Review | Open Access

Extracellular Vesicles and Circulating Nucleic Acids

Yang *et al. Extracell Vesicles Circ Nucleic Acids.* 2026;7:2114-38 **DOI:**10.20517/evcna.2026.164

Regulatory mechanisms and targeted therapeutic strategies of extracellular vesicles in aging-related diseases

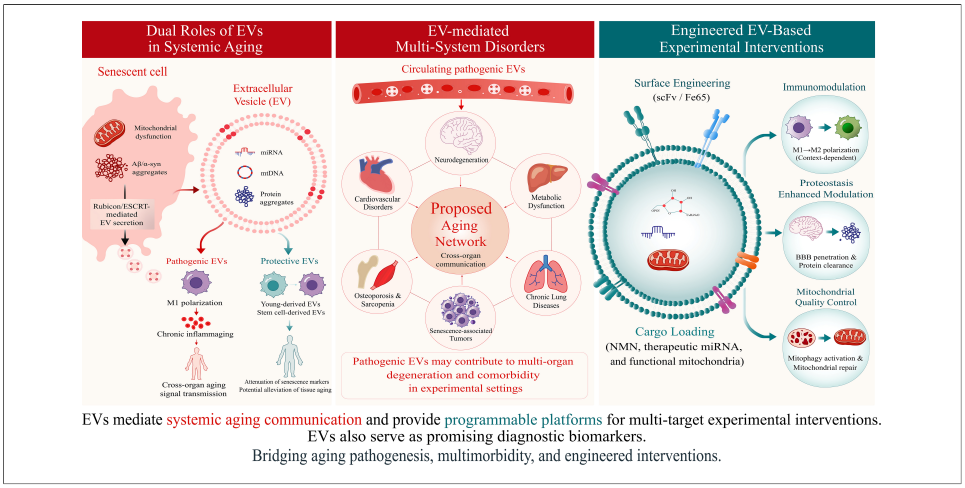
Jing Yang[1,#], Wanyao He[1,#], Ruiqi Wu[1,#], Heyu Zeng[1], Zhongyuan Li[1], Na Zhang[1], Mingqiang Lai[2], Wenchong Zou[1]

Keywords:
Extracellular vesicles, age-related diseases, intercellular communication, targeted therapy, diagnostic biomarkers

Citation: Yang J, He W, Wu R, Zeng H, Li Z, Zhang N, Lai M, Zou W. Regulatory mechanisms and targeted therapeutic strategies of extracellular vesicles in aging-related diseases. *Extracell Vesicles Circ Nucleic Acids.* 2026;7:2114-38. https://dx.doi.org/10.20517/evcna.2026.164

Received: 23 Jul 2026
First Decision: 16 Oct 2026
Revised: 5 Nov 2026
Accepted: 13 Nov 2026
Published: 23 Nov 2026

Academic Editors:
Yoke Peng Loh, Shenglin Huang
Copy Editor:
Ting-Ting Hu
Production Editor:
Ting-Ting Hu



EVs mediate systemic aging communication and provide programmable platforms for multi-target experimental interventions.
EVs also serve as promising diagnostic biomarkers.
Bridging aging pathogenesis, multimorbidity, and engineered interventions.

Abstract

Cellular senescence represents one of the core hallmarks of aging and contributes to the development and progression of multiple age-related disorders. Senescent cells remodel local and systemic microenvironments via the senescence-associated secretory phenotype (SASP). Extracellular vesicles (EVs) can function as components of the SASP and as mediators of intercellular communication. Carrying bioactive cargoes, including proteins, microRNAs (miRNAs), mitochondrial DNA, and mitochondrial components, EVs convey biological signals between senescent and normal cells, potentially influencing senescence-associated phenotypes in recipient cells. EVs exert context-dependent effects in aging: senescence-associated EVs can transmit inflammatory and degenerative signals, whereas EVs derived from young donors or stem cells have reduced senescence-associated phenotypes and supported tissue repair in experimental models. These contrasting activities may influence the aging microenvironment and the progression of age-related

[1]Zhejiang Key Laboratory of Medical Epigenetics, Department of Pathology and Pathophysiology, School of Basic Medical Sciences, Hangzhou Normal University, Hangzhou 310000, Zhejiang, China.
[2]Department of Physiology, School of Basic Medical Sciences, Southern Medical University, Guangzhou 510515, Guangdong, China.
[#]These authors contributed equally to this work and are co-first authors.

Correspondence to: Dr. Wenchong Zou (Lead Contact), Zhejiang Key Laboratory of Medical Epigenetics, Department of Pathology and Pathophysiology, School of Basic Medical Sciences, Hangzhou Normal University, Hangzhou 310000, Zhejiang, China. E-mail: zouwc1024@hznu.edu.cn; Dr. Mingqiang Lai, Department of Physiology, School of Basic Medical Sciences, Southern Medical University, Guangzhou 510515, Guangdong, China. E-mail: lmq520@smu.edu.cn

diseases. This narrative review examines the molecular mechanisms of EVs in aging and summarizes their biological functions as well as diagnostic and therapeutic potential in age-related conditions, covering neurodegeneration, cardiovascular diseases, metabolic disorders, osteoarticular degenerative diseases, respiratory diseases, and cancer.

INTRODUCTION

Aging involves progressive changes in tissue and organ function and is a major risk factor for a wide range of chronic diseases[1]. Aging and age-related disorders involve a set of interconnected, evolutionarily conserved hallmarks, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication[2]. Among these, disrupted intercellular communication, particularly the senescence-associated secretory phenotype (SASP), may amplify age-related processes, transmitting aging-related signals locally and systemically, remodeling the aging microenvironment, and accelerating the initiation and progression of age-related pathologies[3,4].

Extracellular vesicles (EVs) are heterogeneous, lipid bilayer-enclosed particles released by cells. They mediate cell-to-cell and organ-to-organ communication relevant to the aging microenvironment[5]. EV preparations can contain proteins, lipids, nucleic acids, and mitochondrial components[6]. This review focuses on the cargo classes discussed in the disease-specific evidence, particularly microRNAs (miRNAs), proteins, and mitochondrial DNA (mtDNA), rather than providing a comprehensive account of circulating or genomic DNA. Whether a detected component is enclosed within vesicles, associated with their surface, or co-isolated requires experimental assessment[7].

EV populations are heterogeneous: their cargo and biological effects vary with cellular origin, donor-cell state, and the fraction isolated. Small and large EVs are operational size categories, whereas the designation "exosome" implies endosomal biogenesis that cannot be established from size or common EV markers alone. Similarly, EVs recovered from blood or other biofluids cannot be assigned to a specific releasing cell without additional evidence. Differential centrifugation, precipitation, size-exclusion chromatography, and affinity capture enrich different particle populations and may retain non-vesicular components. Consequently, EV source attribution, subtype terminology, and isolation procedures require consideration when comparing functional and biomarker findings across diseases [Table 1]. Wallis *et al.* demonstrated co-isolation of soluble SASP factors after differential ultracentrifugation and improved separation using size-exclusion chromatography in senescent-cell models[20]. This illustrates why a vesicular mechanism cannot be inferred from an enriched pellet alone. The Minimal Information for Studies of Extracellular Vesicles (MISEV2023) reporting framework offers practical criteria for describing EV separation, characterization, and functional attribution[7].

