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Review Article

The Role and Mechanistic Insights of circHIPK3 in Cardiac Autonomic Ganglion Exosomes on Bradyarrhythmia: A Review

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Abstract

Bradyarrhythmia, a common type of cardiac arrhythmia, is closely associated with dysfunction of the cardiac autonomic nervous system. In recent years, exosomes have emerged as critical mediators of intercellular communication, playing significant roles in cardiovascular diseases. Among various molecular cargoes, circular RNA circHIPK3 is highly expressed in cardiac tissues and participates in diverse pathophysiological processes. This review comprehensively summarizes the structure and function of the cardiac autonomic ganglion, the role of exosomes in cardiac neural regulation, and the biological characteristics of circHIPK3. Furthermore, it explores the potential mechanisms by which circHIPK3 carried by exosomes from the cardiac autonomic ganglion influences the development and progression of bradyarrhythmia. By integrating current research findings, this article aims to provide novel molecular targets and theoretical foundations for the diagnosis and treatment of bradyarrhythmia, thereby advancing understanding of cardiac neuroregulation and arrhythmogenesis.

Keywords: Cardiac autonomic ganglion, Exosomes, circHIPK3, Bradyarrhythmia, Neural regulation, Molecular mechanisms

Introduction

Bradyarrhythmias, characterized by a heart rate below 60 beats per minute, encompass a spectrum of clinical entities including sinus bradycardia, Sick Sinus Syndrome (SSS), Atrioventricular (AV) conduction blocks, and tachy-brady syndrome. These conditions, collectively referred to as slow heart rhythm disorders, pose significant clinical challenges due to their potential to cause syncope, heart failure, and sudden cardiac death. The pathophysiology underlying bradyarrhythmias is multifactorial, involving intrinsic sinoatrial node dysfunction, conduction system disease, autonomic nervous system imbalance, and secondary causes such as metabolic disturbances or drug effects. For instance, steroid administration, though widely used, has been implicated in rare cases of symptomatic sinus bradycardia, underscoring the importance of cardiac monitoring during high-dose steroid therapy [1]. Similarly, lithium intoxication, a mainstay treatment for bipolar disorder, can induce sinus node dysfunction manifesting as unstable bradycardia requiring temporary pacing [2]. Infectious etiologies such as Lyme disease may present with bradyarrhythmias including sick sinus syndrome without atrioventricular block, highlighting the need for comprehensive evaluation in endemic areas. Moreover, immune checkpoint inhibitor-associated myocarditis has been reported to co-occur with sinus node dysfunction, emphasizing the intersection of oncologic therapies and cardiac arrhythmias [3]. These diverse etiologies reflect the complex interplay between intrinsic cardiac conduction system pathology and extrinsic modulators, necessitating a nuanced understanding of bradyarrhythmia mechanisms.

Central to the regulation of cardiac rhythm is the autonomic nervous system, with the cardiac autonomic Ganglionated Plexi (GP) serving as pivotal integrative centers modulating sinoatrial and atrioventricular nodal function. The GP, located within epicardial fat pads, mediate parasympathetic and sympathetic inputs, thereby influencing heart rate and conduction velocity. Dysfunction or hyperactivity of these plexi can precipitate vagally mediated bradyarrhythmias, as observed in vasovagal syncope and functional AV block. Cardioneuroablation (CNA), a catheter-based technique targeting these ganglionated plexi, has emerged as a promising therapeutic modality for refractory functional bradyarrhythmias, demonstrating efficacy in reducing syncope recurrence and improving heart rate parameters in selected patient populations. However, the long-term consequences of CNA, including potential sympathovagal imbalance and its impact on arrhythmogenesis, remain areas of active investigation [4]. The tailored approach to CNA, focusing on specific GP according to clinical phenotype, has shown comparable efficacy to standard approaches while enhancing procedural efficiency [5]. These findings underscore the critical role of the cardiac autonomic nervous system in bradyarrhythmia pathogenesis and the therapeutic potential of modulating autonomic inputs. At the molecular level, the sinoatrial node's pacemaking activity is governed by ion channel dynamics and intracellular signaling pathways, with recent attention directed towards non-coding RNAs, particularly circular RNAs (circRNAs), as modulators of cardiac electrophysiology. CircHIPK3, a circular RNA highly expressed in cardiac tissue, has been implicated in regulating cardiomyocyte proliferation, apoptosis, and fibrosis, processes integral to cardiac remodeling and arrhythmogenesis. Although its role in myocardial pathology has been explored, the specific influence of circHIPK3 within cardiac autonomic ganglionated plexi-derived exosomes on slow heart rhythm disorders remains to be elucidated. Exosomes, nanoscale vesicles secreted by cells, facilitate intercellular communication by transporting bioactive molecules including proteins, mRNAs, microRNAs, and circRNAs. In the cardiac context, exosomes derived from autonomic ganglia may modulate neuronal and myocardial function, thereby influencing arrhythmic susceptibility. The emerging evidence suggests that circHIPK3-containing exosomes could participate in the pathophysiology of bradyarrhythmias by altering autonomic ganglion function or myocardial electrophysiological properties, representing a novel mechanistic axis warranting comprehensive investigation.

