

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.

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)

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 document ation
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-1 β) and chemokines (MCP-1), driving the phenotypic transformation and fibrosis of valve cells.	[22]
	TGF- β 1 induces intervalvular mesenchymal cell ossification through the Smad signaling pathway	[23]
	Inflammatory cytokines exacerbate inflammatory cell infiltration and activation through the NF- κ B 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- β 1) and regulate the local inflammatory environment to promote valve calcification	[27,28]
	The effect of TGF- β 1 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) –

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- β 1 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-1 β , activate NF- κ B 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-1 β , and TNF- α , and modulate NF- κ B 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- β 1 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- κ B 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

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).

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

Key challenges	Specific direction	reference docume ntation
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.

References

- [1] Aluru JS, Barsouk A, Saginala K, Rawla P, Barsouk A. Valvular Heart Disease Epidemiology. *Med Sci (Basel)*. 2022 Jun 15; 10(2): 32.
- [2] Kisling A, Gallagher R. Valvular Heart Disease. *Prim Care*. 2024 Mar; 51(1): 95-109.
- [3] David Messika-Zeitoun, Helmut Baumgartner, Ian G Burwash, Alec Vahanian, Jeroen Bax, Philippe Pibarot, Vince Chan, Martin Leon, Maurice Enriquez-Sarano, Thierry Mesana, Bernard Iung, Unmet needs in valvular heart

- disease, *European Heart Journal*, Volume 44, Issue 21, 1 June 2023, Pages 1862–1873
- [4] Doyle LM, Wang MZ. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. *Cells*. 2019 Jul 15; 8(7): 727.
 - [5] Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol*. 2013 Feb 18; 200(4): 373-83.
 - [6] Moghassemi S, Dadashzadeh A, Sousa MJ, Vlieghe H, Yang J, León-Félix CM, Amorim CA. Extracellular vesicles in nanomedicine and regenerative medicine: A review over the last decade. *Bioact Mater*. 2024 Mar 2; 36: 126-156.
 - [7] Kulus M, Farzaneh M, Sheykhi-Sabzehpoush M, Ghaedrahmati F, Mehravar F, Józkwia M, Piotrowska-Kempisty H, Bukowska D, Antosik P, Podhorska-Okołów M, Zabel M, Mozdziak P, Dzięgiel P, Kempisty B. Exosomes and non-coding RNAs: Exploring their roles in human myocardial dysfunction. *Biomed Pharmacother*. 2025 Feb; 183: 117853.
 - [8] Li J, Sun S, Zhu D, Mei X, Lyu Y, Huang K, Li Y, Liu S, Wang Z, Hu S, Lutz HJ, Popowski KD, Dinh PC, Butte AJ, Cheng K. Inhalable Stem Cell Exosomes Promote Heart Repair After Myocardial Infarction. *Circulation*. 2024 Aug 27; 150(9): 710-723.
 - [9] Tao Shouqi. Etiology and Pathophysiology of Mitral Valve Disease [J]. *Chinese Circulation Journal*, 1990, (04): 274-275.
 - [10] Di Gioia G, Bartunek J, Tesorio T, Vukcevic V, Aleksandric S, Dobric M, Franco D, Barbato E, Banovic M. Pathophysiology, Diagnosis, and Treatment of Patients with Concomitant Severe Aortic Stenosis and Coronary Artery Disease: A Closer Look to the Unresolved Perplexity. *J Clin Med*. 2021 Apr 11; 10(8): 1617..