During aging, the biogenesis, cargo sorting, secretion, and functional properties of EVs can undergo substantial changes. Senescent cells may increase EV release as a route for exporting cellular components and transmitting senescence-associated signals, while senescence-associated EVs (SA-EVs) can transfer cargoes implicated in genomic instability, mitochondrial dysfunction, impaired proteostasis, chronic inflammation, and stem cell dysfunction in experimental recipient-cell systems, thus disrupting cellular homeostasis.

Conversely, EVs derived from young donors or stem cells have shown potential protective or regenerative effects in experimental models, including reduced senescence-associated phenotypes, oxidative stress, and inflammation, as well as improved mitochondrial function and tissue repair[21-23]. EVs may therefore contribute to aging-associated pathology or support repair, depending on their origin and cargo, making them candidates for further therapeutic investigation.

Table 1. Representative studies illustrating EV heterogeneity, cellular origin, isolation approaches, and interpretative limitations in aging-related diseases

Disease/Ref.	EV source and subtype	Isolation/preparation	Major finding	Interpretive limitation
AD[8]	Urinary GM1-binding EVs; cell of origin unknown	CTB capture; single-EV protein profiling	Disease-associated EV surface signatures	Captured subpopulation may not represent all urinary EVs
Atherosclerosis[9]	Steatotic hepatocyte sEVs; serum sEVs also tested	Differential ultracentrifugation; density-gradient characterization	miR-30a-3p reduces ABCA1-mediated cholesterol efflux	Experimental hepatic origin cannot automatically be assigned to circulating EVs
Atherosclerosis[10]	M2 macrophage EVs fused with platelet-membrane vesicles	Ultracentrifugation; membrane extrusion/fusion	Improved plaque targeting and reduced lesions in mice	Engineered hybrids cannot be equated with native EV populations
Obesity/T2DM[11]	Visceral/subcutaneous adipose-explant EVs; plasma EVs	Differential ultracentrifugation; proteomics/ELISA	Depot-dependent cargo; TGFBI and Mimecan associations	Whole adipose explants contain several cell types
Sarcopenia[12]	Plasma sEV-enriched fraction; cell origin unknown	Size-exclusion chromatography; ultrafiltration	PF4 and C1R candidate biomarkers	Cellular origin unresolved; co-isolated proteins may contribute
Osteoporosis[13]	Hepatocyte sEVs in models; human plasma sEVs	Cell EV ultracentrifugation; plasma EV enrichment	SIRT2-LRG1 axis inhibits osteoclast differentiation	Cell-defined mechanism and human plasma association are different evidence
Osteoporosis[14]	Osteoclast exosome-enriched fractions	Differential centrifugation/ultracentrifugation; reagent-based isolation for some assays	miR-214 transfer suppresses osteoblast activity	Particle size and markers alone do not prove endosomal origin
Osteoporosis[15]	Serum microvesicle-enriched fraction; cell origin unknown	Differential centrifugation; 10,000 × *g* collection	Profilin-1 candidate marker	Sedimentation fraction does not uniquely define biogenesis
COPD[16]	16HBE epithelial-cell EVs; patient plasma EVs	Differential centrifugation at 16,000 × *g*	miR-191-5p inflammatory effects; DLCO association	Cell identity established *in vitro*, not for circulating EVs
ILD[17]	Serum PS-positive small EVs	MagCapture phosphatidylserine-affinity enrichment	EV-associated SFTPB linked to disease progression	Results apply to captured PS-positive EV population
B-cell malignancy[18]	Engineered HEK293T CD19/IL-12 EVs	UVB-stimulated production; filtration; 14,000 × *g*	Enhanced CAR-T function in preclinical models	Engineering/production may change cargo; clinical efficacy unproven
B-cell lymphoma[19]	NK-cell exosome- and microvesicle-enriched fractions	Differential centrifugation (10,000/100,000 × *g*)	Combined fractions exhibited antitumor effects	Sedimentation fractions do not definitively establish biogenesis

Studies were selected to illustrate methodological contrasts among examples discussed in the text, without systematic sampling or numerical quality scoring. For interpretation using MISEV2023[7], relevant reporting domains include the source and pre-analytical conditions, separation procedures, particle and protein characterization, assessment of co-isolated material, and functional controls distinguishing vesicular from non-vesicular effects. These domains identify questions for critical reading; they do not imply that every listed study has undergone a complete compliance audit. EV terminology reflects the operational designations and isolation procedures reported in the original studies. Enrichment by particle size, sedimentation, or affinity capture does not independently establish vesicle biogenesis or cellular origin. The descriptions of unassigned cellular origin refer to the analyzed biofluid fraction, not to producer cells used in separate experiments. AD: Alzheimer's disease; ABCA1: ATP-binding cassette transporter A1; C1R: complement C1r subcomponent; CAR-T: chimeric antigen receptor T cell; COPD: chronic obstructive pulmonary disease; CTB: cholera toxin B; DLCO: diffusing capacity for carbon monoxide; EV: extracellular vesicle; IL-12: interleukin-12; ILD: interstitial lung disease; LRG1: leucine-rich alpha-2 glycoprotein 1; NK: natural killer; PF4: platelet factor 4; PS: phosphatidylserine; sEV: small extracellular vesicle; SFTPB: surfactant protein B; SIRT2: sirtuin 2; T2DM: type 2 diabetes mellitus; TGFBI: transforming growth factor beta-induced protein; 16HBE: 16HBE human bronchial epithelial cell line.

This review focuses on the roles of EVs in the aging microenvironment and age-related diseases, as well as their value as biomarkers of pathological aging states and as therapeutic agents. Previous reviews have described EV-mediated aging-associated communication, disease mechanisms, and therapeutic opportunities[5,24,25]. This review extends those accounts by comparing EV source attribution, isolation approaches, validation and interpretative limits across disease-specific biomarker studies [Tables 1 and 2], and by organizing candidate therapeutic strategies around interconnected inflammation, proteostasis and mitochondrial pathways.

Relevant literature for this narrative review was identified through PubMed searches focused on extracellular vesicles, aging, cellular senescence, and the age-related diseases discussed here. Studies were considered according to their relevance to EV sources and cargo, disease mechanisms, biomarker applications, and therapeutic potential. In evaluating the evidence, we considered study design, EV isolation and characterization, cohort size, and validation where reported, while also drawing on relevant foundational and methodological literature. Literature selection was narrative rather than based on a formal systematic screening protocol.

ROLES OF EXTRACELLULAR VESICLES IN THE AGING MICROENVIRONMENT

Quantitative and qualitative alterations in EV biogenesis during aging

In the context of aging, the quantity and cargo composition of secreted EVs can change in ways that contribute to remodeling of the aging microenvironment.

Senescent cells may increase EV secretion through several regulatory pathways. Rubicon, a negative regulator of autophagy, has been reported to increase during aging. Rubicon recruits WIPI2d to endosomes, where WIPI2d interacts with endosomal sorting complexes required for transport (ESCRT) components involved in intraluminal vesicle formation, thereby promoting multivesicular body (MVB) formation and exosome release[32]. Impairment of the autophagy-lysosomal system can also reduce the clearance of damaged proteins and organelles; cells under autophagic stress can activate compensatory secretory pathways[33].

Changes in EV cargo composition are also important. In non-senescent cells, regulated EV cargo sorting supports physiological intercellular signaling. In senescent cells, EV cargo profiles can change, including the release of EV-associated miRNAs implicated in paracrine signaling[34]. EV-associated mtDNA is detectable in human plasma, but its abundance was reported to decrease with age in the adult cohort studied[35]. Thus, aging-related changes in EV cargo should not be assumed to involve a uniform increase in potentially harmful components.