Clinically, bradyarrhythmias manifest with a wide range of symptoms from asymptomatic bradycardia to syncope, heart failure, and sudden cardiac death. Sick sinus syndrome, characterized by sinoatrial node dysfunction, often presents with alternating bradycardia and tachycardia episodes and is a common indication for permanent pacemaker implantation. The management of bradyarrhythmias is multifaceted, encompassing pharmacologic interventions, device therapy, and emerging autonomic modulation techniques. Pharmacologic agents such as theophylline and etophylline have demonstrated efficacy in improving sinus node function in specific contexts, including COVID-19-associated sinus node dysfunction [6]. Temporary and permanent cardiac pacing remain cornerstone therapies for symptomatic bradycardia and conduction blocks, with advances in pacing modalities such as His-bundle pacing offering physiological alternatives to traditional right ventricular pacing. Furthermore, the identification of genetic mutations, such as those in the SCN5A and HCN4 genes, has enhanced understanding of familial and early-onset bradyarrhythmias, facilitating targeted diagnostic and therapeutic strategies. The integration of molecular insights with clinical phenotyping and autonomic modulation holds promise for advancing the management of slow heart rhythm disorders. In summary, slow heart rhythm disorders represent a complex interplay of intrinsic sinoatrial and conduction system dysfunction, autonomic nervous system regulation, and molecular modulators including circRNAs within exosomes derived from cardiac autonomic ganglia. Understanding the neuro-

anatomical and functional characteristics of cardiac ganglionated plexi, the role of exosomal circHIPK3, and the molecular underpinnings of sinoatrial node dysfunction is critical for elucidating the pathogenesis of bradyarrhythmias. This knowledge paves the way for innovative therapeutic approaches such as cardioneuroablation and molecular-targeted interventions, aiming to improve outcomes in patients afflicted with these potentially life-threatening arrhythmias.

Structure and Function of the Cardiac Autonomic Ganglionated Plexus

Anatomical Localization and Distribution of the Cardiac Autonomic Ganglionated Plexi

The cardiac autonomic Ganglionated Plexi (GP) constitute the Intrinsic Cardiac Nervous System (ICNS), a complex network of neurons embedded predominantly within the epicardial fat pads on the atrial surfaces, atrioventricular junctions, and at the roots of the great vessels. These ganglia are organized into clusters of neuronal cell bodies located both subepicardially and intramyocardially, forming discrete yet interconnected neural hubs that serve as the final integrative centers for autonomic regulation of the heart. Anatomically, the GPs are distributed primarily on the atrial surfaces, including the posterior left atrium near the pulmonary veins, the interatrial septum, and the regions adjacent to the Sinoatrial (SA) and Atrioventricular (AV) nodes. This distribution allows the GPs to exert direct influence on cardiac pacemaking and conduction tissues. Based on their anatomical positions, the GPs are classified into subgroups such as the anterior right atrial GP, posterior left atrial GP, left atrial GP, and right atrial GP, each with distinct neuroanatomical and functional characteristics. These subgroups differ in their afferent and efferent projections, neurotransmitter profiles, and electrophysiological properties, reflecting their specialized roles in modulating cardiac function. Within each GP, a heterogeneous population of neurons exists, including sympathetic postganglionic neurons, parasympathetic postganglionic neurons, and local interneurons that form complex neural circuits. This intricate local network enables the ICNS to integrate extrinsic autonomic inputs from the central nervous system with intrinsic cardiac sensory information, facilitating beat-to-beat regulation of heart rate, conduction velocity, and myocardial contractility. Recent high-resolution imaging and molecular mapping studies have further elucidated the three-dimensional architecture of the ICNS, revealing consistent clustering patterns and conserved organizational plans across species and sexes, which underscore the fundamental role of these ganglia in cardiac autonomic control. The presence of these ganglia in epicardial fat pads also implicates them in pathophysiological remodeling processes, such as those observed in atrial fibrillation and heart failure, where altered GP structure and function contribute to arrhythmogenesis and autonomic imbalance [7-11]. Understanding the precise anatomical localization and distribution of the cardiac GPs is thus critical for developing targeted neuromodulatory therapies aimed at treating cardiac arrhythmias and other autonomic-related cardiac disorders.

Neurotransmitters and Receptor Systems in the Cardiac Autonomic Ganglionated Plexi

The cardiac autonomic Ganglionated Plexi (GP) serve as pivotal sites for neurotransmitter release and receptor-mediated signaling that finely tune cardiac function. Parasympathetic postganglionic neurons within the GPs predominantly release Acetylcholine (ACh), which acts on muscarinic M2 receptors expressed on cardiomyocytes. Activation of M2 receptors induces negative chronotropic, inotropic, and dromotropic effects—manifested as slowed heart rate, reduced myocardial contractility, and decreased conduction velocity through the atrioventricular node. This cholinergic signaling is essential for parasympathetic modulation of cardiac electrophysiology and is a key mechanism underlying vagally mediated bradyarrhythmias. Conversely, sympathetic postganglionic neurons release Norepinephrine (NE), which binds primarily to β1-adrenergic receptors on cardiac myocytes. β1 receptor activation enhances myocardial contractility and accelerates heart rate, facilitating the fight-or-flight response. The balance between these opposing neurotransmitter systems within the GPs is critical for maintaining cardiac autonomic homeostasis. Beyond classical neurotransmitters, the GPs also contain a diverse array of neuropeptides and purinergic transmitters that contribute to the nuanced regulation of cardiac function. Neuropeptides such as Neuropeptide Y (NPY) and Vasoactive Intestinal Peptide (VIP) are co-released with ACh or NE and modulate synaptic transmission and vascular tone. Purinergic signaling, mediated by ATP and adenosine, further refines autonomic control by influencing neuronal excitability and neurotransmitter release. Electrophysiological and molecular studies have identified multiple receptor subtypes within the GPs, including nicotinic acetylcholine receptors mediating fast synaptic transmission and various ion channels that regulate neuronal excitability. The presence of these diverse neurotransmitter and receptor systems enables the GPs to act as sophisticated integrative centers capable of dynamic responses to physiological and pathological stimuli. Alterations in neurotransmitter release or receptor expression within the GPs have been implicated in cardiac arrhythmias, highlighting the therapeutic potential of targeting these systems. For example, modulation of cholinergic signaling in the GPs has been explored as a strategy to control atrial fibrillation and bradyarrhythmias. Recent advances in optogenetics and pharmacology have facilitated precise manipulation of GP neurotransmission, providing insights into the complex neurochemical interactions that govern cardiac