 - [11] Pibarot P, Dumesnil JG. New concepts in valvular hemodynamics: implications for diagnosis and treatment of aortic stenosis. *Can J Cardiol*. 2007 Oct; 23 Suppl B(Suppl B): 40B-47B.
 - [12] Côté N, Simard L, Zenses AS, Tastet L, Shen M, Clisson M, Clavel MA. Impact of Vascular Hemodynamics on Aortic Stenosis Evaluation: New Insights Into the Pathophysiology of Normal Flow-Small Aortic Valve Area-Low Gradient Pattern. *J Am Heart Assoc*. 2017 Jul 7; 6(7): e006276.
 - [13] Linhart JW, Hildner FJ, Barold SS, Samet P. The hemodynamic consequences of the acute development of aortic valvular insufficiency in man. *J Thorac Cardiovasc Surg*. 1969 Oct; 58(4): 592-600.
 - [14] Baumbach A, Patel KP, Rudolph TK, Delgado V, Treede H, Tamm AR. Aortic regurgitation: from mechanisms to management. *EuroIntervention*. 2024 Sep 2; 20(17): e1062-e1075.
 - [15] Unger P, Lancellotti P, Amzulescu M, David-Cojocariu A, de Cannière D. Pathophysiology and management of combined aortic and mitral regurgitation. *Arch Cardiovasc Dis*. 2019 Jun-Jul; 112(6-7): 430-440.
 - [16] KAPLAN MH. The concept of autoantibodies in rheumatic fever and in the postcommissurotomy state. *Ann N Y Acad Sci*. 1960 Jun 30; 86: 974-91.
 - [17] Passos LSA, Nunes MCP, Aikawa E. Rheumatic Heart Valve Disease Pathophysiology and Underlying Mechanisms. *Front Cardiovasc Med*. 2021 Jan 18; 7: 612716.
 - [18] Raynes JM, Frost HR, Williamson DA, Young PG, Baker EN, Steemson JD, Loh JM, Proft T, Dunbar PR, Atatoa Carr PE, Bell A, Moreland NJ. Serological Evidence of Immune Priming by Group A Streptococci in Patients with Acute Rheumatic Fever. *Front Microbiol*. 2016 Jul 22; 7: 1119.
 - [19] Passos LSA, Jha PK, Becker-Greene D, Blaser MC, Romero D, Lupieri A, Sukhova GK, Libby P, Singh SA, Dutra WO, Aikawa M, Levine RA, Nunes MCP, Aikawa E. Prothymosin Alpha: A Novel Contributor to Estradiol Receptor Alpha-Mediated CD8⁺ T-Cell Pathogenic Responses and Recognition of Type 1 Collagen in Rheumatic Heart Valve Disease. *Circulation*. 2022 Feb 15; 145(7): 531-548.
 - [20] Kemeny E, Grieve T, Marcus R, Sareli P, Zabriskie JB. Identification of mononuclear cells and T cell subsets in rheumatic valvulitis. *Clin Immunol Immunopathol*. 1989 Aug; 52(2): 225-37.
 - [21] Guilherme L, Cury P, Demarchi LM, Coelho V, Abel L, Lopez AP, Oshiro SE, Aliotti S, Cunha-Neto E, Pomerantzeff PM, Tanaka AC, Kalil J. Rheumatic heart disease: proinflammatory cytokines play a role in the progression and maintenance of valvular lesions. *Am J Pathol*. 2004 Nov; 165(5): 1583-91.
 - [22] Hajishengallis G, Netea MG, Chavakis T. Trained immunity in chronic inflammatory diseases and cancer. *Nat Rev Immunol*. 2025 Jan 31.
 - [23] Jiang Weijian, Fang Ming, Su Jinwen, et al. Effects and Mechanisms of MicroRNA-486 and TGF-β1 on Aortic Valve Calcification in Homo sapiens [J]. *Chinese Journal of Modern Medicine*, 2018, 28(32): 25-32.
 - [24] Anilkumar S, Wright-Jin E. NF-κB as an Inducible Regulator of Inflammation in the Central Nervous System. *Cells*. 2024 Mar 11; 13(6): 485.
 - [25] Dogan S, Kimyon G, Ozkan H, Kacmaz F, Camdeviren B, Karaaslan I. TNF-alpha, IL-6, IL-10 and fatty acids in rheumatoid arthritis patients receiving cDMARD and bDMARD therapy. *Clin Rheumatol*. 2022 Aug; 41(8): 2341-2349.

