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Mechanism and Therapeutic Potential of Exosomes in Valvular Heart Disease

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Abstract. Valvular heart disease (VHD), a category of diseases severely affecting circulatory system function caused by structural or functional abnormalities in heart valves, significantly reduces patients 'quality of life and life expectancy. Although pharmacological interventions and surgical procedures can alleviate clinical symptoms to some extent, achieving valve tissue regeneration and functional reconstruction remains challenging. In recent years, exosomes have gained widespread attention as an emerging therapeutic strategy. These nanoscale vesicles secreted by cells are rich in various bioactive components and play crucial roles in intercellular communication, inflammation regulation, tissue repair, and pathological process modulation. Studies indicate that during the development of cardiac valvular lesions, exosomes demonstrate significant therapeutic potential by regulating inflammatory responses, promoting tissue regeneration, and improving valve function. However, the specific mechanisms of exosomes in valvular disease treatment remain complex, with clinical translation facing multiple challenges including improvements in isolation and purification techniques, enhancement of in vivo stability, and systematic elucidation of action mechanisms. This systematic review examines the pathogenesis of valvular heart disease, discusses exosomes' biological characteristics and their potential as biomarkers and targeted therapies, while exploring current research progress and key scientific issues to provide theoretical foundations for further exploration and clinical application in this field.

Keywords: valvular heart disease, exosomes, therapeutic targets, biomarkers

1. Introduction

Valvular heart disease, a category of circulatory disorders caused by structural abnormalities or functional impairments in cardiac valves, significantly impacts patients' quality of life and survival rates [1]. As a critical component of cardiovascular diseases, it often leads to severe complications such as heart failure and thromboembolism [2]. Although current pharmacological treatments and surgical interventions can alleviate symptoms to some extent, they still struggle to achieve regeneration and functional recovery of damaged valve tissues [3]. Therefore, there is an urgent need to identify and validate new therapeutic targets to optimize clinical management strategies for valvular heart disease.

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In recent years, exosomes – nanoscale (30-150 nm) vesicles secreted by cells – have garnered significant attention for their crucial role in intercellular communication [4]. These biological entities, widely distributed in bodily fluids, carry bioactive molecules including RNA, proteins, lipids, and even DNA, enabling them to mediate cellular interactions and participate in various physiological and pathological processes [5]. Research indicates that exosomes demonstrate remarkable potential in regulating inflammatory responses, promoting tissue repair, and improving cardiac function, offering novel therapeutic approaches for valvular heart disease [6-7]. However, the specific mechanisms of exosomes in valve disease treatment remain complex, with their clinical translation still facing multiple challenges.

Building on this foundation, this paper will systematically review the pathogenesis of valvular heart disease, with a focus on exploring the mechanisms and therapeutic potential of exosomes in this condition. By integrating current research advancements, we analyze key mechanisms of exosomes in valvular heart disease, including cellular communication, tissue remodeling, inflammatory regulation, and immune modulation. This analysis aims to provide theoretical support and practical guidance for future research directions and clinical applications.

2. Pathogenesis of valvular heart disease

2.1. Valve stenosis and insufficiency

Valvular heart disease is a disease caused by abnormal structure or function of the valve. Its main pathological feature is valvular stenosis or insufficiency, resulting in blood flow obstruction or reflux, resulting in increased cardiac load and ventricular hypertrophy, and eventually developing into heart failure [8].

Valve stenosis occurs when a valve cannot fully open during blood flow, causing obstruction. For example, mitral stenosis restricts blood flow from the left atrium to the left ventricle, increasing left atrial pressure and creating a significant pressure gradient between the chambers to maintain cardiac output. Prolonged elevated left atrial pressure may lead to pulmonary congestion, pulmonary edema, and even pulmonary hypertension, ultimately resulting in right ventricular hypertrophy and right heart failure [9-10]. Aortic stenosis impedes left ventricular ejection, elevating left ventricular systolic pressure and triggering left ventricular hypertrophy with prolonged ejection time. This increases myocardial oxygen consumption while raising left ventricular end-diastolic pressure, further burdening the heart [11-12]. Valvular regurgitation causes blood backflow, increasing ventricular load and leading to ventricular dilation and hypertrophy, which may progress to heart failure [13-15].

2.2. Inflammation and immune response

Inflammation and immune response play a key role in the occurrence and development of valvular heart disease. Inflammation and immune mechanisms are not only involved in the pathogenesis of rheumatic heart disease in the traditional sense, but also play an important role in non-rheumatic valvular heart disease.