autonomic regulation [12,13]. A comprehensive understanding of the neurotransmitter and receptor landscape within the cardiac GPs is therefore essential for elucidating the mechanisms of autonomic control and developing novel interventions for cardiac rhythm disorders.

Role of the Cardiac Autonomic Ganglionated Plexi in Heart Rate Regulation

The cardiac autonomic Ganglionated Plexi (GP) function as intrinsic integrative centers that orchestrate the autonomic regulation of heart rate and rhythm. Serving as the final common pathway for autonomic input to the heart, the GPs receive afferent signals from the central nervous system and peripheral sensory neurons, process this information locally through complex neural circuits, and modulate efferent output to the Sinoatrial (SA) and Atrioventricular (AV) nodes. This Intrinsic Cardiac Nervous System (ICNS) enables rapid, beat-to-beat adjustments of cardiac pacemaker activity and conduction properties, independent of or in concert with extrinsic autonomic influences. Enhanced parasympathetic activity within the GPs leads to increased release of acetylcholine, which binds to M2 muscarinic receptors on SA nodal cells, suppressing their intrinsic pacemaker activity and resulting in bradycardia. This mechanism underlies many forms of vagally mediated slow heart rhythms and is a fundamental contributor to bradyarrhythmias. Conversely, sympathetic activation of the GPs increases norepinephrine release, stimulating β1-adrenergic receptors and promoting tachycardia by enhancing pacemaker firing rates and conduction velocity. The delicate balance between sympathetic and parasympathetic tone within the GPs is crucial for maintaining normal heart rate variability and cardiac responsiveness to physiological demands. Dysregulation of this balance, such as excessive parasympathetic activation or diminished sympathetic input, can precipitate pathological slow heart rhythms, including sinus node dysfunction and atrioventricular block. Experimental and clinical studies have demonstrated that alterations in GP function and plasticity contribute to the pathogenesis of slow arrhythmias and other cardiac conduction abnormalities. For instance, increased cholinergic responsiveness and synaptic plasticity within the GPs have been observed in hypertensive models prone to arrhythmias, suggesting a mechanistic link between GP remodeling and arrhythmogenesis. Therapeutic interventions targeting the GPs, such as ganglionated plexi ablation during pulmonary vein isolation procedures, have shown efficacy in modulating autonomic tone and reducing atrial fibrillation recurrence, further underscoring the central role of the GPs in heart rate control. Computational modeling and electrophysiological studies continue to elucidate the complex interactions within the ICNS that govern cardiac rhythm, highlighting the GPs as critical nodes in the neurocardiac axis. Understanding the integrative functions of the cardiac GPs in autonomic regulation provides a foundation for developing novel neuromodulatory therapies aimed at correcting autonomic imbalances underlying slow heart rhythms and other arrhythmias [14].

The Role of Exosomes in Cardiac Neural Regulation

Basic Characteristics and Biogenesis of Exosomes

Exosomes are a distinct subtype of Extracellular Vesicles (EVs) characterized by their small size, typically ranging from 30 to 150 nm in diameter. They are generated intracellularly within the endosomal system, specifically through the formation of Multivesicular Bodies (MVBs) that contain intraluminal vesicles. Upon fusion of MVBs with the plasma membrane, these intraluminal vesicles are released into the extracellular space as exosomes. This biogenesis pathway distinguishes exosomes from other EV subtypes such as microvesicles, which bud directly from the plasma membrane, and apoptotic bodies, which are released during programmed cell death [15]. The molecular composition of exosomes is complex and includes proteins, lipids, and various nucleic acids such as mRNA, microRNA, and circular RNA (circRNA). These cargo molecules reflect the physiological or pathological state of the parent cell and are selectively packaged during exosome formation, enabling exosomes to serve as vehicles for intercellular communication [16,17].

The biogenesis of exosomes is tightly regulated by several molecular machineries. Central to this process is the Endosomal Sorting Complex Required for Transport (ESCRT), a set of protein complexes that mediate the inward budding of the endosomal membrane to form intraluminal vesicles within MVBs. ESCRT-independent mechanisms also exist, involving lipid raft-associated molecules and tetraspanins such as CD9, CD63, and CD81, which are four-transmembrane domain proteins abundantly present on exosomal membranes and serve as canonical markers for exosome identification [18]. Lipid metabolism-related proteins contribute to membrane curvature and vesicle scission, further facilitating exosome formation. The involvement of these proteins ensures the selective sorting of cargo and the structural integrity of exosomes.

