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Research Advances on Extracellular Vesicles in Hypertension and Target Organ Damage

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Abstract: ***Hypertension represents a major global public health challenge and is the primary risk factor for target organ damage (TOD), including cardiovascular disease, stroke, and chronic kidney disease. Extracellular vesicles (EVs), as a class of nanoscale membrane structures secreted by cells that encapsulate bioactive molecules such as proteins, nucleic acids, and lipids, have emerged as key mediators of intercellular communication. Increasing evidence in recent years indicates that EVs play a pivotal role in the pathophysiology of hypertension development, target organ damage, and associated complications. They regulate key pathological processes—including endothelial function, inflammatory responses, vascular remodeling, and fibrosis—through their specific cargo (e.g., microRNAs, proteins). This review systematically summarizes recent advances in extracellular vesicle research concerning hypertension and target organ damage, emphasizing the molecular mechanisms of EVs in hypertension and its cardiovascular, renal, and pulmonary circulatory target organ damage, as well as their potential as biomarkers, thereby laying the foundation for future clinical applications.***

Keywords: Extracellular vesicles, Hypertension, Target organ damage, Pathogenesis, Biomarkers.

1. Introduction

Hypertension is a clinical syndrome primarily characterized by persistently elevated systemic arterial blood pressure, ranking among the leading causes of death and disability worldwide [1-2]. Long-term uncontrolled hypertension can lead to structural and functional damage in vital target organs such as the heart, brain, and kidneys, including left ventricular hypertrophy, atherosclerosis, heart failure, chronic kidney disease, and cerebrovascular accidents. These complications constitute the primary burden of hypertension-related mortality and morbidity [3-5].

In recent years, extracellular vesicles (EVs) have rapidly emerged as a focal point in cardiovascular and metabolic disease research due to their role as key carriers of intercellular communication. EVs are nanoscale vesicles with a lipid bilayer structure secreted by all eukaryotic cells. These vesicles can specifically "deliver" bioactive molecules from their source cells—such as proteins, nucleic acids (mRNA, miRNA, etc.), lipids, and metabolites—to target cells, altering their gene expression and function. They play a central role in cellular communication [6-8]. This mode of information transfer not only maintains organismal homeostasis but also drives the onset and progression of various diseases, particularly in the cardiovascular field [9-10]. Evidence indicates that EV levels and their contents correlate closely with blood pressure, vascular injury severity, and target organ function [11-14].

2. Biological Overview of Extracellular Vesicles

Extracellular vesicles (EVs) are defined by the International Society for Extracellular Vesicles (ISEV) as "nanoparticles naturally released by cells, enclosed by a lipid bilayer, and incapable of self-replication." This definition encompasses all membrane structures secreted by cells into the extracellular space. Based on their origin, size, and biological functions, they are primarily classified into three major categories: Exosomes (diameter ~50-150 nm), originating from multivesicular bodies formed by endocytosis and released through fusion with the cell membrane; Microvesicles (diameter ~100-1000 nm), formed by direct budding and shedding from the cell membrane; and Apoptotic bodies (diameter ~100-5000 nm), products of programmed cell death. Given the central role of exosomes and microvesicles in active intercellular signaling, current research typically focuses on them collectively as EVs [15].

The core biological function of EVs lies in mediating intercellular communication. As a natural nanocarrier system, EVs can stably transport and deliver specific bioactive "cargo" from their parent cells—including proteins, lipids, metabolites, and various nucleic acids (such as mRNA, miRNA, lncRNA, and DNA fragments)—to recipient cells [8]. This mode of information transfer exhibits high specificity and efficiency. First, EVs express specific ligands or adhesion molecules on their membranes, enabling them to recognize and bind corresponding receptors on target cell surfaces, thereby triggering signaling cascades [15]. Second, EVs can fuse directly with target cell membranes, releasing their internal cargo into the cytoplasm and altering the target cell's proteomic and metabolomic states. Finally, EVs can also be internalized by target cells via endocytosis, macropinocytosis, or receptor-mediated endocytosis, releasing their cargo intracellularly to regulate gene expression and cellular functions [15]. Consequently, EVs mediate complex dialogues within local microenvironments and even between distant organs, serving as key messengers in maintaining tissue homeostasis or driving pathological processes.

