroxide (H2O2) at low steady-state levels, thereby indirectly protecting HCN4 channels from oxidative damage. This protective role ensures the stable generation of If current and the maintenance of normal pacemaker frequency. Experimental evidence from PRDX3 knockout mice demonstrates a roughly 40% reduction in HCN4 protein expression in SAN tissue, accompanied by a significant decrease in If current density and a concomitant reduction in heart rate to approximately

70% of control levels. These findings confirm that PRDX3 is essential for preserving HCN4 channel function and, by extension, pacemaker rhythm regulation. Mechanistically, PRDX3 modulates mitochondrial ROS levels, which in turn influence the Protein Kinase A (PKA) signaling pathway. Physiological levels of ROS inhibit the phosphatase PP2A, maintaining HCN4 phosphorylation and channel open probability. However, PRDX3 deficiency leads to excessive ROS accumulation, activating PP2A, reducing HCN4 phosphorylation, and decreasing channel open probability. This cascade results in diminished If current and impaired pacemaker activity. Thus, PRDX3 serves as a critical regulator of HCN4 channel function by modulating mitochondrial ROS and downstream phosphorylation signaling pathways, highlighting its integral role in the molecular mechanisms underlying slow cardiac arrhythmias associated with SAN dysfunction [11–13].

PRDX3 Regulation of Cardiomyocyte Calcium Homeostasis and Pacemaker Rhythm

Calcium (Ca^{2+}) signaling between mitochondria and the Endoplasmic Reticulum (ER) is fundamental for the spontaneous activity of pacemaker cells. Mitochondria regulate local Ca^{2+} concentrations and energy metabolism through the Mitochondrial Calcium Uniporter (MCU), which mediates Ca^{2+} uptake into the mitochondrial matrix. PRDX3 plays a crucial role in this process by scavenging mitochondrial ROS, thereby protecting the MCU complex and other mitochondrial Ca^{2+} transporters from oxidative damage. This protection preserves mitochondrial Ca^{2+} uptake capacity, ensuring stable intracellular Ca^{2+} transients critical for rhythmic pacemaker activity. Loss of PRDX3 leads to elevated mitochondrial ROS, which oxidatively modifies thiol groups on MCU, impairing its function and reducing mitochondrial Ca^{2+} buffering. Consequently, cytoplasmic Ca^{2+} levels become abnormally elevated, activating Ca^{2+}/Calmodulin-Dependent Protein Kinase II (CaMKII). Activated CaMKII phosphorylates L-type calcium channels, altering their inactivation kinetics and disrupting the frequency of pacemaker action potentials. Functional studies in isolated SAN cells reveal that PRDX3 overexpression lowers resting cytoplasmic Ca^{2+} levels and improves the regularity of spontaneous beating. Conversely, PRDX3 knockdown induces arrhythmic beating patterns and reduced pacemaker frequency. These findings underscore PRDX3's essential role in maintaining Ca^{2+} homeostasis and normal pacemaker rhythm by mitigating mitochondrial oxidative stress and preserving mitochondrial Ca^{2+} handling machinery integrity [12-14].

Interaction Between PRDX3 and Mitochondrial Quality Control Systems

Mitochondrial quality control encompasses biogenesis, dynamics (fusion and fission), and mitophagy, processes vital for maintaining mitochondrial function and cellular homeostasis. PRDX3 contributes multifaceted support to these systems by regulating mitochondrial matrix H2O2 levels, thereby protecting key regulatory proteins from oxidative damage. Specifically, PRDX3 safeguards components of the PINK1/Parkin pathway, which identifies and targets damaged mitochondria for autophagic clearance. Overexpression of PRDX3 promotes the expression of mitochondrial fusion protein Mitofusin 2 (Mfn2) and inhibits phosphorylation-mediated activation of the fission protein Dynamin-Related Protein 1 (Drp1), favoring a fused, elongated mitochondrial network that enhances mitochondrial functional reserve. In cardiac-specific PRDX3 transgenic mice, aging-induced mitochondrial vacuolization is reduced, and autophagy markers such as the LC3-II/I ratio normalize, indicating improved mitochondrial turnover and quality control. These effects collectively delay age-associated SAN functional decline, suggesting that PRDX3-mediated modulation of mitochondrial dynamics and mitophagy is critical for preserving mitochondrial integrity and cardiac pacemaker function during aging. Thus, PRDX3 acts as a central modulator within the mitochondrial quality control network, coordinating redox homeostasis with mitochondrial morphology and turnover to sustain cardiac rhythm stability [1,12,15].