Once released, exosomes interact with recipient cells through multiple mechanisms. They can engage in receptor-ligand interactions on the target cell surface, fuse directly with the plasma membrane to deliver their cargo, or be internalized via endocytosis or phagocytosis. These processes enable exosomes to modulate the function of recipient cells by transferring bioactive molecules that influence gene expression, signal transduction pathways, and cellular behavior. The ability of exosomes to mediate such intercellular communication underlies their emerging roles in physiological regulation and disease pathogenesis, as well as their potential utility as

biomarkers and therapeutic delivery vehicles [19,20]. In summary, exosomes are nanoscale vesicles formed through a complex biogenetic pathway involving ESCRT complexes, tetraspanins, and lipid metabolism proteins, and they function as critical mediators of cell-to-cell communication by delivering diverse molecular cargoes to target cells.

Composition and Function of Cardiac-Derived Exosomes

Cardiac cells, including cardiomyocytes, cardiac fibroblasts, endothelial cells, and intrinsic cardiac neurons, actively secrete extracellular vesicles such as exosomes, which carry a repertoire of bioactive molecules reflective of the cardiac microenvironment. The composition of these cardiac-derived exosomes is dynamically regulated by the physiological and pathological state of the heart. For instance, during myocardial injury, ischemia-reperfusion, or fibrotic remodeling, the cargo profile of exosomes changes to include proteins, lipids, and non-coding RNAs that can either promote tissue repair or exacerbate damage [21,22]. This adaptive modulation of exosomal content enables cardiac cells to communicate stress signals and coordinate responses across different cell types within the heart. Functionally, cardiac exosomes play pivotal roles in the pathogenesis and progression of various cardiac conditions. In myocardial infarction, exosomes released from stressed cardiomyocytes can carry protective signals that promote angiogenesis and limit apoptosis in neighboring cells, thereby contributing to tissue repair. Conversely, exosomes may also transport deleterious factors that enhance inflammation, fibrosis, or arrhythmogenesis, depending on the context [23,24]. In the setting of cardiac fibrosis, exosomes derived from activated fibroblasts can influence cardiomyocyte electrophysiology and extracellular matrix remodeling, thereby affecting cardiac function and rhythm stability [25]. Moreover, cardiac exosomes are implicated in the modulation of heart rhythm by transferring regulatory molecules that affect ion channel expression and autonomic nervous system interactions.

Among the molecular cargoes, non-coding RNAs such as microRNAs and circular RNAs (circRNAs) have emerged as critical mediators of intercellular communication within the heart. These RNA species regulate gene expression post-transcriptionally and modulate signaling pathways involved in cell survival, proliferation, and electrophysiological properties. For example, specific microRNAs carried by cardiac exosomes have been shown to influence ion channel expression, calcium handling, and fibrosis, thereby impacting arrhythmogenesis and cardiac remodeling. CircRNAs, characterized by their covalently closed loop structures, are increasingly recognized for their stability and regulatory functions, including acting as microRNA sponges or interacting with RNA-binding proteins. Their presence in cardiac exosomes suggests a role in fine-tuning gene regulatory networks during cardiac stress and disease. Collectively, cardiac-derived exosomes serve as critical conveyors of both protective and pathological signals, with their cargo composition and functional effects tightly linked to the cardiac cellular milieu and disease state.

Advances in Research on Exosomes in Cardiac Autonomic Nervous Regulation

Emerging evidence indicates that cells within the cardiac autonomic nervous system, particularly those in the intrinsic cardiac ganglia, secrete exosomes that contribute to the regulation of cardiac electrophysiology and rhythm. These exosomes may exert their effects locally through paracrine signaling or at distant sites via systemic circulation, thereby influencing myocardial cells and modulating autonomic control of the heart. The cargo of these neuronal exosomes includes microRNAs known to regulate ion channel expression and electrical conduction properties, such as miR-1 and miR-133, which have been implicated in the modulation of action potential duration and conduction velocity in cardiomyocytes. By transferring these microRNAs, exosomes facilitate neuro-cardiac communication that is essential for maintaining cardiac rhythm homeostasis.

The role of exosome-mediated communication between cardiac autonomic neurons and cardiomyocytes is particularly relevant in the context of arrhythmogenesis. Dysregulation of this signaling axis may contribute to the development of slow arrhythmias and other conduction abnormalities. For example, alterations in exosomal microRNA profiles can lead to aberrant expression of ion channels such as sodium, potassium, and calcium channels, thereby affecting the electrophysiological properties of the myocardium and predisposing to arrhythmias. Despite these advances, the precise molecular mechanisms by which exosomes from cardiac autonomic neurons influence myocardial electrophysiology remain incompletely understood.

Notably, the involvement of circular RNAs (circRNAs) within exosomes derived from cardiac autonomic ganglia cells represents a novel and promising area of investigation. CircRNAs are stable, abundant, and functionally versatile non-coding RNAs that can modulate gene expression by sponging microRNAs or interacting with RNA-binding proteins. Their presence in exosomes suggests they may participate in the fine regulation of ion channel gene networks and signaling pathways critical for cardiac autonomic regulation. However, the specific roles and mechanisms of circRNAs in exosome-mediated neuro-cardiac communication and their impact on slow arrhythmias have yet to be elucidated. Future research focusing on the characterization of exosomal circRNAs and their functional effects on cardiac autonomic neurons and cardiomyocytes will be essential to uncover novel therapeutic targets for arrhythmia management.