Small extracellular vesicles (sEVs) released by senescent cells can induce paracrine senescence in experimental recipient-cell systems, with EV-associated interferon-induced transmembrane protein 3 (IFITM3) contributing to this effect[36]. However, the quantitative contribution of sEVs to senescence propagation under physiological aging conditions, particularly relative to soluble SASP factors, remains unclear. Thus, "contagious senescence" should be regarded as a context-dependent working model rather than an established mechanism of self-amplifying systemic aging.

Pathological remodeling of the local microenvironment by EVs

The quantitative and qualitative alterations in EV production described above do not remain confined to the secretory cell. When released into the local tissue microenvironment, these EVs may contribute to microenvironmental remodeling, including changes in tissue-resident immune cells such as macrophages. EV-associated miR-30b-5p can activate macrophages through the sirtuin 1 (SIRT1)/nuclear factor kappa B (NF-κB) pathway[34]. Separately, NLR family pyrin domain containing 3 (NLRP3)-dependent macrophage-senescent-cell crosstalk has been implicated in inflammatory tissue remodeling[37], and mitochondrial danger signals can activate NLRP3 in experimental systems[38,39]. EV-associated macrophage signaling may contribute to persistent low-grade inflammation during aging[34,40].

EVs may contribute to local extracellular matrix (ECM) remodeling. For example, vesicle-associated membrane type 1 matrix metalloproteinase (MT1-MMP) can support matrix degradation in experimental systems[41]. More broadly, EV-associated signals can alter recipient-cell responses[42], but these findings do not establish that pathological EVs globally overwhelm physiological communication during aging.

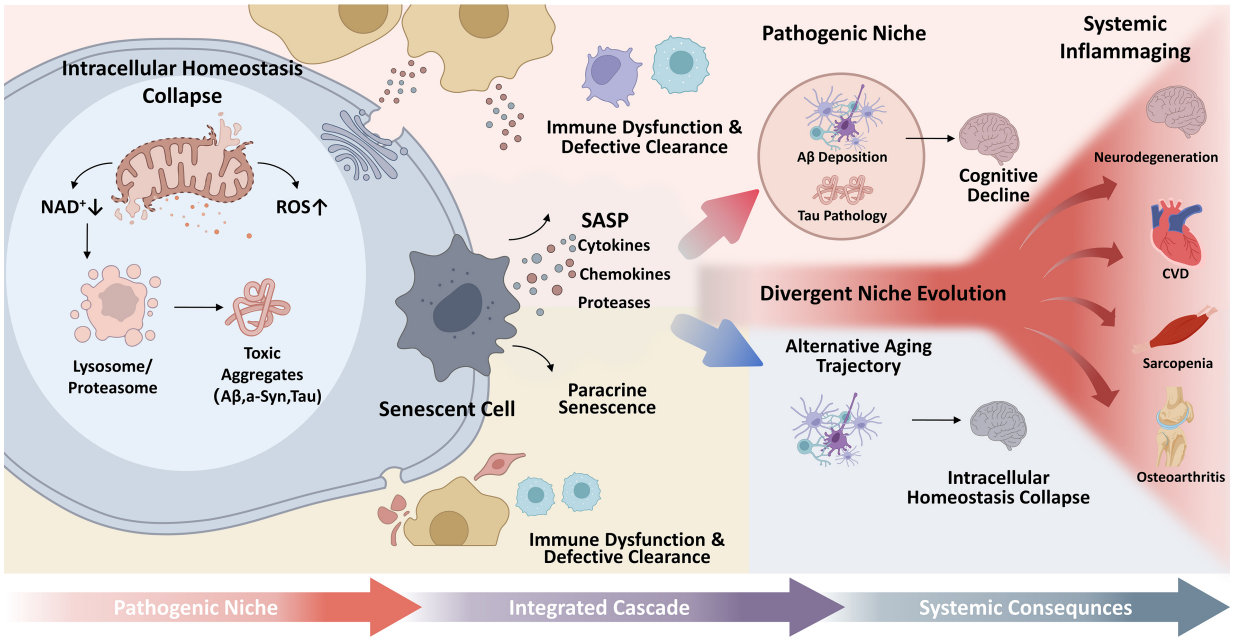


Figure 1. EV-associated remodeling of the aging microenvironment. Age-related proteostatic and mitochondrial stress, senescence-associated secretory activity, and altered EV signaling can reshape local tissue environments. EV cargo transfer contributes to paracrine senescence and may influence inflammatory signaling, extracellular matrix remodeling, and inter-organ communication[24,25,33,34,36,41,44,45]. Together, these processes connect impaired cellular homeostasis with diverse tissue-level consequences of aging. The labels "pathogenic niche," "divergent niche evolution," "alternative aging trajectory," "integrated cascade," and "systemic inflammaging" denote the conceptual progression from local senescence-associated signaling to heterogeneous tissue and systemic inflammatory outcomes, rather than separate validated EV pathways. Local niche remodeling corresponds to Section "Pathological remodeling of the local microenvironment by EVs", and the proposed systemic connections correspond to Section "Circulating EVs and the formation of cross-organ aging networks". EV: Extracellular vesicle; SASP: senescence-associated secretory phenotype; ROS: reactive oxygen species; NAD+: nicotinamide adenine dinucleotide; Aβ: amyloid-beta; α-syn: alpha-synuclein; Tau: microtubule-associated protein tau; CVD: cardiovascular disease.

Disrupted intercellular signaling may also affect tissue regeneration. Stem cell self-renewal and lineage-specific differentiation depend on appropriate signaling inputs from the microenvironment. A functionally disrupted microenvironment not only fails to supply normal regenerative signals but also directly interferes with stem cell fate decisions through pathological EVs, inducing premature senescence or aberrant differentiation and potentially impairing tissue repair capacity[24,43].

Circulating EVs and the formation of cross-organ aging networks

EV-associated signaling may extend beyond the local tissue microenvironment. When pathological EVs breach tissue barriers and enter the systemic circulation, their sphere of influence expands from the local microenvironment to the entire organism, potentially contributing to cross-organ signaling. Such signaling provides one possible mechanism linking pathological changes across organs during aging.

Circulating EVs may carry molecular features associated with the state of their releasing tissues and transmit signals to distant sites[25]. For instance, hepatocyte-derived small EVs in hepatic steatosis can inhibit macrophage cholesterol efflux and aggravate atherosclerosis in experimental systems[9]; EVs released from damaged skeletal muscle can act on the kidney via the circulation, mediating cross-organ injury along the muscle-kidney axis[44]. These findings suggest that organ-specific alterations may have consequences beyond the tissue in which they originate.

These inter-organ interactions provide a rationale for the conceptual trajectories in Figure 1, from local pathogenic niches to divergent tissue responses and integrated systemic inflammatory signaling. This framework may help interpret multimorbidity without assuming that all organs share the same EV-dependent trajectory.

Circulating EVs can also exert protective effects in experimental aging models. Small EVs isolated from young plasma improved mitochondrial energy metabolism and age-related functional outcomes in mice[21]. These results support investigation of circulating EV interventions, but do not establish that EVs from all young donors or stem-cell sources reverse systemic aging. The relative contributions of harmful and protective EV populations remain to be defined [Figure 1].