3. Role of EVs in the Pathogenesis of Hypertension

3.1 EVs and Vascular Endothelial Dysfunction

Vascular endothelial dysfunction is considered the initiating event and core pathological feature in hypertension [16]. Under hypertensive conditions, multiple risk factors (e.g., hyperglycemia, oxidative stress, inflammatory cytokines) damage endothelial cells, leading to reduced nitric oxide (NO) bioavailability and increased expression of vasoconstrictors such as endothelin-1 (ET-1), thereby inducing endothelial dysfunction [17-18]. EVs play a dual role in this process: on one hand, they represent the outcome of endothelial injury and dysfunction; while also acting as effector molecules that amplify and propagate injury signals to neighboring cells, further exacerbating endothelial dysfunction [18-20].

In the circulatory systems of hypertensive patients, levels of endothelial-derived microvesicles (EMPs) are significantly elevated, and their concentration correlates positively with blood pressure, arterial stiffness, and cardiovascular event risk [21]. Elevated EMPs not only serve as markers of endothelial injury but also possess intrinsic biological activity [22]. Studies reveal that EMPs isolated from the plasma of hypertensive patients significantly increase reactive oxygen species (ROS) production and reduce nitric oxide (NO) generation in human umbilical vein endothelial cells (HUVECs), thereby directly impairing endothelial function [23]. Lugo-Gavidia LM et al. demonstrated that plasma EMP and platelet-derived microparticle (PMP) levels were significantly elevated in patients with severe untreated hypertension compared to those with mild hypertension and healthy controls, and positively correlated with systolic and diastolic blood pressure levels. This suggests EMPs and PMPs may serve as circulating markers of endothelial injury in arterial hypertension [22]. Furthermore, Varela-López E et al. discovered that EVs derived from activated platelets carry von Willebrand factor (vWF) and P-selectin, mediating platelet-endothelial adhesion and promoting inflammatory responses [24]. Evidence indicates that EVs, by carrying and transmitting injurious signaling molecules, profoundly contribute to the development of endothelial dysfunction in hypertension through multiple pathways, including disruption of endothelium-dependent vasodilation, increased oxidative stress, and promotion of inflammatory responses.

3.2 EVs and Inflammatory Response

Chronic low-grade inflammation constitutes a critical pathological basis for hypertension and its target organ damage. EVs serve as highly efficient carriers of inflammatory signals, playing pivotal roles as hubs within the inflammatory network of hypertension. First, EVs themselves carry diverse inflammation-related molecules. For instance, platelet-derived EVs (PEVs) mediate heterotypic adhesion with monocytes via P-selectin and PSGL-1, leading to rapid accumulation of GPIbα on monocytes and promoting their recruitment in inflammatory environments [25]. Beyond surface molecules, the internal cargo of EVs is also rich in inflammatory mediators. One study revealed that endothelial microvesicles (EMVs) isolated from hypertensive patients dose-dependently induced human umbilical vein endothelial cells (HUVECs) to produce interleukin-6 (IL-6) and interleukin-8 (IL-8), while activating key inflammatory signaling pathways such as NF-κB and p38-MAPK [26]. Evidence indicates that EVs not only transmit "inflammatory invitations" between cells but also directly activate inflammatory programs in target cells. Furthermore, EVs regulate inflammatory responses by delivering nucleic acids, particularly miRNAs. Studies have revealed significantly elevated levels of miR-27a in plasma EVs from hypertensive patients. Upon uptake by endothelial cells, these EVs target and suppress Mas receptor and eNOS expression, thereby attenuating the vasodilatory effects of angiotensin-(1-7) [Ang-(1-7)] and exacerbating inflammation and tissue damage [27]. These studies reveal EVs' multi-faceted, multi-level regulatory role within the hypertensive inflammatory network. By carrying and delivering inflammatory molecules, adhesion molecules, and regulatory miRNAs, they effectively translate local inflammatory signals into systemic vascular damage, driving the pathological progression of hypertension.