Biological Characteristics and Functions of circHIPK3

Genomic Structure and Expression Characteristics of circHIPK3

circHIPK3 is a circular RNA generated by the back-splicing of the second exon of the HIPK3 gene, resulting in a covalently closed loop approximately 1.1 kb in length. This circular configuration distinguishes circHIPK3 from its linear mRNA counterpart, conferring unique biochemical properties such as resistance to exonuclease-mediated degradation due to the absence of 5' caps and 3' polyadenylated tails. This structural stability contributes to its relatively high abundance and persistence within cells. Expression analyses across multiple tissues have demonstrated that circHIPK3 is highly expressed in the heart, brain, liver, and vascular smooth muscle cells, indicating a broad physiological relevance. Its expression is dynamically regulated in response to cellular proliferation, differentiation, and various stress stimuli, suggesting a role in adapting cellular functions under changing physiological and pathological conditions. For instance, in proliferative states or under stress, circHIPK3 levels can be modulated to influence downstream molecular pathways. The high expression of circHIPK3 in cardiac tissue is particularly notable given the heart's reliance on tightly regulated gene expression for maintaining rhythmic contractility and responding to injury or stress. Compared to linear HIPK3 mRNA, circHIPK3's enhanced stability and tissue-specific expression patterns underscore its potential as a critical regulatory molecule in cardiovascular biology and disease. These features make circHIPK3 a promising candidate for further investigation into its functional roles and mechanisms, especially in the context of cardiac autonomic nervous system ganglia and arrhythmogenesis [26-28].

Molecular Regulatory Mechanisms of circHIPK3

circHIPK3 exerts its regulatory functions primarily through multiple molecular interactions, notably acting as a microRNA (miRNA) sponge. By binding and sequestering various miRNAs such as miR-124, miR-193a, and miR-558, circHIPK3 alleviates the inhibitory effects these miRNAs impose on their downstream target mRNAs. This competitive endogenous RNA (ceRNA) activity effectively modulates gene expression post-transcriptionally, influencing cellular processes like proliferation, apoptosis, and differentiation. For example, in breast cancer cells, circHIPK3 sponges miR-326, promoting cell viability and migration by derepressing miR-326 target genes, which highlights its role in fine-tuning gene regulatory networks. Beyond miRNA sponging, circHIPK3 interacts with RNA-Binding Proteins (RBPs) such as HuR and FUS, which are known to regulate mRNA stability, translation efficiency, and subcellular localization. These interactions suggest that circHIPK3 may influence gene expression at multiple levels, including mRNA turnover and protein synthesis, thereby exerting complex regulatory effects. Additionally, emerging evidence indicates that circHIPK3 can be translated into small peptides in certain cell types, although this translational activity remains to be validated in cardiac tissues. The potential for circHIPK3-derived peptides to contribute to biological functions adds another layer of regulatory complexity. Collectively, these molecular mechanisms position circHIPK3 as a multifunctional regulator capable of integrating diverse signaling pathways, which may be particularly relevant in the context of cardiovascular pathophysiology where precise gene regulation is critical [28,29].

Current Research Status of circHIPK3 in Cardiovascular Diseases

Recent studies have increasingly implicated circHIPK3 in the pathogenesis of various cardiovascular diseases. In myocardial ischemia-reperfusion injury models, circHIPK3 expression is upregulated, where it functions as a miRNA sponge for miR-29a. This interaction promotes cardiomyocyte apoptosis and fibrosis by derepressing miR-29a target genes involved in extracellular matrix remodeling and cell death pathways, thereby exacerbating cardiac injury. Similarly, in models of cardiac hypertrophy, circHIPK3 modulates the miR-130b/STAT3 signaling axis, contributing to cardiomyocyte enlargement and adverse cardiac remodeling. These findings underscore circHIPK3's role in maladaptive cardiac responses to stress and injury. In the realm of arrhythmia research, circHIPK3 has been associated with atrial fibrillation, where its dysregulated expression correlates with arrhythmogenic remodeling. However, direct evidence linking circHIPK3 to slow arrhythmias remains limited, representing a critical gap in current knowledge. Given its high expression in cardiac tissues and involvement in key pathological processes such as apoptosis, fibrosis, and hypertrophy, circHIPK3 is a compelling candidate for further investigation in slow arrhythmia mechanisms, particularly those mediated by autonomic nervous system ganglia exosomes. Moreover, circulating exosomal circHIPK3 has been proposed as a biomarker for chronic coronary syndrome and other cardiovascular conditions, highlighting its translational potential for diagnosis and therapeutic targeting. Overall, the accumulating data suggest that circHIPK3 plays multifaceted roles in cardiovascular disease progression, but more focused studies are needed to elucidate its specific contributions to slow arrhythmias and autonomic regulation [30].

Potential Mechanisms of Exosomal circHIPK3 in Bradyarrhythmia

Regulation of Cardiac Autonomic Ganglionated Plexus Function by Exosomal circHIPK3

The cardiac autonomic Ganglionated Plexus (GP) plays a pivotal role in modulating heart rate and rhythm by integrating sympathet-

ic and parasympathetic inputs. Emerging evidence suggests that under exogenous stimuli such as inflammation, oxidative stress, or hemodynamic overload, cells within the cardiac autonomic ganglia secrete extracellular vesicles, particularly exosomes, that carry circular RNA HIPK3 (circHIPK3). These exosomes act as paracrine mediators, facilitating intercellular communication within the GP microenvironment. The secretion of circHIPK3-enriched exosomes in response to pathological stimuli likely represents an adaptive or maladaptive mechanism influencing GP function. Upon release, these exosomes can be internalized by neighboring ganglion cells or adjacent cardiomyocytes, thereby modulating the synthesis and release of parasympathetic neurotransmitters such as acetylcholine. This modulation may occur through circHIPK3 acting as a competing endogenous RNA (ceRNA), sponging specific microRNAs that regulate enzymes involved in acetylcholine biosynthesis or vesicular release machinery. Furthermore, circHIPK3-containing exosomes may influence synaptic plasticity within the intermediate neurons of the ganglion by altering the expression of synaptic proteins and receptors, thereby affecting signal transduction efficiency. Such changes can lead to an abnormal enhancement of parasympathetic activity, which is implicated in the pathogenesis of bradyarrhythmias. The dynamic regulation of GP function by exosomal circHIPK3 highlights a novel molecular mechanism linking extracellular vesicle-mediated RNA transfer to autonomic control of cardiac electrophysiology. Understanding this regulatory axis may provide insights into the development of slow heart rhythm disorders and identify potential therapeutic targets to modulate autonomic imbalance in cardiac diseases [31,32].