ROLES OF EXTRACELLULAR VESICLES IN THE MECHANISMS OF AGE-RELATED DISEASES

As core mediators of intercellular and inter-organ communication within the aging microenvironment, EVs contribute to intercellular signaling relevant to the initiation and progression of multiple age-related diseases. By transporting miRNAs, proteins, lipids, and other cargoes, EVs can influence pathological mechanisms across neurological, cardiovascular, metabolic, skeletal, respiratory, and oncological systems. These six categories illustrate that EVs may contribute to disease-related signaling while also being investigated as therapeutic delivery systems. Although EV cargoes and recipient cells vary across organs, recurring themes include pathological signal propagation and microenvironmental remodeling.

Neurodegenerative diseases

Aging increases the risk of Alzheimer's disease (AD) and Parkinson's disease (PD), in part through impaired brain bioenergetics and inflammation[46]. Their characteristic protein pathologies include amyloid-beta (Aβ) plaques and tau tangles in AD and alpha-synuclein (α-syn)-containing Lewy bodies in PD[47,48]. EVs have been implicated in the intercellular transfer and seeding of these proteins[49]. Cryo-electron tomography (Cryo-ET) of brain-derived EVs from AD tissue revealed tau filaments tethered within vesicles[50]. This structural observation concerns tau and should not be generalized to all pathogenic EV-associated proteins.

EV biomarker research is expanding from single-analyte detection to multiparameter profiling [Table 2]. Exploratory studies have identified disease-associated urinary EV surface-protein signatures and metabolic differences in post-mortem brain tissue-derived EVs[8,26]. However, these findings do not establish a validated method for early AD diagnosis. Differences in study populations, EV enrichment methods, and validation strategies limit direct comparison of diagnostic performance and clinical translation.

Non-neuronal EVs have been implicated in neural injury. Astrocyte-derived EVs (A-EVs) directly induce neurovascular unit damage and synaptic loss by carrying pro-inflammatory miRNAs or upregulating aquaporin-4 (AQP4)[51,52]. EV-associated signaling along the gut-brain axis has also attracted research interest. Outer membrane vesicles (OMVs) released by gut microbiota can cross biological barriers to reach the central nervous system (CNS), activate glial cells, and exacerbate Aβ deposition, suggesting a route for gut-associated inflammatory signaling to affect the brain[53]. Together, these findings suggest that EV-mediated intercellular communication may complement local protein aggregation mechanisms in neurodegenerative disease. In this framework, the gut microbiome, peripheral immune system, and CNS exist in a continuous dialogue facilitated by EVs, although the contribution of this communication to disease progression remains under investigation. Peripheral EVs may provide accessible clues to CNS-associated pathology, but their performance relative to cerebrospinal fluid (CSF) biomarkers remains uncertain. Therapeutic studies must distinguish effects on intercellular signaling from effects on intracellular pathology.

Cardiovascular diseases

Aging is a major risk factor for cardiovascular disease (CVD) and is associated with progressive changes in cardiac and vascular function.

In atherosclerosis, EVs mediate phenotypic switching of vascular wall cells and ECM remodeling. For instance, senescent vascular smooth muscle cells (VSMCs) upregulate SOX9 to drive EV secretion, altering ECM stiffness and reinforcing senescence[54]. Moreover, EVs mediate cross-organ pathological

Table 2. Extracellular vesicle biomarkers for Alzheimer's and Parkinson's diseases: cohorts, diagnostic performance and limitations

Study	EV source and cohorts	EV enrichment and analysis	Candidate biomarker(s)	Discrimination and diagnostic performance	Validation and limitations
Hernandez *et al.* (2025)[26] AD	Post-mortem temporal cortex and tissue-derived EVs; 15 AD and 10 controls (*n* = 25), based on the reported cohort table	Tissue digestion, differential centrifugation, size-exclusion chromatography and ultracentrifugation; NTA, Western blot and cryo-EM; untargeted UHPLC-Q-ToF-MS metabolomics	Twelve discriminating MS features, including NAA fragments, GSSG, GABA, creatine, isoleucine/leucine, tryptophan, phenylalanine, and two unidentified features	Partial least squares discriminant analysis (PLS-DA) group discrimination: R^2Y = 0.906; Q^2 = 0.383. Diagnostic accuracy: NR	Internal PLS-DA assessment; no independent clinical validation. Small post-mortem cohort; applicability to biofluid-based or early diagnosis remains unestablished
Cai Y *et al.* (2024)[8] AD	Urinary EVs; single-center cohort of 18 AD and 20 cognitively normal controls (*n* = 38)	Cholera toxin B-mediated capture of GM1-bearing EVs; single-EV surface profiling by PBA with antibody-DNA probes and sequencing; random-forest classification	PLAU, ITGAX and ANXA1 in the PCDHA1-positive urinary EV subpopulation	Internal test AUC = 0.875	Internal testing using generated pseudo-samples; no independent participant cohort. Participant-level separation of training and test data was not specified. Small single-center cohort; cellular origin remains uncertain
Cai H *et al.* (2022)[27] AD	Plasma EVs. Discovery cohort: *n* = 40 (20 AD, 20 controls). Independent protein-validation cohort: *n* = 114 (58 AD, 56 controls). Total: *n* = 154 (78 AD, 76 controls)	Ultracentrifugation; TEM, Western blot, and EV-marker ELISA; label-free LC-MS/MS discovery followed by PRM protein validation	Six-protein panel: A0A0G2JRQ6, C1QC, C9, GP1BB, RSU1 and ADAM10	AUC = 0.978 in cohort 2	Protein differences confirmed in an independent cohort; the final panel was developed and assessed in that same cohort without a separate model test set. Cross-sectional design; MCI and longitudinal progression were not evaluated
Wu *et al.* (2025)[28] ADD and PD	Plasma; *n* = 40, comprising 10 ADD, 10 PDD, 10 PDCN and 10 HCN participants	Mag-Net strong anion-exchange magnetic-bead enrichment of membrane particles, protein aggregation capture, and on-bead digestion; DIA LC-MS/MS	Proteomic classifier; 204 differential proteins identified for ADD *vs.* the remaining groups	ADD *vs.* PDD + PDCN + HCN: cross-validated AUC = 0.98 ± 0.06 (SD)	Ten repetitions of five-fold stratified cross-validation; no independent clinical cohort. Small groups and imperfect age matching; possible unrecognized impairment in HCN. EV specificity and CNS origin of the enriched fraction remain unestablished
Kumar *et al.* (2023)[29] AD and cognitive impairment	Plasma; *n* = 39: CN, 11; MCI, 11; MCI-AD, 6; AD dementia, 11	ExoQuick precipitation followed by anti-L1CAM/streptavidin magnetic-bead enrichment; NTA, EV-marker arrays, immunogold TEM and flow cytometry; qRT-PCR	miR-106b-5p in L1CAM-enriched sEVs	AD dementia *vs.* CN: AUC = 1.000 in the development sample (age-/sex-adjusted model)	No held-out testing, cross-validation, or independent validation reported. Small sample; differences in age, APOE status, and treatment, with limited confounder adjustment. Enrichment markers are not specific to individual brain cell types or the CNS
Kluge *et al.* (2022)[30] PD	Plasma; 30 PD and 50 non-PD controls (*n* = 80)	Polymer precipitation and anti-L1CAM immunoprecipitation; detergent extraction; native dot immunoblotting and six-round α-synuclein seed amplification with ThT fluorescence	Pathological α-synuclein conformers and seeding activity in L1CAM-enriched EVs	Post-amplification immunoblot signals did not overlap between 30 PD patients and 50 controls. Formal diagnostic accuracy estimates: NR	Nonblinded proof-of-concept study without independent validation or an established diagnostic cutoff. Performance in prodromal disease and other synucleinopathies, assay standardization, and exclusive CNS origin require further evaluation