- [26] CHEN Shisong, HUANG Kai, XU Hongjie, XU Zhiyun, HAN Lin, LIU Xiaohong. Causal relationship between 91 inflammatory proteins and 5 cardiovascular diseases: a bidirectional Mendelian randomization. *Academic Journal of Naval Medical University*. 2024, 45(5): 558-568.
- [27] Small AM, Yutzey KE, Binstadt BA, Voigts Key K, Bouatia-Naji N, Milan D, Aikawa E, Otto CM, St Hilaire C; American Heart Association Council on Genomic and Precision Medicine; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; and Council on Cardiovascular and Stroke Nursing. Unraveling the Mechanisms of Valvular Heart Disease to Identify Medical Therapy Targets: A Scientific Statement From the American Heart Association. *Circulation*. 2024 Aug 6; 150(6): e109-e128.
- [28] Martin M, Motta SE, Emmert MY. Have we found the missing link between inflammation, fibrosis, and calcification in calcific aortic valve disease? *Eur Heart J*. 2023 Mar 7; 44(10): 899-901.
- [29] Li F, Fang R, Rao L, Meng F, Zhao X. [Research progress on exosomes in diagnosis and treatment of cardiovascular diseases]. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2018 May 25; 47(3): 320-326.
- [30] Zhang TR, Huang WQ. Angiogenic Exosome-Derived microRNAs: Emerging Roles in Cardiovascular Disease. *J Cardiovasc Transl Res*. 2021 Oct; 14(5): 824-840.
- [31] Pan Y, Wu W, Jiang X, Liu Y. Mesenchymal stem cell-derived exosomes in cardiovascular and cerebrovascular diseases: From mechanisms to therapy. *Biomed Pharmacother*. 2023 Jul; 163: 114817.
- [32] Bakhshian Nik A, Hutcheson JD, Aikawa E. Extracellular Vesicles As Mediators of Cardiovascular Calcification. *Front Cardiovasc Med*. 2017 Dec 11; 4: 78.
- [33] Wortzel I, Dror S, Kenific CM, Lyden D. Exosome-Mediated Metastasis: Communication from a Distance. *Dev Cell*. 2019 May 6; 49(3): 347-360.
- [34] Amrute JM, Luo X, Penna V, Yang S, Yamawaki T, Hayat S, Bredemeyer A, Jung IH, Kadyrov FF, Heo GS, Venkatesan R, Shi SY, Parvathaneni A, Koenig AL, Kuppe C, Baker C, Luehmann H, Jones C, Kopecky B, Zeng X, Bleckwehl T, Ma P, Lee P, Terada Y, Fu A, Furtado M, Kreisel D, Kovacs A, Stitzel NO, Jackson S, Li CM, Liu Y, Rosenthal NA, Kramann R, Ason B, Lavine KJ. Targeting immune-fibroblast cell communication in heart failure. *Nature*. 2024 Nov; 635(8038): 423-433.
- [35] Akhmerov A, Parimon T. Extracellular Vesicles, Inflammation, and Cardiovascular Disease. *Cells*. 2022 Jul 18; 11(14): 2229.
- [36] You Y, Tian Y, Guo R, Shi J, Kwak KJ, Tong Y, Estania AP, Hsu WH, Liu Y, Hu S, Cao J, Yang L, Bai R, Huang P, Lee LJ, Jiang W, Kim BYS, Ma S, Liu X, Shen Z, Lan F, Phuong Nguyen PK, Lee AS. Extracellular vesicle-mediated VEGF-A mRNA delivery rescues ischaemic injury with low immunogenicity. *Eur Heart J*. 2025 Jan 20: ehae883.
- [37] Zheng H, Liang X, Liu B, Huang X, Shen Y, Lin F, Chen J, Gao X, He H, Li W, Hu B, Li X, Zhang Y. Exosomal miR-9-5p derived from iPSC-MSCs ameliorates doxorubicin-induced cardiomyopathy by inhibiting cardiomyocyte senescence. *J Nanobiotechnology*. 2024 Apr 20; 22(1): 195.
- [38] Ma X, Liu B, Fan L, Liu Y, Zhao Y, Ren T, Li Y, Li Y. Native and engineered exosomes for inflammatory disease. *Nano Res*. 2023; 16(5): 6991-7006.
- [39] Greening DW, Gopal SK, Xu R, Simpson RJ, Chen W. Exosomes and their roles in immune regulation and cancer. *Semin Cell Dev Biol*. 2015 Apr; 40: 72-81.
- [40] Yu P, Han Y, Meng L, Tang Z, Jin Z, Zhang Z, Zhou Y, Luo J, Luo J, Han C, Zhang C, Kong L. The incorporation of acetylated LAP-TGF- β 1 proteins into exosomes promotes TNBC cell dissemination in lung micro-metastasis. *Mol Cancer*. 2024 Apr 25; 23(1): 82.
- [41] Du YM, Zhuansun YX, Chen R, Lin L, Lin Y, Li JG. Mesenchymal stem cell exosomes promote immunosuppression of regulatory T cells in asthma. *Exp Cell Res*. 2018 Feb 1; 363(1): 114-120.
- [42] Meng WT, Zhu J, Wang YC, Shao CL, Li XY, Lu PP, Huang MY, Mou FF, Guo HD, Ji G. Targeting delivery of miR-146a via IMTP modified milk exosomes exerted cardioprotective effects by inhibiting NF- κ B signaling pathway after myocardial ischemia-reperfusion injury. *J Nanobiotechnology*. 2024 Jul 1; 22(1): 382.
- [43] Zhang B, Yin Y, Lai RC, Tan SS, Choo AB, Lim SK. Mesenchymal stem cells secrete immunologically active exosomes. *Stem Cells Dev*. 2014 Jun 1; 23(11): 1233-44.
- [44] Zhang B, Yeo RWY, Lai RC, Sim EWK, Chin KC, Lim SK. Mesenchymal stromal cell exosome-enhanced regulatory T-cell production through an antigen-presenting cell-mediated pathway. *Cytotherapy*. 2018 May; 20(5): 687-696.
- [45] Araujo-Abad S, Berna JM, Lloret-Lopez E, López-Cortés A, Saceda M, de Juan Romero C. Exosomes: from basic research to clinical diagnostic and therapeutic applications in cancer. *Cell Oncol (Dordr)*. 2024 Sep 19.
- [46] Chen AQ, Gao XF, Wang ZM, Wang F, Luo S, Gu Y, Zhang JJ, Chen SL. Therapeutic Exosomes in Prognosis and Developments of Coronary Artery Disease. *Front Cardiovasc Med*. 2021 May 31; 8: 691548.