PRDX3 Regulation of Redox Signaling Pathways Affecting Cardiac Electrical Conduction

Beyond its antioxidant activity, PRDX3 participates actively in redox signaling by cycling through oxidized and reduced states during peroxide detoxification, thereby modulating downstream signaling cascades. In SAN tissue, PRDX3 regulates the ROS-ASK1-p38/JNK axis, which influences pacemaker cell survival and function. PRDX3 deficiency leads to enhanced oxidative activation of Apoptosis Signal-Regulating Kinase 1 (ASK1), promoting phosphorylation of p38 and JNK kinases, which triggers apoptosis and loss of pacemaker activity. Additionally, PRDX3 modulates the nuclear factor erythroid 2-related factor 2 (Nrf2)/Antioxidant Response Element (ARE) pathway. Initial ROS elevation due to reduced PRDX3 activity induces Nrf2 nuclear translocation and upregulation of antioxidant enzymes, constituting a compensatory protective mechanism. Moreover, PRDX3-mediated clearance of mitochondrial ROS preserves Nitric Oxide (NO) signaling by preventing the formation of peroxynitrite from NO and ROS. This protection maintains soluble guanylate cyclase activity and cGMP-mediated responses essential for SAN adaptation to neurohumoral regulation. Collectively, PRDX3 integrates mitochondrial redox balance with multiple signaling pathways that govern cardiac electrical conduction and pacemaker cell viability, underscoring its therapeutic potential in managing slow cardiac arrhythmias [12,13,15].

Progress in Research on Diagnosis and Treatment of Bradyarrhythmias Based on PRDX3

PRDX3 as a Potential Early Diagnostic Biomarker

Peroxiredoxin 3 (PRDX3), a mitochondrial antioxidant enzyme, has emerged as a promising candidate for early diagnosis of bradyarrhythmias due to its unique pathophysiological behavior

under myocardial injury and oxidative stress conditions. Under normal physiological states, circulating levels of PRDX3 protein in peripheral blood are extremely low, reflecting its primary localization within mitochondria. However, during myocardial damage or oxidative stress, mitochondrial membrane disruption leads to the release of PRDX3 into the interstitial space and subsequently into the peripheral circulation, rendering it a detectable biomarker in plasma. Clinical studies have demonstrated a positive correlation between plasma PRDX3 concentrations and the severity of sinoatrial node dysfunction in patients with bradycardia. Specifically, individuals exhibiting heart rates below 50 beats per minute showed plasma PRDX3 levels approximately 3.2 times higher than those of healthy controls, indicating a high diagnostic sensitivity for PRDX3 in identifying sinoatrial node impairment. Beyond total PRDX3 quantification, the oxidative post-translational modifications of PRDX3, particularly the hyperoxidized forms at cysteine 47 (PRDX3-SO_2H/SO_3H), have been proposed as more specific indicators of myocardial oxidative stress. These oxidized isoforms may better reflect the redox state of cardiac mitochondria and the extent of oxidative injury than total PRDX3 levels alone. Technological advancements have enabled the sensitive and quantitative detection of both total and oxidized PRDX3 in plasma using high-sensitivity mass spectrometry and Enzyme-Linked Immunosorbent Assays (ELISA). Despite these promising developments, the clinical utility of PRDX3 as a routine diagnostic biomarker for bradyarrhythmias requires validation through large-scale prospective cohort studies to establish its sensitivity, specificity, and predictive value. Such studies would also clarify the temporal dynamics of PRDX3 release relative to the onset and progression of sinoatrial node dysfunction. In summary, PRDX3's mitochondrial origin, release pattern under oxidative stress, and measurable presence in peripheral blood position it as a valuable early biomarker candidate for the diagnosis of slow heart rhythm disorders, with potential to improve timely detection and intervention strategies in clinical cardiology [6,16].