3.3 EVs and Vascular Remodeling

Vascular remodeling constitutes a key pathological basis for hypertension maintenance and target organ damage, with EVs playing a crucial driving role through mediating intercellular communication, regulating VSMC phenotype, and promoting fibroblast activation. First, EVs from different cellular sources directly influence VSMC biological behavior. Studies reveal that epiththelial fibroblast-derived EVs significantly increase ACE levels in spontaneously hypertensive rats (SHR), catalyzing AngII production via ACE transfer to activate AT1 receptors and promote VSMC migration and proliferation [28-30]. simultaneously enriched with miR-135a-5p and miR-21-3p, which exacerbate VSMC proliferation by targeting FNDC5 and SORBS2, respectively [31-32]. Moreover, EVs-carried miRNAs serve as key regulators of vascular remodeling: Upregulated miR-423-5p and miR-320d in plasma EVs from hypertensive patients induce VSMC transition to a synthetic phenotype by modulating Mybl2, leading to arterial stiffness [28]. Ang II-stimulated endothelial cells release EVs rich in miR-92a, which directly downregulates VSMC contraction marker genes [33]. Notably, miR-155-5p exerts a protective role in vascular remodeling: WKY rat adventitial fibroblast EVs suppress ACE expression via miR-155-5p targeting, mitigating VSMC migration and oxidative stress, while knocking down this miRNA abolishes the protective effect [30, 34]. Furthermore, EVs participate in vascular fibrosis: endothelial cell EVs induce an inflammatory VSMC phenotype via HMGB proteins, promoting VCAM-1 expression [35]; perivascular adipose tissue-derived EVs suppress PGC-1α through miR-221-3p, leading to downregulation of VSMC contraction genes and adventitial remodeling [36]. Thus, under hypertensive stress, vascular wall cells form complex regulatory networks by releasing EVs carrying specific "cargo" cross-talking to jointly drive VSMC phenotypic conversion, proliferation, migration, and extracellular matrix deposition, ultimately leading to irreversible vascular structural remodeling and functional deterioration.

4. Specific Roles of Extracellular Vesicles in Hypertension-Induced Target Organ Damage

4.1 Cardiovascular Damage

Hypertension-induced cardiovascular damage primarily encompasses left ventricular hypertrophy (LVH), atherosclerosis (AS), aortic valve stenosis, and heart failure. EVs profoundly engage in these pathological processes through intercellular signaling between cardiac and vascular cells. In atherosclerosis, blood flow shear stress and pulsatile pressure under hypertensive conditions damage arterial endothelium. Activated endothelial cells and platelets release microvesicles carrying adhesion molecules (e. g., P-selectin, vWF) and inflammatory factors (e. g., IL-1β, IL-6), thereby mediating monocyte recruitment and promoting their differentiation into macrophages. These macrophages phagocytose oxidized low-density lipoprotein (ox-LDL) to form foam cells, facilitating lipid streaking—an early pathological manifestation of AS [37]. Further studies reveal that lipopolysaccharide (LPS)-stimulated endothelial cell-derived EVs promote vascular smooth muscle cell (VSMC) proliferation and migration via miR-27a-3p and miR-126-5p [38]; LPS-treated macrophage EVs, rich in proinflammatory cytokines, significantly enhance VSMC calcification under calcification conditions by upregulating osteogenic markers and downregulating contractile markers [39]. Furthermore, Kalirin protein levels in circulating EVs from hypertensive patients with albuminuria were significantly elevated and positively correlated with the endothelial dysfunction marker E-selectin (R^2=0.59, p=5.96E-11), suggesting its potential as a biomarker for cardiovascular risk [40]. EVs also play a crucial role in myocardial hypertrophy and heart failure. Pressure or volume overload induces the release of EVs from cardiomyocytes, fibroblasts, and endothelial cells. EVs derived from activated fibroblasts deliver fibrotic factors like TGF-β to cardiac endothelial cells, exacerbating myocardial interstitial fibrosis and leading to increased cardiac stiffness and diastolic dysfunction [41]. During the heart failure stage, circulating EV levels and their cargo undergo significant alterations. Studies reveal elevated levels of immune cell-derived EVs in chronic heart failure (CHF) patients, correlated with NYHA functional classification and activated in both preserved and reduced ejection fraction heart failure [42]. Notably, EVs derived from healthy adult cardiomyocytes carry anti-fibrotic miRNAs (Let-7i-5p, miR-21-5p, etc.), which mitigate cardiac fibrosis by inhibiting the TGFβ signaling pathway [43], offering novel therapeutic insights. These studies indicate that EVs not only participate in the initial stages of cardiovascular structural remodeling induced by hypertension but also play a persistent role as a key driver propelling disease progression toward end-stage conditions such as heart failure.