- [47] Lotfy A, AboQuella NM, Wang H. Mesenchymal stromal/stem cell (MSC)-derived exosomes in clinical trials. *Stem Cell Res Ther.* 2023 Apr 7; 14(1): 66.
- [48] Jin X, Xu W, Wu Q, Huang C, Song Y, Lian J. Detecting early-warning biomarkers associated with heart-exosome genetic-signature for acute myocardial infarction: A source-tracking study of exosome. *J Cell Mol Med.* 2024 Apr; 28(8): e18334.
- [49] Jayaraman S, Gnanasampanthapandian D, Rajasingh J, Palaniyandi K. Stem Cell-Derived Exosomes Potential Therapeutic Roles in Cardiovascular Diseases. *Front Cardiovasc Med.* 2021 Aug 10; 8: 723236.
- [50] Saleem M, Shahzad KA, Marryum M, Singh S, Zhou Q, Du S, Wang S, Shao C, Shaikh II. Exosome-based therapies for inflammatory disorders: a review of recent advances. *Stem Cell Res Ther.* 2024 Dec 18; 15(1): 477.
- [51] Xu Y, Wan W, Zeng H, Xiang Z, Li M, Yao Y, Li Y, Bortolanza M, Wu J. Exosomes and their derivatives as biomarkers and therapeutic delivery agents for cardiovascular diseases: Situations and challenges. *J Transl Int Med.* 2023 Dec 20; 11(4): 341-354.
- [52] Lin Z, Wu Y, Xu Y, Li G, Li Z, Liu T. Mesenchymal stem cell-derived exosomes in cancer therapy resistance: recent advances and therapeutic potential. *Mol Cancer.* 2022 Sep 13; 21(1): 179.
- [53] Yuan J, Yang H, Liu C, Shao L, Zhang H, Lu K, Wang J, Wang Y, Yu Q, Zhang Y, Yu Y, Shen Z. Microneedle Patch Loaded with Exosomes Containing MicroRNA-29b Prevents Cardiac Fibrosis after Myocardial Infarction. *Adv Healthc Mater.* 2023 May; 12(13): e2202959.
- [54] Lee BC, Kang I, Yu KR. Therapeutic Features and Updated Clinical Trials of Mesenchymal Stem Cell (MSC)-Derived Exosomes. *J Clin Med.* 2021 Feb 11; 10(4): 711.
- [55] Chen J, Li P, Zhang T, Xu Z, Huang X, Wang R, Du L. Review on Strategies and Technologies for Exosome Isolation and Purification. *Front Bioeng Biotechnol.* 2022 Jan 5; 9: 811971.
- [56] Tang J, Jia X, Li Q, Cui Z, Liang A, Ke B, Yang D, Yao C. A DNA-based hydrogel for exosome separation and biomedical applications. *Proc Natl Acad Sci U S A.* 2023 Jul 11; 120(28): e2303822120.
- [57] Lázaro-Ibáñez E, Faruqu FN, Saleh AF, Silva AM, Tzu-Wen Wang J, Rak J, Al-Jamal KT, Dekker N. Selection of Fluorescent, Bioluminescent, and Radioactive Tracers to Accurately Reflect Extracellular Vesicle Biodistribution in Vivo. *ACS Nano.* 2021 Feb 23; 15(2): 3212-3227.
- [58] Bakadia BM, Qaed Ahmed AA, Lamboni L, Shi Z, Mutu Mukole B, Zheng R, Pierre Mbang M, Zhang B, Gauthier M, Yang G. Engineering homologous platelet-rich plasma, platelet-rich plasma-derived exosomes, and mesenchymal stem cell-derived exosomes-based dual-crosslinked hydrogels as bioactive diabetic wound dressings. *Bioact Mater.* 2023 May 17; 28: 74-94.
- [59] Yin Hang. Clinical Application Prospects and Industrialization Outlook of Exosomes [J]. *Progress in Pharmaceutical Sciences*, 2023, 47(11): 801-803.
- [60] Han L, Zhao Z, He C, Li J, Li X, Lu M. Removing the stumbling block of exosome applications in clinical and translational medicine: expand production and improve accuracy. *Stem Cell Res Ther.* 2023 Apr 1; 14(1): 57.
- [61] Lee KWA, Chan LKW, Hung LC, Phoebe LKW, Park Y, Yi KH. Clinical Applications of Exosomes: A Critical Review. *Int J Mol Sci.* 2024 Jul 16; 25(14): 7794.