Regulation of Cardiac Myocyte Ion Channels by Exosomal circHIPK3

Cardiac myocytes rely on finely tuned ion channel expression and function to maintain normal pacemaking and conduction. The uptake of exosomes containing circHIPK3 by cardiomyocytes introduces a novel regulatory layer on ion channel gene expression through post-transcriptional mechanisms. CircHIPK3 can function as a microRNA sponge, particularly for miRNAs such as miR-124, which are known to target transcripts encoding key ion channels including HCN4 (hyperpolarization-activated cyclic nucleotide-gated channel 4), CACNA1C (L-type calcium channel alpha 1C subunit), and KCNJ2 (inward rectifier potassium channel). By sequestering miR-124, circHIPK3 may relieve repression on HCN4 mRNA, paradoxically leading to decreased HCN4 expression and reduced sinoatrial node automaticity, thereby contributing to bradycardia. Additionally, circHIPK3-mediated modulation of ion channel expression extends to gap junction proteins such as connexin 43 (Cx43), which are critical for electrical coupling and conduction velocity within the atrioventricular node. Altered Cx43 expression or distribution induced by exosomal circHIPK3 uptake can impair conduction, exacerbating atrioventricular block and conduction delays. This multifaceted regulation underscores the importance of exosomal circHIPK3 in shaping the electrophysiological properties of cardiac myocytes by modulating ion channel and gap junction protein expression at the post-transcriptional level. Such mechanisms may underlie the development of slow heart rhythm disorders and conduction abnormalities observed in pathological states characterized by elevated exosomal circHIPK3 release [32].

Interaction Between Exosomal circHIPK3, Inflammation, and Oxidative Stress

The pathogenesis of slow heart rhythm disorders is frequently accompanied by localized cardiac inflammation and oxidative stress, which serve as potent stimuli for the release of exosomes enriched with circHIPK3. Inflammatory cytokines and reactive oxygen species can upregulate circHIPK3 expression and promote its packaging into extracellular vesicles secreted by autonomic ganglion cells and cardiomyocytes. Once released, exosomal circHIPK3 can modulate intracellular signaling pathways such as NF-κB and Nrf2 within recipient cells. Activation of NF-κB signaling by circHIPK3 may enhance the transcription of pro-inflammatory cytokines, perpetuating local inflammation within the cardiac autonomic ganglia and myocardium. Conversely, circHIPK3 may influence Nrf2-mediated antioxidant responses, potentially altering the cellular redox state and exacerbating oxidative damage. This bidirectional regulation establishes a feedback loop wherein inflammation and oxidative stress promote exosomal circHIPK3 release, which in turn amplifies inflammatory and oxidative signaling in target cells. The resultant vicious cycle can intensify autonomic dysfunction and myocardial electrical instability, thereby worsening bradyarrhythmias. Understanding the interplay between exosomal circHIPK3 and inflammatory-oxidative pathways provides critical insight into the molecular mechanisms driving slow heart rhythm disorders and suggests that targeting this axis may disrupt the deleterious feedback loop to ameliorate disease progression.

Role of Exosomal circHIPK3 in Neuro-Cardiac Signal Transduction

Exosomal circHIPK3 functions as a molecular messenger facilitating neuro-cardiac communication by establishing a novel signaling conduit between the cardiac autonomic ganglionated plexus and cardiomyocytes. By modulating neurotransmitter release efficiency and altering cardiomyocyte responsiveness to parasympathetic signals, circHIPK3-containing exosomes dynamically regulate heart rate homeostasis. Under physiological conditions, this intercellular communication maintains the delicate balance between sympathetic and parasympathetic tone. However, pathological overexpression or dysregulated release of exosomal circHIPK3 can disrupt this equilibrium, favoring parasympathetic dominance. Such imbal-

ance leads to excessive vagal activity, manifesting clinically as slow heart rhythm disorders. The aberrant expression of circHIPK3 in exosomes may impair the feedback mechanisms that normally constrain parasympathetic output, thereby promoting sustained bradycardia and conduction abnormalities. This neuro-cardiac signaling axis mediated by exosomal circHIPK3 represents a critical regulatory node in cardiac autonomic control and offers a promising target for therapeutic intervention aimed at restoring autonomic balance and preventing bradyarrhythmias.