Yan *et al.* (2024)[31] Prodromal PD risk	Serum; total *n* = 576. Derivation: 97 iRBD + 73 HC (*n* = 170). Validation 1: 75 iRBD + 47 HC (*n* = 122). PPMI: 27 iRBD, 20 hyposmic, 146 non-manifest *GBA1* p.N409S carriers, 20 HC, 50 sporadic PD, and 21 *GBA1*-PD (*n* = 284)[a]	Direct immunocapture of L1CAM-positive EVs from 250 µL serum; total α-synuclein and syntenin-1 measured by MSD U-Plex electrochemiluminescence; blinded processing	Total L1CAM-positive EV-associated α-synuclein	iRBD *vs.* HC: derivation AUC 0.85 (95%CI: 0.79-0.91), Se/Sp 0.77/0.82; validation 1 AUC 0.91 (0.86-0.96), Se/Sp 0.87/0.82. PPMI > 80% *vs.* < 5% prodromal probability: AUC 0.80 (0.71-0.89), Se/Sp 0.72/0.78. Pooled high-risk *vs.* current/historic HC: AUC 0.90 (0.87-0.93), Se/Sp 0.81/0.87[b]	Independent cohorts evaluated the Oxford-derived threshold. Cross-sectional design; individual clinical utility and wider population validity remain unestablished. Predominantly White participants; L1CAM-positive EVs may also originate from peripheral nerves; total α-synuclein is not pathology-specific

PLS-DA model statistics and experimental signal separation are not estimates of clinical diagnostic accuracy. Sample sizes denote participants. Values after ± are SDs. [a]PPMI included 284 participants; 263 formed the primary validation group, and 21 *GBA1*-PD participants served as an additional reference group; [b]Sensitivity and specificity depend on the cutoff and comparison: 17.75 pg/mL for the derivation and fixed-threshold iRBD validation; 20.35 pg/mL for PPMI > 80% *vs.* < 5% probability; and 18.54 pg/mL for pooled high-risk *vs.* HC. The last two cutoffs were optimized separately using the Youden index; they do not validate the fixed Oxford cutoff. AD: Alzheimer's disease; ADD: AD dementia; AUC: area under the receiver operating characteristic curve; CI: confidence interval; CN: normal cognition; CNS: central nervous system; cryo-EM: cryo-electron microscopy; DIA: data-independent acquisition; EV: extracellular vesicle; GABA: γ-aminobutyric acid; GSSG: oxidized glutathione; HC: healthy control; HCN: healthy cognitively normal; iRBD: isolated rapid eye movement sleep behavior disorder; LC-MS/MS: liquid chromatography-tandem mass spectrometry; MCI: mild cognitive impairment; MCI-AD: MCI conversion to AD dementia; MS: mass spectrometry; MSD: Meso Scale Discovery; NAA: N-acetylaspartate; NR: not reported for the specified measure; NTA: nanoparticle tracking analysis; PBA: proximity barcoding assay; PD: Parkinson's disease; PDCN: cognitively normal PD; PDD: PD with dementia; PLS-DA: partial least squares discriminant analysis; PPMI: Parkinson's Progression Markers Initiative; PRM: parallel reaction monitoring; qRT-PCR: quantitative reverse-transcription polymerase chain reaction; SD: standard deviation; Se: sensitivity; sEV: small extracellular vesicle; Sp: specificity; TEM: transmission electron microscopy; ThT: thioflavin T; UHPLC-Q-ToF-MS: ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry.

communication: hepatocyte-derived sEVs loaded with miR-30a-3p inhibit macrophage cholesterol efflux, accelerating foam cell formation and plaque progression[9]. Targeting this process, platelet membrane-modified engineered M2 macrophage-derived EVs have shown targeted delivery and reduced plaque progression in experimental models[10].

EVs participate in inflammatory and repair responses following myocardial infarction (MI). During the ischemic injury phase, EVs within the post-ischemic microenvironment can convey inflammatory and mitochondrial-stress signals that contribute to myocardial injury and remodeling[55-59]. During repair, EV-associated miRNAs have been implicated in cardioprotection, angiogenesis, and the regulation of fibrosis[60-65] [Figure 2].

In a clinical study including 13 patients with acute myocardial infarction, 176 with angina pectoris, and 127 controls, circulating plasma miR-133a increased after infarction and correlated with coronary artery stenosis[67]. Importantly, this study did not specifically measure EV-associated miR-133a. In contrast, miR-221/222-enriched adipose-derived stem cell exosomes attenuated particulate matter-exacerbated myocardial ischemia-reperfusion injury by modulating mitophagy and apoptosis in experimental models[68], providing preclinical therapeutic rather than clinical biomarker evidence. Together, these studies distinguish a circulating non-EV miRNA association from an experimental EV intervention. Future therapeutic approaches may benefit from selectively enhancing protective EV activities rather than broadly suppressing EV signaling.

Sex-related differences also warrant consideration in EV-mediated vascular aging. A longitudinal study of 411 women found greater increases in aortic pulse wave velocity during the menopausal transition, although EVs were not assessed[69]. In postmenopausal women, estrogen-based hormone therapy has been associated with differences in exercise-responsive EV- and high-density lipoprotein-associated small RNAs[70].