PRDX3-Targeted Pharmacological Intervention Strategies

Therapeutic strategies targeting PRDX3 focus on enhancing its expression or enzymatic activity to mitigate mitochondrial oxidative damage and preserve cardiac function in bradyarrhythmias. Several natural compounds have demonstrated cardioprotective effects mediated through upregulation of PRDX3. Resveratrol, a polyphenolic compound, activates the Sirt1-PGC-1α signaling pathway, which in turn promotes transcriptional upregulation of PRDX3, thereby enhancing mitochondrial antioxidant defenses. This pathway is critical for mitochondrial biogenesis and redox homeostasis, making resveratrol a promising agent for PRDX3 modulation. Additionally, mitochondria-targeted antioxidants such as MitoQ, a mitochondria-penetrating ubiquinone derivative, indirectly support PRDX3 function by improving the mitochondrial redox environment. By maintaining a favorable oxidative-reductive balance, MitoQ helps preserve PRDX3's reduced, catalytically active state, thereby sustaining its hydrogen peroxide scavenging capacity. Small molecule thiol donors like N-Acetylcysteine Amide (NACA) have also been shown to restore PRDX3 from its overoxidized inactive forms back to the active state by replenishing mitochondrial thiol pools, thus enhancing its enzymatic clearance of H_2O_2. Beyond direct antioxidant support, pharmacological agents that transcriptionally activate PRDX3 gene expression have been explored. Peroxisome Proliferator-Activated Receptor Delta (PPARδ) agonists and AMP-Activated Protein Kinase (AMPK) activators such as AICAR have demonstrated efficacy in increasing myocardial PRDX3 mRNA and protein levels in preclinical models. These agents modulate metabolic and oxidative stress pathways, contributing to improved mitochondrial resilience. Currently, these pharmacological approaches are undergoing preclinical toxicity and efficacy evaluations to determine their safety profiles and therapeutic windows. The integration of natural compounds, mitochondrial antioxidants, and gene expression modulators targeting PRDX3 represents a multifaceted strategy to counteract mitochondrial oxidative stress and improve cardiac conduction system function in bradyarrhythmias. Future clinical translation will depend on rigorous validation of these agents' efficacy and safety in human studies [17,18].

PRDX3 Gene Therapy and Cellular Protection Strategies

Gene therapy and cell-based approaches targeting PRDX3 offer innovative avenues for restoring sinoatrial node function and protecting cardiac tissue in bradyarrhythmias. Adeno-Associated Virus (AAV)-mediated myocardial delivery of PRDX3 has shown significant therapeutic potential in small animal models of bradycardia. A single intramyocardial injection of AAV9 vectors encoding PRDX3 achieved sustained overexpression in the sinoatrial node region for up to eight weeks, resulting in improved heart rate and conduction stability. This targeted gene delivery approach leverages the cardiac tropism of AAV9 and the longevity of transgene expression to provide durable antioxidant protection. Concurrently, CRISPR/Cas9-based gene editing techniques are being explored to enhance endogenous PRDX3 expression. The use of catalytically inactive dCas9 fused to transcriptional activators (e.g., VP64) targeting the PRDX3 promoter region enables precise transcriptional upregulation without altering the genomic sequence. This epigenetic modulation strategy holds promise for fine-tuning PRDX3 levels with reduced off-target effects. Combining PRDX3 overexpression with Mesenchymal Stem Cell (MSC) transplantation has demonstrated synergistic benefits. MSCs engineered to overexpress PRDX3 improve sinoatrial node electrophysiology in bradycardia models through paracrine signaling and mitochondrial transfer mechanisms, enhancing cellular bioenergetics and reducing oxidative stress. However, long-term safety concerns remain regarding PRDX3 overexpression, as excessive clearance of mitochondrial hydrogen peroxide may disrupt physiological redox signaling pathways essential for normal cellular function. Therefore, therapeutic strategies must carefully balance PRDX3 expression levels within an optimal window

to avoid adverse effects. Additionally, early-stage development of synthetic small molecule PRDX3 activator peptides aims to directly enhance the catalytic efficiency of existing PRDX3 protein without altering expression, representing a novel pharmacological modality. Collectively, gene therapy and cell-based interventions targeting PRDX3 provide promising platforms for restoring cardiac pacemaker function and protecting against oxidative injury in slow heart rhythm disorders, pending further optimization and safety validation [6,17].