2.2.1. Rheumatic heart disease and immune response

Rheumatic heart disease is an autoimmune disorder caused by infection with Group A beta-hemolytic streptococcus (GAS) [16], with its pathogenesis primarily mediated through molecular mimicry and immune cross-reactivity [17]. The antigenic components of GAS (e.g., M protein)

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share epitopes with cardiac valve antigens, which activate CD4+ T cells and B cells to produce autoantibodies targeting both the valvular endothelium and endocardium [18]. These antibodies bind to the valve surface, triggering complement activation that induces inflammatory cell infiltration (including macrophages and T cells) and the release of pro-inflammatory cytokines such as IFN-γ, IL-17, and TNF-α. This process leads to chronic inflammation, fibrosis, and calcification of the valves [19-20]. Additionally, pro-inflammatory cytokines promote the transformation of valve fibroblasts into osteogenic cells, further exacerbating valvular calcification [21].

2.2.2. Non-rheumatic valvular disease and immune response

In recent years, it has been found that non-rheumatic valvular disease is also closely related to inflammation and immune response (Table 1).

Table 1. Role of immune response in the development of non-rheumatic valvular disease

machine-processed	specific description	reference documentation
Immune cell infiltration	In non-rheumatic valvular disease, macrophages, T cells and B cells infiltrate the valve tissue and release pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and chemokines (MCP-1), driving the phenotypic transformation and fibrosis of valve cells.	[22]
	TGF-β1 induces intervalvular mesenchymal cell ossification through the Smad signaling pathway	[23]
	Inflammatory cytokines exacerbate inflammatory cell infiltration and activation through the NF-κB signaling pathway.	[24]
The role of cytokines	The elevation of pro-inflammatory cytokines (TNF-α and IL-6) accelerates inflammatory response and tissue damage.	[25]
	The anti-inflammatory cytokine IL-10 exerts a protective effect by inhibiting the activity of pro-inflammatory factors.	[26,27]
Immune regulation during calcification	Macrophages secrete calcification-promoting factor (TGF-β1) and regulate the local inflammatory environment to promote valve calcification	[27,28]
	The effect of TGF-β1 is concentration-dependent: it inhibits inflammation at low concentrations and promotes fibrosis and calcification at high concentrations.	[11,27]

3. Mechanism of exosomes in the treatment of valvular heart disease

Exosomes, serving as crucial intercellular communication mediators, carry bioactive molecules such as proteins, mRNA, and miRNA. They play multifaceted regulatory roles in the development of valvular heart disease, including cellular communication, tissue remodeling, inflammatory regulation, and immune modulation. These mechanisms collectively influence the functional state of valve tissues and provide promising new therapeutic strategies for valvular heart disease.

3.1. Cell communication

Exosomes mediate intercellular signaling by carrying bioactive molecules, regulating cellular functions and phenotypic changes within valve tissues [29]. Studies demonstrate that miRNAs in exosomes can specifically target genes, influencing the phenotypic transformation of vascular intima-media cells (VICs) [30]. Notably, exosomes derived from mesenchymal stem cells (MSCs) –

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termed MSC-exosomes (MSC-Exos) – promote the M1-to-M2 macrophage transition through miR-182-mediated signaling pathways, thereby alleviating myocardial ischemia/reperfusion injury [31]. Additionally, exosomes trigger downstream signaling cascades by binding to specific cell surface receptors, further enhancing intercellular functional connections [32].

3.2. Organizational remodeling

Exosomes play a crucial regulatory role in valvular tissue remodeling by delivering signaling molecules that promote calcification and fibrosis, thereby accelerating osteoblastic phenotypic transformation of vascular intima-media cells (VICs) and advancing valvular calcification. Research has demonstrated that TGF-β1 in exosomes specifically activates the Smad signaling pathway, promoting tissue fibrosis [33]. However, MSC-Exos can inhibit miR-155 expression to block the activation of cardiac fibrosis-related signaling pathways, thereby slowing the progression of valvular fibrosis [34]. This mechanism provides important theoretical support for the application of MSC-Exos in the prevention and treatment of valvular heart disease.

3.3. Inflammatory regulation

Inflammatory responses play a pivotal role in the development of valvular heart disease. Exosomes influence this pathological process by regulating inflammatory cell activation and cytokine release. Research indicates that exosomes transport inflammatory mediators such as TNF-α and IL-1β, activate NF-κB signaling pathways, and promote inflammatory cell recruitment with [35] activation. Additionally, miRNAs within exosomes specifically bind to anti-inflammatory genes, enabling precise regulation of inflammation levels [36]. For instance, miR-146a-modified adipose-derived mesenchymal stem cell exosomes inhibit early growth response factor 1 expression, reduce secretion of IL-6, IL-1β, and TNF-α, and modulate NF-κB signaling pathways, thereby alleviating inflammation associated with valvular heart disease [37]. Furthermore, MSC-exosomes enhance M2 macrophage polarization to further suppress inflammatory responses, slowing the progression of valvular fibrosis and calcification [38].