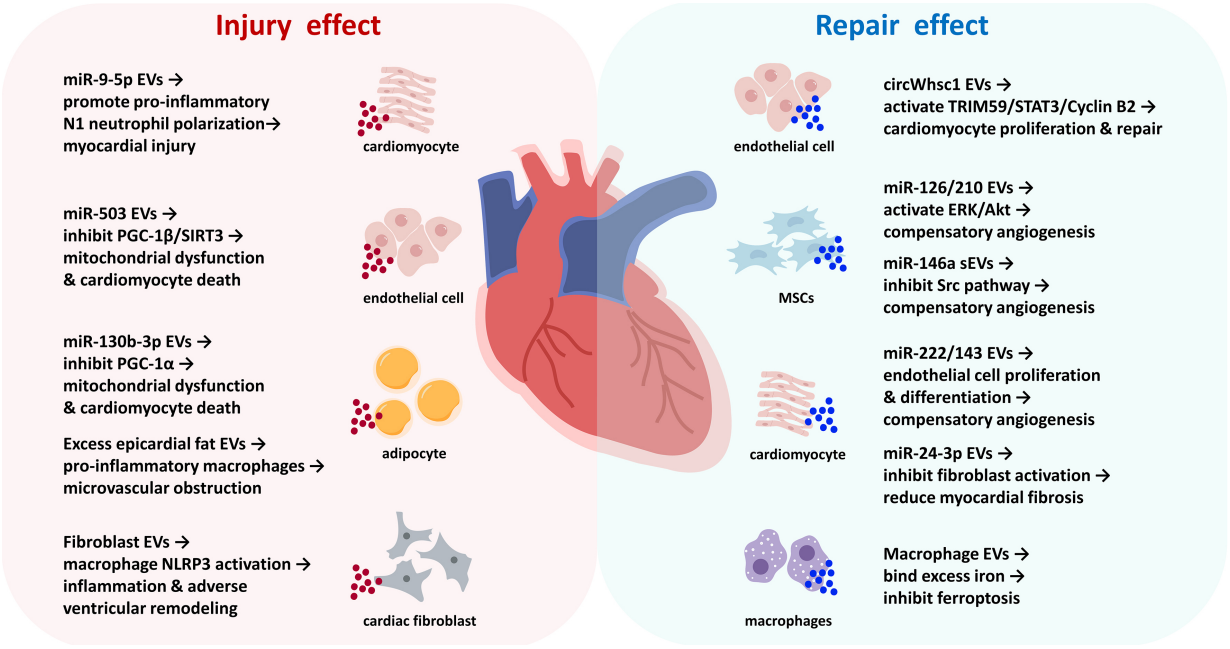


Figure 2. Injury- and repair-associated EV signaling after MI. Injury-associated EVs released by cardiomyocytes, endothelial cells, adipocytes, and cardiac fibroblasts can amplify neutrophil activation, mitochondrial stress, and inflammation in experimental ischemic heart injury. Specifically, endothelial EV-associated miR-503 targets PGC-1β/SIRT3 to induce mitochondrial dysfunction and cardiomyocyte death[57], whereas adipocyte-derived EV-associated miR-130b-3p suppresses PGC-1α and triggers mitochondrial dysfunction and cardiomyocyte apoptosis[55]. Other injury-related EV pathways include cardiomyocyte EV-associated miR-9-5p promoting pro-inflammatory N1 neutrophil polarization[59] and cardiac fibroblast-derived mitochondria-enriched EVs regulating inflammation and adverse ventricular remodeling through the NLRP3 pathway[58]. Epicardial adipose tissue-derived EVs can also contribute to macrophage inflammatory polarization[56]. Repair-associated pathways include endothelial EV-derived *circWhsc1* acting through TRIM59/STAT3/Cyclin B2[64], HIF-1-enhanced endothelial EV miR-126/miR-210 promoting cardiac progenitor-cell survival[62], ischemic cardiomyocyte EV miR-143/miR-222 promoting angiogenic responses[61], cardiomyocyte EV miR-24-3p modulating fibrosis[60], and macrophage EV-mediated iron sequestration[65]. Separately, MSC-derived sEV miR-146a has been reported to reduce Src signaling and improve endothelial angiogenic function in vascular aging and wound-healing models[66]. The cell labels identify EV-releasing cells; recipient cells and downstream effects are specified in the corresponding pathways. These examples come from distinct experimental settings and do not represent one unified post-infarction sequence. EV: Extracellular vesicle; MI: myocardial infarction; miR: microRNA; MSC: mesenchymal stem cell; PGC-1α/β: peroxisome proliferator-activated receptor gamma coactivator-1α/β; SIRT3: sirtuin 3; ERK: extracellular signal-regulated kinase; Akt: protein kinase B; Src: SRC proto-oncogene non-receptor tyrosine kinase; STAT3: signal transducer and activator of transcription 3; TRIM59: tripartite motif-containing protein 59; circWhsc1: circular RNA derived from Whsc1; HIF-1: hypoxia-inducible factor 1; sEV: small EV; NLRP3: NLR family pyrin domain containing 3.

Separately, an exercise-training study in young adults identified sex-dependent changes in circulating EV abundance and miRNA responses[71]. Whether these EV differences contribute directly to sex-specific cardiovascular risk remains to be established.

Metabolic diseases

The contribution of EV biogenesis and cross-organ EV transport to type 2 diabetes mellitus (T2DM) requires disease-specific evidence. RAB31-dependent exosome biogenesis has been demonstrated in a separate mechanistic context[72]; it does not directly establish liver-muscle-adipose EV transfer in T2DM. In hypercholesterolemia models, circulating EV lipid profiles changed in rats, while cholesterol exposure increased EV release and altered the EV proteome in cultured human cardiomyocytes[73]. These results concern the tested lipid-stress models and should not be generalized to all metabolic disease settings.

EVs from diverse sources form a cross-organ communication network that may contribute to T2DM pathophysiology and its complications through organ-to-organ signal transmission [Table 3]. Mechanisms and source-specific evidence are summarized by row in Table 3; associative serum EV findings are distinguished from cell-based causal experiments.

Table 3. EV-related mechanisms and associated evidence in T2DM and its complications

Source and evidence type	Cargo	Recipient or context	Mechanism and evidence	Outcome
Visceral adipose tissue (mature adipocytes)	miR-9-3p	Hippocampal neurons	EV transfer inhibits neuronal BDNF expression	Hippocampal synapse loss and metabolic disorder-related cognitive impairment[74]
Erythrocytes; serum EVs with unassigned cellular origin	Arginase-1	Vascular endothelium	Erythrocyte mechanism[75] is not EV-specific. Serum EV arginase-1 evidence[76] is associative	Endothelial dysfunction; EV origin and causality not established by the association
Fibroblasts under high glucose	Mitochondrial components, including mtDNA	Skin wound tissue	Oxidative stress and mitochondrial injury; reduced collagen deposition and angiogenesis	Impaired diabetic wound healing[77]
Bacteroides fragilis	dsDNA	Macrophages and VSMCs	STING-MEF2D-TRIB1-associated M2 polarization and Serpine1-associated VSMC osteogenic differentiation	Experimental T2DM-associated vascular calcification[78]

Evidence includes vesicle-transfer experiments, a non-EV erythrocyte experiment and a serum EV association; these designs are not interchangeable. M2 denotes an experimental macrophage phenotype and does not imply a uniformly protective effect. EV: Extracellular vesicle; T2DM: type 2 diabetes mellitus; BDNF: brain-derived neurotrophic factor; mtDNA: mitochondrial DNA; dsDNA: double-stranded DNA; VSMC: vascular smooth muscle cell; STING: stimulator of interferon genes; MEF2D: myocyte enhancer factor 2D; TRIB1: tribbles pseudokinase 1; Serpine1: serpin family E member 1, encoding plasminogen activator inhibitor 1.

EV cargoes are being explored as candidate markers of metabolic disease. Camino *et al.*[11] reported elevated circulating EV-associated transforming growth factor beta-induced protein (TGFBI) in obese individuals with a history of type 2 diabetes and increased EV-associated Mimecan in obese individuals without diabetes compared with lean controls (n = 28). However, the small sample size and lack of independent clinical validation prevent conclusions about diagnostic utility. For diabetic kidney disease, a multicohort study of urinary EV miRNAs (n = 490) identified miR-192-5p among candidate markers associated with kidney function decline, with independent replication[79]. Separately, urinary microvesicle-bound uromodulin was associated with albuminuria-defined disease severity in a cross-sectional study of 100 patients with type 2 diabetes and 31 healthy controls[80]. These findings support further biomarker evaluation but do not establish prospective clinical prediction or routine clinical utility. Urinary kidney-disease markers and circulating obesity-associated proteins address different populations, matrices, and endpoints; their reported associations should not be treated as interchangeable diagnostic performance estimates.

Mechanistic studies provide a separate line of evidence: apolipoprotein E (ApoE)-sufficient macrophage-derived EVs exert anti-inflammatory effects, whereas ApoE-deficient or aged liver-derived EVs (enriched with miR-23b-3p) propagate senescence and abnormal lipid metabolism signals[81,82]. These findings suggest potential approaches for investigating EV-associated metabolic signaling. EV-mediated communication may contribute to a feedback loop in metabolic disease: metabolic dysregulation alters EV biogenesis and cargo composition, and the resulting aberrant EVs propagate metabolic dysfunction to previously healthy tissues. Interrupting these EV-associated feedback processes may represent a therapeutic strategy complementary to conventional glucose- and lipid-lowering approaches.

The concept of EV-mediated self-reinforcing pathology extends beyond metabolic organs to the musculoskeletal system, where EV populations may influence the balance between anabolic and catabolic signaling.