Integration and Prospects of PRDX3 Research in the Multi-Omics Era

The advent of multi-omics technologies has revolutionized the understanding of PRDX3's role in the complex pathogenesis of bradyarrhythmias by enabling integrative analyses across transcriptomic, proteomic, epigenomic, and genomic layers. Combined transcriptomic and proteomic profiling of myocardial tissue from heart failure patients with concomitant bradycardia has revealed coordinated alterations in multiple redox-related proteins beyond PRDX3, suggesting that PRDX3 functions within a broader oxidative stress regulatory network. This systems biology perspective underscores the necessity of examining PRDX3 in the context of interacting molecular pathways rather than in isolation. Single-cell RNA sequencing has been successfully applied to dissect the molecular heterogeneity of sinoatrial node pacemaker cells, providing unprecedented resolution to characterize PRDX3 expression patterns among distinct cellular subpopulations. Such analyses facilitate the identification of cell type-specific roles of PRDX3 and its contribution to functional heterogeneity within the cardiac conduction system. Epigenetic investigations have begun to elucidate dynamic modifications at the PRDX3 promoter, including DNA methylation and histone modifications, which may underlie age-related declines in PRDX3 expression and increased susceptibility to bradyarrhythmias. Elevated DNA methylation at the PRDX3 locus correlates with reduced transcriptional activity, implicating epigenetic regulation as a modifiable factor in disease progression. Furthermore, large-scale genomic studies employing Mendelian randomization and genome-wide association analyses have identified significant associations between PRDX3 intronic Single Nucleotide Polymorphisms (SNPs), such as rs488663, and the risk of sinoatrial node dysfunction, providing genetic evidence for PRDX3's involvement in bradycardia susceptibility. These findings pave the way for the development of personalized medicine approaches based on PRDX3-related genetic and epigenetic profiles. Future research should focus on integrating multi-omics datasets to construct comprehensive regulatory network models of PRDX3, enabling a holistic understanding of its multifaceted role in slow heart rhythm disorders. Such integrative models will facilitate the identification of novel therapeutic targets and the design of individualized treatment strategies that leverage the molecular complexity of PRDX3 regulation and function [6,17].

Conclusion

Peroxiredoxin 3 (PRDX3) has emerged as a pivotal mitochondrial antioxidant enzyme intricately involved in the pathophysiology of bradyarrhythmias through its multifaceted roles in maintaining mitochondrial redox homeostasis, preserving HCN4 channel function, modulating Ca^{2+} signaling pathways, and orchestrating mitochondrial quality control within cardiomyocytes. From an expert perspective, the development of research on PRDX3 underscores a critical paradigm shift in understanding the molecular underpinnings of slow heart rhythm disorders, moving beyond traditional electrophysiological frameworks to incorporate mitochondrial dynamics and oxidative stress as central contributors. The convergence of oxidative stress and mitochondrial dysfunction as shared pathological mechanisms in sinoatrial node pacemaker impairment and atrioventricular conduction abnormalities highlights the indispensable role of PRDX3. Its deficiency or functional inactivation not only exacerbates mitochondrial oxidative damage but also disrupts key ion channel activities and intracellular calcium handling, thereby precipitating the onset and progression of bradyarrhythmias. This integrative insight balances prior research that often-treated oxidative stress and electrophysiological disturbances as discrete phenomena, emphasizing instead their interdependence mediated by mitochondrial antioxidant defenses. Clinically, the identification of circulating PRDX3 and its oxidatively modified isoforms as promising biomarkers offers a novel avenue for early diagnosis and dynamic disease monitoring in patients with slow heart rhythms. This potential biomarker role aligns with the growing emphasis on precision medicine, where molecular signatures can guide risk stratification and therapeutic decision-making. However, translating these findings into routine clinical practice necessitates rigorous validation through large-scale, longitudinal studies to establish sensitivity, specificity, and prognostic value across diverse patient populations.

Therapeutically, preclinical investigations into gene therapy, pharmacological modulation, and cellular protection strategies targeting PRDX3 have demonstrated encouraging cardioprotective effects. These approaches aim to restore mitochondrial redox balance and preserve electrophysiological integrity, thereby addressing the root causes of bradyarrhythmias rather than merely managing symptoms. Nonetheless, the transition from bench to bedside requires comprehensive clinical trials to evaluate long-term efficacy, safety profiles, and potential off-target effects, ensuring that interventions are both effective and sustainable. Looking forward, advancing the understanding of PRDX3's regulatory networks demands the integration of multi-omics technologies and systems biology approaches. Such methodologies will enable the dissection of dynamic molecular interactions and feedback loops governing mitochondrial function and cardiac electrophysiology. This holistic perspective is essential for developing precision diagnostic tools and targeted therapies centered on PRDX3, ultimately offering new hope for patients afflicted with slow heart rhythm disorders. In conclusion, the evolving body of evidence positions PRDX3 as a central mediator in the complex interplay between mitochondrial oxidative stress and cardiac conduction system dysfunction. Balancing diverse research perspectives-

from molecular mechanisms to clinical applications-highlights the enzyme's potential as both a biomarker and therapeutic target. Continued interdisciplinary efforts are imperative to translate these insights into tangible clinical benefits, paving the way for innovative strategies that improve outcomes for individuals with bradyarrhythmias.

Ethics Approval and Informed Consent

Not applicable.

Consent for Publication

The authors confirm that patient consent is not applicable to this article.

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