4.2 Renal Damage

The kidneys serve as both blood pressure regulatory organs and primary targets for hypertensive injury. Extracellular vesicles (EVs) play a dual role in hypertensive nephropathy: they serve as injury indicators and act as key mediators driving fibrosis. First, urinary EVs (uEVs) provide rich information for non-invasive monitoring and are emerging as a critical tool for ultra-early diagnosis of hypertensive kidney injury. Recent proteomics studies reveal that in hypertensive patients with normal albumin-to-creatinine ratio (ACR) (10-30 mg/g), uEVs already harbor 43 differentially expressed proteins, including significantly reduced levels of long-chain fatty acid transporter SLC27A2 and apical membrane protein AMN. This decline synchronizes with downregulated expression in tubular tissues, indicating that altered uEV protein profiles may precede microalbuminuria onset, offering a clinical warning window for injury [44]. Furthermore, studies indicate that uEV-derived miR-200a-3p is significantly elevated in hypertensive kidney injury patients (AUC=0.75). By targeting SIRT1, it induces damage to renal tubular epithelial cells. Inhibiting this miRNA mitigates pathological changes, suggesting uEVs-miRNA possesses dual value as both a diagnostic biomarker and therapeutic target [45]. Second, new evidence reinforces EVs' core mediating role in driving renal fibrosis. Plasma exosomal RNA-seq analysis in hypertensive patients with renal injury revealed that 55% of 31 differentially expressed miRNAs were pro-fibrotic FibromiRs, while 26% belonged to oxidative stress-related RedoximiRs. Among these, miR-21-5p was upregulated 3. 83-fold and positively correlated with urinary albumin excretion rate (r=0.64), achieving an AUC of 0.82 for diagnosing kidney injury. This molecule, induced by TGF-β1 and simultaneously regulating fibrosis and oxidative stress pathways, was defined as a "RedoxifibromiR"—serving both as a circulating biomarker and a functional driver of pathological progression [46]. Studies confirm that exosomes secreted by damaged tubular epithelial cells carry miR-21. Upon uptake by mesenchymal fibroblasts, miR-21 inhibits PTEN to activate the PI3K/Akt pathway, directly promoting fibroblast activation and collagen deposition. Targeted intervention of this pathway significantly alleviates fibrosis [47].

4.3 Pulmonary Arterial Hypertension

EVs play a dual role in the pathophysiology of pulmonary arterial hypertension (PAH), serving as both biomarkers and pathological mediators driving vascular remodeling. First, the circulating EV profile reflects the clinical phenotype of PAH. Tonello et al. 's clinical cohort study on systemic sclerosis (SSc)-associated PAH revealed markedly elevated levels of platelet- and T-cell-derived EVs in the circulation of SSc patients with PAH, suggesting that lymphocyte-derived EVs could serve as early warning markers and risk stratification tools for PAH complications [48]. Second, EVs mediate pathological communication between pulmonary vascular wall cells. Mechanistic studies indicate that under platelet-derived growth factor (PDGF) stimulation, PASMCs secrete EVs carrying miR-409-5p. When these EVs are internalized by pulmonary arterial endothelial cells (PAECs), they reduce nitric oxide synthesis and impair PAEC function, thereby paradoxically promoting abnormal PASMC proliferation and forming a vicious positive feedback loop [19]. This finding confirms the active pathogenic role of PASMC-derived EVs in pulmonary vascular remodeling. Furthermore, EVs exhibit both pro-inflammatory and pro-thrombotic properties. Mendoza-Zambrano et al. 's studies using chronic thromboembolic pulmonary hypertension (CTEPH) animal models and clinical cohorts demonstrated that leukocyte-derived EVs (CD45+) and endothelial-derived EVs sustain pulmonary vascular remodeling and in situ microthrombus formation by persistently activating inflammatory signaling pathways [49]. Thus, EVs form a vicious cycle in the pathological progression of PAH: vascular injury and inflammation drive EV release, which in turn exacerbates vascular remodeling, inflammation, and thrombosis, progressively worsening patient outcomes.