Skeletal system diseases

Experimental EV studies implicate intercellular signaling in sarcopenia and osteoporosis. In sarcopenia, EVs derived from atrophic muscle fibers or senescent satellite cells can impair muscle homeostasis through miR-690- or miR-335-5p-associated pathways[83-85]. EV-associated miR-21a-3p also participates in

muscle-kidney crosstalk following denervation-induced muscle injury[44]. Conversely, mesenchymal stem/stromal cell (MSC)-derived or engineered EVs can alleviate muscle atrophy in experimental models by regulating AMP-activated protein kinase (AMPK)/Unc-51-like autophagy activating kinase 1 (ULK1)-mediated autophagy and SIRT1/forkhead box O (FoxO)-associated mitochondrial function[84,86]. However, most mechanistic evidence remains preclinical, limiting its direct translation to human sarcopenia.

In osteoporosis, EVs participate in the regulation of bone formation and resorption through local and cross-organ communication[13,14,87-90]. In experimental models, mature osteoblast-derived small osteoblast vesicles (SOVs) suppress osteoblast differentiation and promote osteoclastogenesis, in part through miR-143-associated signaling[89]. Conversely, adipose tissue-derived stem cell EVs attenuate bone loss in ovariectomized mice by inhibiting osteoclast differentiation through osteoprotegerin and miR-21-5p-related mechanisms[90]. Osteoclast-derived exosomes transfer miR-214 to osteoblasts through ephrinA2-EphA2-mediated interactions, suppressing osteoblast activity[14]. Lin *et al.* further identified a hepatocyte sirtuin 2 (SIRT2)-dependent liver-bone axis in which leucine-rich alpha-2 glycoprotein 1 (LRG1)-enriched small EVs (sEVs) inhibit osteoclast differentiation and attenuate bone loss in mice[13]. These therapeutic effects remain supported primarily by experimental evidence.

EV-associated molecules also show potential as circulating biomarkers of musculoskeletal disorders. Aparicio *et al.* identified platelet factor 4 (PF4) and complement C1r subcomponent (C1R) as candidate sarcopenia biomarkers through proteomic discovery (n = 32) and subsequent ELISA-based evaluation (n = 78)[12]. Their respective areas under the curve (AUCs) were 0.8921 and 0.7476. However, overlapping discovery and validation samples and differences in age between groups indicate the need for further independent validation.

In osteoporosis, Sun *et al.* reported elevated serum exosomal miR-214 and ephrinA2 levels in patients with osteoporosis, whereas Lin *et al.* observed a positive association between plasma sEV-associated LRG1 and bone mineral density (BMD)[13,14]. Zhi *et al.* investigated serum exosomal hsa_circ_0006859 in 168 postmenopausal women and reported an AUC of 0.8974 [95% confidence interval (CI): 0.8248-0.9700] for distinguishing osteoporosis from healthy controls[91]. Shi *et al.* identified several BMD-associated serum exosomal miRNAs in 34 participants, while Huo *et al.* reported an AUC of 0.74 for microvesicle-associated Profilin-1, following proteomic discovery and preliminary validation in a cohort comprising 84 participants[15,92]. The AUC estimates address different markers and selected populations and cannot be ranked as head-to-head comparisons. Across these studies, small or selected cohorts, limited independent validation, and differences in EV isolation and analytical methods constrain reproducibility and clinical applicability.

Overall, EVs provide insights into the regulation of muscle-bone homeostasis and offer potential diagnostic and therapeutic targets [Figure 3]. Nevertheless, larger independent cohorts and standardized EV methodologies are required to establish their clinical utility.

Respiratory system diseases

Aging, oxidative stress and environmental exposures contribute to chronic obstructive pulmonary disease (COPD). In experimental pulmonary systems, EV-associated signals have been linked to senescence, inflammation, extracellular matrix damage, and changes in airway remodeling[97-100] [Figure 4]. These effects vary with the releasing cell, cargo, and model.

EV-associated signaling has been implicated in the spread of senescence within the lung[101], whereas direct evidence for EV-mediated fibrotic signaling comes mainly from experimental models of pulmonary injury rather than from idiopathic pulmonary fibrosis (IPF) itself. In paraquat-induced pulmonary fibrosis models,

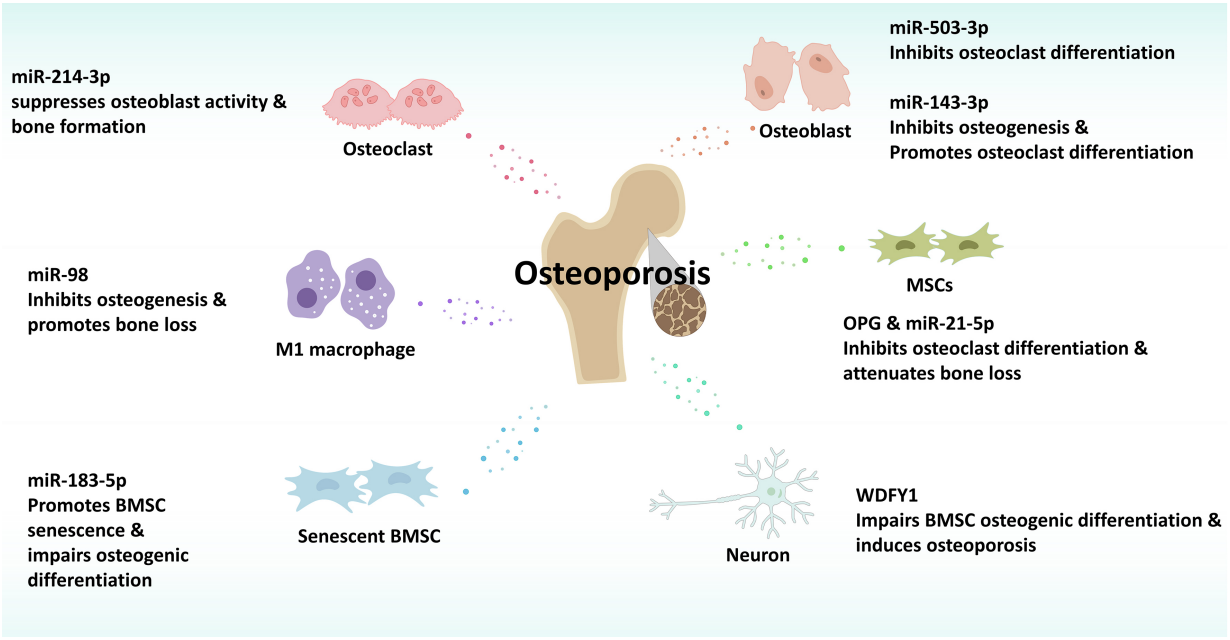


Figure 3. Source- and cargo-dependent regulation of bone remodeling by EVs. EVs influence bone formation and resorption through distinct signaling routes. Osteoclast-derived miR-214-3p and mature osteoblast-derived miR-143-3p can inhibit osteoblast activity or favor osteoclastogenesis, whereas osteoblast EV-associated miR-503-3p inhibits osteoclast differentiation[88,89,93]. M1 macrophage EV-associated miR-98 and aged bone-marrow EV-associated miR-183-5p are linked to impaired osteogenesis and bone loss or cellular senescence[94,95]. Neuronal WDFY1-bearing EVs contribute to brain-bone signaling[96], while adipose stem cell-derived EVs containing OPG and miR-21-5p reduce osteoclast differentiation in experimental models[90]. EV: Extracellular vesicle; miR: microRNA; MSC: mesenchymal stem/stromal cell; BMSC: bone marrow mesenchymal stromal cell; WDFY1: WD repeat and FYVE domain-containing protein 1; OPG: osteoprotegerin.