3.4. Immunoregulation

Exosomes play a crucial role in immune regulation of valvular heart disease, maintaining immune homeostasis and reducing pathological damage through multiple mechanisms [39]. Studies indicate that TGF-β1 carried by exosomes inhibits T cell proliferation and differentiation while promoting the generation of regulatory T cells (Tregs), thereby sustaining immune tolerance in the body [40,41]. Additionally, miRNAs within exosomes specifically target key signaling molecules in immune cells, suppressing the activation of the NF-κB signaling pathway to modulate immune response intensity [42]. Notably, exosomes can further influence immune cell function by altering their metabolic state, demonstrating profound effects in immune microenvironment regulation [43-44].

4. The potential of exosomes as biomarkers and targeted therapies

4.1. The application value of biomarkers

Exosomes, rich in biomolecules such as miRNAs, proteins, and lipids, can accurately reflect the pathophysiological characteristics of diseases with high sensitivity and specificity [45]. Their stable

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biomarker-carrying capacity, combined with convenient collection, storage, and in vivo transport properties, demonstrates significant potential in disease diagnosis and prognosis assessment [46]. Studies have shown that miRNAs, proteins, and lipids in exosomes are widely used for early screening of cardiovascular diseases and malignancies[47,48]. Notably, circulating exosomal miRNAs from the circulatory system are particularly recommended for diagnosing myocardial injury, stroke, and endothelial dysfunction, along with their prognostic evaluation [49].

4.2. Targeted therapy strategies for exosomes

Exosomes have demonstrated remarkable potential in targeted therapies for various diseases, particularly showing exceptional efficacy in managing inflammatory and cardiovascular disorders [50]. By regulating immune functions, suppressing the release of inflammatory mediators, and promoting tissue regeneration, they effectively mitigate pathological processes [51]. For instance, mesenchymal stem cell-exosomes (MSC-Exos) secreted by mesenchymal stem cells (MSCs) have been proven crucial in treating conditions like myocardial infarction and liver fibrosis, exhibiting potent anti-inflammatory and immune-regulating capabilities [52]. Furthermore, exosomes serve as efficient drug delivery systems that enable precise administration of miRNA, proteins, and small-molecule drugs, which not only enhances drug stability and bioavailability but also reduces toxic side effects [53].

5. Research progress and challenges

In recent years, extracellular vesicles (exosomes) have made significant strides in cardiovascular valve disease research. As crucial intercellular messengers, exosomes containing miRNAs, proteins, and lipid molecules have been shown to regulate cellular activity [54]. In valvular heart diseases, exosomes mitigate pathological damage through mechanisms such as anti-inflammatory effects, free radical scavenging, and inhibition of programmed cell death. Notably, MSC-Exos can influence cellular signaling pathways and gene regulation networks, demonstrating remarkable efficacy in improving valve tissue injury [29]. Furthermore, animal studies reveal that novel non-invasive delivery methods (e.g., nebulized exosome inhalation) show promising therapeutic potential, opening new avenues for clinical application [8]. Despite the broad application prospects of exosomes in valvular heart disease treatment, multiple challenges remain to be addressed (Table 2).

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Table 2. Current challenges in the application of exosomes in the treatment of valvular heart disease

Key challenges	Specific direction	reference documentation
Limitations of extraction and purification techniques	Current exosome isolation techniques (e.g., ultracentrifugation and polymer precipitation) still need to be optimized in terms of yield, purity and standardization, which affect their large-scale production and clinical application	[55-56]
Insufficient internal stability	Exosomes have a short retention time in vivo and poor biological stability, which affects their long-term therapeutic effect	[57-58]
The mechanism of action is not clear	Although the regulatory role of exosomes in valvular heart disease has been preliminarily confirmed, its specific molecular mechanisms have not been fully elucidated, especially the specific regulatory networks in cell communication, tissue remodeling and immune regulation need to be further studied.	
Lack of standardized treatment procedures	The lack of standardized operating procedures and safety evaluation system for the clinical application of exosomes limits their feasibility and promotion in clinical treatment	[59-61]

6. Summary and outlook

Exosomes, as an innovative therapeutic strategy, offer novel approaches for cardiac valvular disease intervention by facilitating information exchange, regulating inflammation, and promoting regeneration. However, research in this field remains in its infancy, with practical clinical applications still facing numerous technical barriers and scientific challenges.

To address these challenges, subsequent research should prioritize three key areas: First, improving exosome isolation techniques and delivery vectors by enhancing production efficiency, purity, and stability. Second, conducting in-depth investigations into exosomes 'functional mechanisms in valvular heart diseases, particularly clarifying their specific roles in intercellular communication, tissue remodeling, and immune regulation. Third, strengthening the integration of basic research with clinical practice is crucial, requiring the development of personalized treatment plans to ensure exosome therapy's safety and efficacy. With continuous advancements in biotechnology, targeted modification and large-scale production of exosomes will undoubtedly open new possibilities for clinical applications.

In conclusion, exosomes have a broad development space in the field of heart valve disease treatment. However, to break through the existing bottlenecks, it is necessary to make multidisciplinary collaborative innovation. With continuous in-depth research and technology development, exosomes are expected to become an important tool for heart valve disease treatment, thus providing new treatment options for clinical patients.

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