5. Potential of EVs as Biomarkers for Hypertension and Target Organ Damage

5.1 Diagnostic Value of Vesicle Contents

The protein profile of EVs directly reflects cell type and state. For instance, endothelial cell-derived EVs expressing $CD31^+$ and $CD144^+$ are significantly elevated in hypertensive patients, typically indicating endothelial injury and dysfunction [50]. Urinary EV chymotrypsin activity in hypertensive patients is markedly higher than in those with well-controlled blood pressure, serving as an objective indicator for distinguishing blood pressure control status [51]. At the nucleic acid level, plasma EV levels of miR-423-5p and miR-320d correlate positively with mean arterial pressure [28]. Urinary EV levels of miR-146a negatively correlate with albuminuria, with low levels indicating more severe renal injury [52-53]. Additionally, urinary EVs from patients with primary aldosteronism exhibit distinct protein expression patterns (e. g., AQP1, CD63) compared to those with primary hypertension, aiding in etiological differentiation [54].

5.2 Application Prospects of Multi-Omics Analysis

Single biomolecules struggle to comprehensively reflect complex disease states. Integrating multi-omics data from genomics, proteomics, and other fields enables systematic analysis of EVs. This approach reveals regulatory networks of EVs in physiological and pathological processes across multiple levels and identifies biomarkers with synergistic diagnostic or prognostic value. Reel et al. performed multi-omics analysis on 307 subjects (primary hypertension, primary aldosteronism, pheochromocytoma/paraganglioma, Cushing's syndrome) using eight machine learning classifiers. The random forest classifier achieved a balanced accuracy of 92% in distinguishing the four diseases (approximately 11% higher than the best single-omics classifier), with an AUC of 0. 95 [55]. Recent studies have utilized plasma miRNA profiles (including hsa-miR-15a-5p and hsa-miR-32-5p) to distinguish pheochromocytoma/Cushing's syndrome from essential hypertension with an AUC of 0. 9 [56], providing new tools for precise classification [57]. Evidence suggests that in-depth "multi-omics" analysis of EVs is now feasible, enabling the identification of molecular combinations with the highest diagnostic and predictive value for precise diagnosis and treatment of hypertension and its complications.

5.3 Diagnostic Value for Endocrine Hypertension

Unlike essential hypertension, endocrine hypertension (e.g., primary aldosteronism, pheochromocytoma) has identifiable causes and distinct treatment strategies. Studies reveal significant differences in EVs levels and surface marker profiles among patients with distinct endocrine hypertension subtypes [58-59]. For instance, $CD3^+$ T cell-derived EVs are markedly elevated in chronic thromboembolic pulmonary hypertension [50, 60]. Future multicenter cohort studies may establish "fingerprint" profiles composed of specific miRNAs and proteins, enabling rapid etiological classification and precision treatment.

6. Conclusion

As core mediators of intercellular communication, extracellular vesicles are deeply integrated into the pathophysiological network of hypertension and its target organ damage. From the initiation and maintenance of hypertension to the progression of target organ injury, EVs profoundly engage in core pathological processes—including endothelial dysfunction, chronic inflammation, vascular remodeling, and fibrosis—through their precise intercellular signaling functions. They serve as a "barometer" of disease status, with their levels and molecular cargo reflecting the extent of damage in organs like blood vessels and kidneys. Simultaneously, they act as a 'catalyst' for disease progression, amplifying and propagating local injury signals by transmitting pathogenic signaling molecules, thereby driving a vicious cycle of pathological processes. This systematic analysis of EVs' roles in hypertension and target organ damage reveals their pivotal position as an "information hub" connecting diverse cells and organs. This research aims to provide a novel molecular perspective for understanding hypertension and its complications, thereby further exploring their diagnostic value and therapeutic potential.

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