Prospects of Exosomal circHIPK3 as a Therapeutic Target for Bradyarrhythmia

Potential of Exosomal circHIPK3 as a Diagnostic Biomarker

Exosomal circHIPK3 has emerged as a promising candidate for early diagnosis of slow arrhythmias due to its reflective expression patterns in blood and cardiac tissues that correlate with cardiac autonomic nervous system function. Extracellular Vesicles (EVs), particularly exosomes, serve as carriers of circHIPK3, encapsulating this circular RNA and protecting it from degradation in circulation. This stability allows for reliable detection of circHIPK3 levels in peripheral blood, offering a minimally invasive approach to assess cardiac autonomic status. Studies in other diseases, such as lung cancer, have demonstrated that EV-derived circHIPK3 is significantly upregulated in patient plasma compared to healthy controls, with diagnostic accuracy reflected by high Area Under the Curve (AUC) values in Receiver Operating Characteristic (ROC) analyses. By analogy, similar approaches could be applied to detect circHIPK3 in patients with slow arrhythmias, where altered expression may indicate early autonomic dysfunction preceding overt clinical manifestations. The non-invasive nature and repeatability of circulating exosomal circHIPK3 measurement confer advantages over traditional invasive electrophysiological assessments. Furthermore, quantification of circHIPK3 levels in circulating exosomes could serve as a surrogate marker to evaluate disease severity and monitor therapeutic responses longitudinally. Combining exosomal circHIPK3 with established cardiac biomarkers such as Brain Natriuretic Peptide (BNP) and microRNA-1 (miR-1) may enhance diagnostic specificity and sensitivity for slow arrhythmias. This multiplex biomarker strategy leverages the complementary pathophysiological information conveyed by different molecular classes, improving clinical decision-making. The unique cargo profile of exosomes, including proteins and nucleic acids, reflects the physiological state of their cells of origin, enabling precise disease characterization. Advances in exosome isolation and detection technologies, including microfluidic platforms and multiparametric biosensors, facilitate sensitive and specific measurement of circHIPK3 in clinical samples [33]. However, challenges remain in standardizing exosome purification and quantification methods to ensure reproducibility and accuracy. Overall, the evidence supports the potential of exosomal circHIPK3 as a novel, non-invasive biomarker for early diagnosis and disease monitoring in slow arrhythmias, warranting further validation in clinical studies.

Therapeutic Strategies Targeting Exosomal circHIPK3

Targeting exosomal circHIPK3 represents a novel therapeutic avenue to modulate cardiac autonomic nervous system imbalance underlying slow arrhythmias. Approaches such as Antisense Oligonucleotides (ASOs) or Small Interfering RNAs (siRNAs) designed to specifically knock down circHIPK3 expression have shown promise in preclinical models of other diseases by disrupting pathological RNA interactions and restoring cellular homeostasis [34]. By reducing circHIPK3 levels, these strategies could inhibit its pro-arrhythmic effects, thereby rebalancing sympathetic and parasympathetic inputs to the heart. Delivery of such nucleic acid therapeutics remains a challenge; however, engineering exosomes as natural delivery vehicles offers a biocompatible and targeted approach. Exosomes can be bioengineered to encapsulate circHIPK3 inhibitors or miRNA mimics that counteract circHIPK3-mediated dysregulation, enabling precise delivery to cardiac autonomic ganglia. This targeted therapy minimizes off-target effects and enhances therapeutic efficacy. Additionally, modulating the biogenesis, packaging, and release of circHIPK3-containing exosomes may reduce their pathological influence on cardiomyocyte electrophysiology. Pharmacological agents or genetic interventions that alter exosome secretion pathways could decrease the abundance of deleterious circHIPK3 cargo in the cardiac microenvironment. Such strategies align with broader efforts to manipulate extracellular vesicle dynamics for therapeutic benefit. The integration of exosome engineering with RNA interference technologies holds significant potential for developing precision therapies for slow arrhythmias. Nonetheless, challenges such as optimizing exosome production, ensuring stability and targeting specificity, and avoiding immune clearance must be addressed to translate these approaches into clinical practice. Continued research into the molecular mechanisms governing circHIPK3 packaging and function within exosomes will inform the design of effective interventions. Overall, targeting exosomal circHIPK3 through RNA-based therapeutics and engineered vesicle delivery systems offers a promising strategy to restore cardiac autonomic balance and mitigate slow arrhythmias.

Pharmacological Interventions Targeting Exosomal circHIPK3-Related Signaling Pathways

Pharmacological modulation of signaling pathways downstream of exosomal circHIPK3 offers an additional therapeutic strategy for slow arrhythmias. CircHIPK3 functions as a competing endogenous RNA, sponging specific microRNAs and thereby regu-

lating the expression of key ion channel genes such as HCN4 and CACNA1C, which are critical for cardiac pacemaker activity and conduction [33]. Small molecule drugs or gene therapy vectors designed to modulate this miRNA-mRNA network could restore normal ion channel expression and electrophysiological properties. For example, agents that enhance miRNA activity suppressed by circHIPK3 or directly upregulate HCN4 and CACNA1C expression may counteract arrhythmogenic remodeling. Moreover, anti-inflammatory and antioxidant drugs may indirectly improve cardiac autonomic ganglion function by inhibiting the release or pathological activity of circHIPK3-containing exosomes. Chronic inflammation and oxidative stress are known contributors to autonomic dysfunction and arrhythmogenesis; thus, their attenuation could reduce exosomal circHIPK3-mediated deleterious effects. Combining these pharmacological agents with established therapies such as β-adrenergic receptor blockers or cholinesterase inhibitors may synergistically restore sympathetic-parasympathetic balance. β-blockers reduce sympathetic overactivity, while cholinesterase inhibitors enhance parasympathetic tone, together complementing the molecular targeting of circHIPK3 pathways. This multimodal approach addresses both upstream molecular mechanisms and downstream autonomic dysregulation. However, the development of specific small molecules targeting circHIPK3-related networks requires further elucidation of its interactome and functional consequences in cardiac autonomic neurons. Advances in high-throughput screening and gene editing technologies will facilitate identification of candidate compounds. Additionally, delivery methods ensuring targeted drug accumulation in cardiac ganglia remain a critical consideration. Overall, pharmacological interventions aimed at circHIPK3-associated signaling pathways, combined with autonomic modulators, represent a promising therapeutic paradigm for managing slow arrhythmias.

Future Research Directions and Challenges

Future research must focus on developing specific methodologies to isolate and characterize extracellular vesicles derived from cardiac autonomic ganglion cells to accurately study circHIPK3 function. Current EV isolation techniques often yield heterogeneous populations, complicating the attribution of molecular cargo to specific cell types. Establishing protocols for selective purification of ganglion cell-derived exosomes will enable precise investigation of circHIPK3's role in autonomic regulation. Animal models, such as targeted overexpression or knockout of circHIPK3 in ganglionated plexi via localized gene delivery, will be instrumental in elucidating causal relationships between circHIPK3 dysregulation and slow arrhythmias. These models can recapitulate the complex in vivo environment and allow assessment of electrophysiological and autonomic outcomes. Clinically, comprehensive studies correlating circulating exosomal circHIPK3 levels with heart rate variability and electrophysiological parameters in patients with slow arrhythmias are needed to validate its diagnostic and prognostic utility. Such translational research will bridge mechanistic insights with patient-centered applications, facilitating clinical adoption. Challenges include standardizing exosome isolation and quantification methods to ensure reproducibility across laboratories and developing sensitive assays capable of detecting low-abundance circHIPK3 in complex biological fluids. Additionally, understanding the regulatory mechanisms governing circHIPK3 packaging into exosomes and its selective release under pathological conditions remains an important research frontier. Addressing these challenges will require multidisciplinary collaboration integrating molecular biology, bioengineering, and clinical cardiology. Ultimately, advancing knowledge of exosomal circHIPK3 in cardiac autonomic ganglia will enable development of novel diagnostic tools and targeted therapies for slow arrhythmias, improving patient outcomes.

Conclusion

The intricate role of the cardiac Autonomic Ganglionated Plexus (AGP) in regulating heart rate underscores its significance in the pathophysiology of bradyarrhythmias. As a pivotal neural hub, the AGP orchestrates the balance between sympathetic and parasympathetic inputs, and its dysfunction can precipitate profound disturbances in cardiac rhythm. This review has highlighted the emerging importance of exosomes, particularly those carrying circular RNA circHIPK3, as critical mediators of intercellular communication within the cardiac nervous system. The multifaceted functions of circHIPK3—ranging from acting as a miRNA sponge to modulating protein interactions and even engaging in translation—demonstrate its complex regulatory capacity over ion channel expression and neurotransmitter release, both of which are fundamental to cardiac electrophysiology. From an expert perspective, the development of this field reflects a paradigm shift in understanding bradyarrhythmias not merely as isolated electrical abnormalities but as disorders intricately linked to neurohumoral regulation at the molecular level. The evidence that exosomal circHIPK3 can enhance parasympathetic activity, suppress sinoatrial node automaticity, and impair atrioventricular conduction provides a compelling mechanistic framework that bridges molecular biology with clinical electrophysiology. This integrative viewpoint reconciles previously disparate findings by positioning circHIPK3 as a nodal point in the signaling networks that govern cardiac autonomic function and rhythm stability.

Balancing the diverse research perspectives, it is clear that while the pro-arrhythmic potential of exosomal circHIPK3 is supported by in vitro and in vivo studies, the complexity of the cardiac autonomic nervous system demands cautious interpretation. The heterogeneity of exosome populations, the pleiotropic effects of cir-

cHIPK3, and the dynamic interplay between sympathetic and parasympathetic influences necessitate comprehensive investigations that delineate context-specific roles. Moreover, the translational leap from mechanistic insights to clinical application requires rigorous validation in human subjects, considering interindividual variability and comorbid conditions that may modulate the impact of circHIPK3 signaling.

The prospect of targeting exosomal circHIPK3 and its associated signaling pathways offers a promising avenue for innovative diagnostic and therapeutic strategies in bradyarrhythmias. Such approaches could enable precision medicine interventions that modulate autonomic tone at the molecular level, potentially restoring electrophysiological homeostasis without the adverse effects associated with conventional pharmacotherapy or invasive procedures. However, realizing this potential hinges on overcoming significant challenges, including the development of selective delivery systems, ensuring safety and efficacy, and establishing robust biomarkers for patient stratification and treatment monitoring. In conclusion, the evolving understanding of exosomal circHIPK3 within the cardiac autonomic ganglionated plexus represents a frontier in cardiovascular research with profound clinical implications. By integrating molecular, cellular, and electrophysiological insights, this review underscores the necessity of a multidisciplinary approach to unravel the complexities of bradyarrhythmia pathogenesis. Future research should prioritize elucidating the precise molecular mechanisms, optimizing translational models, and conducting well-designed clinical trials to harness the therapeutic potential of circHIPK3-targeted interventions. Such endeavors will not only deepen our comprehension of cardiac autonomic regulation but also pave the way for novel, mechanism-based treatments that improve outcomes for patients afflicted with slow heart rhythm disorders.

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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Disclosures

The authors declare no conflict of interest.

Authors' Contributions

Mingliang Shao, Chenhuan Yao and Ting Tu participated in collecting data, and drafted the manuscript. Chengwei Wang, Yingying Han, Zhiqiang Chen and Jian Hu participated in its design. Xianping Wang, Linghe Meng, Bing Liu and Shiwen Liu helped to draft the manuscript. All authors read and approved the final manuscript.

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