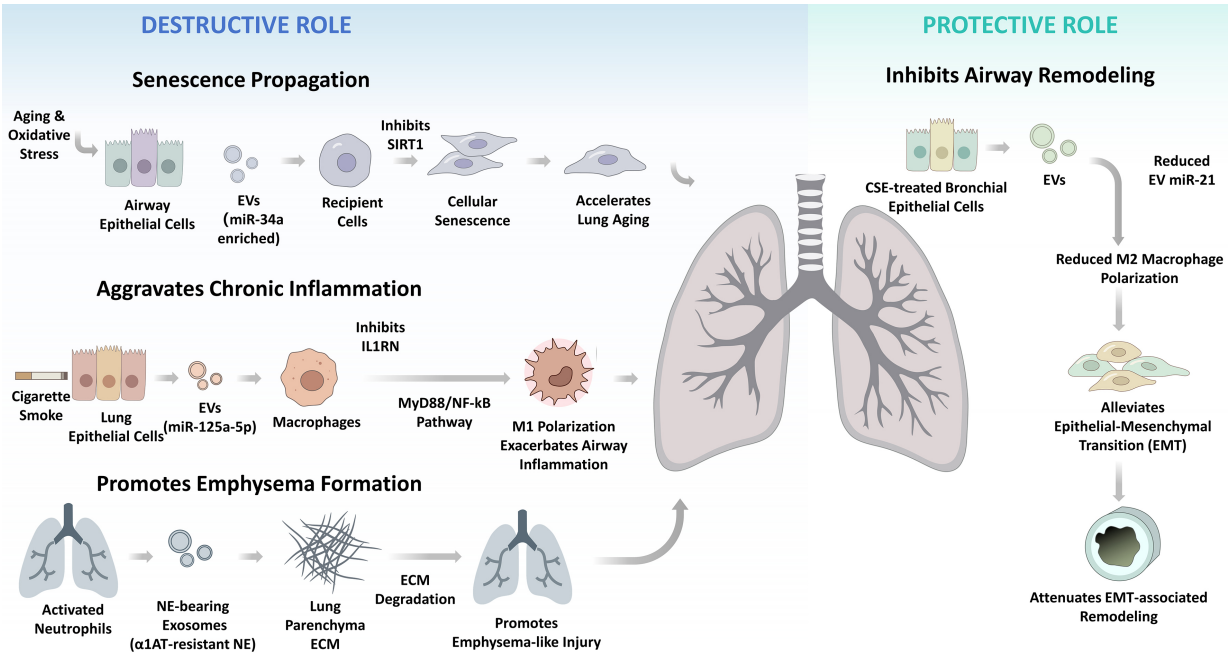


Figure 4. Context-dependent EV signaling in pulmonary aging and COPD. The diagram summarizes distinct experimental pathways in pulmonary disease. Epithelial EV-associated miR-34a regulates SIRT1-dependent senescence signaling[98], while epithelial EV-associated miR-125a-5p acts through IL1RN/MyD88/NF-κB signaling in macrophages[99]. Neutrophil-derived exosomes bearing surface elastase contribute to ECM degradation[100]. In a separate CSE model, bronchial epithelial EVs with reduced miR-21 cargo were associated with reduced M2 macrophage polarization and EMT[97]. Source cells, cargoes and outcomes should therefore be interpreted within each cited experimental context. COPD: Chronic obstructive pulmonary disease; EV: extracellular vesicle; CSE: cigarette smoke extract; miR: microRNA; NE: neutrophil elastase; ECM: extracellular matrix; EMT: epithelial-mesenchymal transition; SIRT1: sirtuin 1; IL1RN: interleukin-1 receptor antagonist; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor kappa B; α1AT: alpha-1 antitrypsin; M1/M2: macrophage activation phenotypes.

senescent epithelial cell-derived exosomes deliver miR-217-5p to fibroblasts, suppressing SIRT1, increasing β-catenin acetylation and Wnt signaling, and promoting fibroblast activation[102]. Whether this mechanism also operates in IPF remains to be established. In sepsis-associated pulmonary fibrosis models, fibroblasts with mitochondrial dysfunction release mtDNA-containing migrasomes that promote macrophage-myofibroblast transition[103]. Migrasomes form on retraction fibers during cell migration and should be distinguished from endosome-derived exosomes. This evidence does not establish the same process in IPF. Moreover, IPF fibroblast-derived EVs may promote lung cancer progression, linking fibrotic microenvironments to malignancy[104].

In acute lung injury (ALI), EVs exert context-dependent effects. Plasma EVs enriched in lipopolysaccharide in metabolic syndrome can activate Toll-like receptor 4 (TLR4)-dependent inflammatory pathways[105], while EV-associated S100A8/A9 contributes to inflammatory lung injury during sepsis[106]. Conversely, neutrophil-derived CD55-positive large EVs can limit complement activation and facilitate inflammation resolution[107]. These findings suggest that EV functions depend on their molecular cargo and inflammatory context, although much of the mechanistic evidence remains experimental.

EV-associated cargoes have also been investigated as potential biomarkers of pulmonary diseases. In 35 patients with stable COPD, Carpi *et al.* observed an inverse association between plasma EV miR-191-5p levels and diffusing capacity for carbon monoxide (DLCO; $R^2 = 0.15$, $P = 0.02$), although independent clinical validation was lacking[16]. In interstitial lung disease (ILD), Enomoto *et al.* reported that serum EV-associated surfactant protein B (SFTPB) predicted progression with an AUC of 0.68, compared with 0.51 for Krebs von den Lungen-6 (KL-6) and 0.63 for surfactant protein D (SP-D); its performance remained modest in a validation cohort (AUC = 0.63)[17]. Eckhardt *et al.* identified 51 plasma EV-miRNAs associated with lung function in a cohort of 656 participants, of which 28 were replicated in independent samples and/or an external cohort[108]. These studies assess different endpoints, including gas transfer, disease progression, and lung function. Replication strengthens an association but does not by itself establish clinical decision thresholds or utility.

Mechanistic injury studies should be distinguished from clinical prognostic studies. In sepsis-associated ALI, EV-associated miR-210-3p and miR-1-3p were implicated in autophagy dysregulation and endothelial injury, respectively, but their clinical prognostic utility was not established[109,110]. Wang *et al.* found reduced plasma exosomal miR-27a-5p in six obese individuals compared with six healthy controls and demonstrated its protective effects against ventilator-induced lung injury in experimental models[111]. However, these findings do not establish age-dependent clinical risk prediction.

Overall, EV-associated molecules offer potential insights into pulmonary disease mechanisms and biomarker development. Nevertheless, differences in cohort size, validation strategies, and EV isolation methods highlight the need for further standardization and independent clinical validation before routine application.

Cancer

Aging and cancer share several biological processes, including altered intercellular communication and senescence-associated signaling[112]. EV-RNA contributes to tumor-associated communication[113], but evidence from cancer models does not by itself establish that an EV mechanism is driven by chronological aging.

EVs participate in tumor-stroma communication and immune regulation[114,115]. Examples of miRNA transfer include colorectal cancer EV miR-10b-associated fibroblast activation through PIK3CA downregulation[116], breast cancer exosomal miR-1246 targeting CCNG2[117], and cancer-secreted miR-105 disrupting endothelial

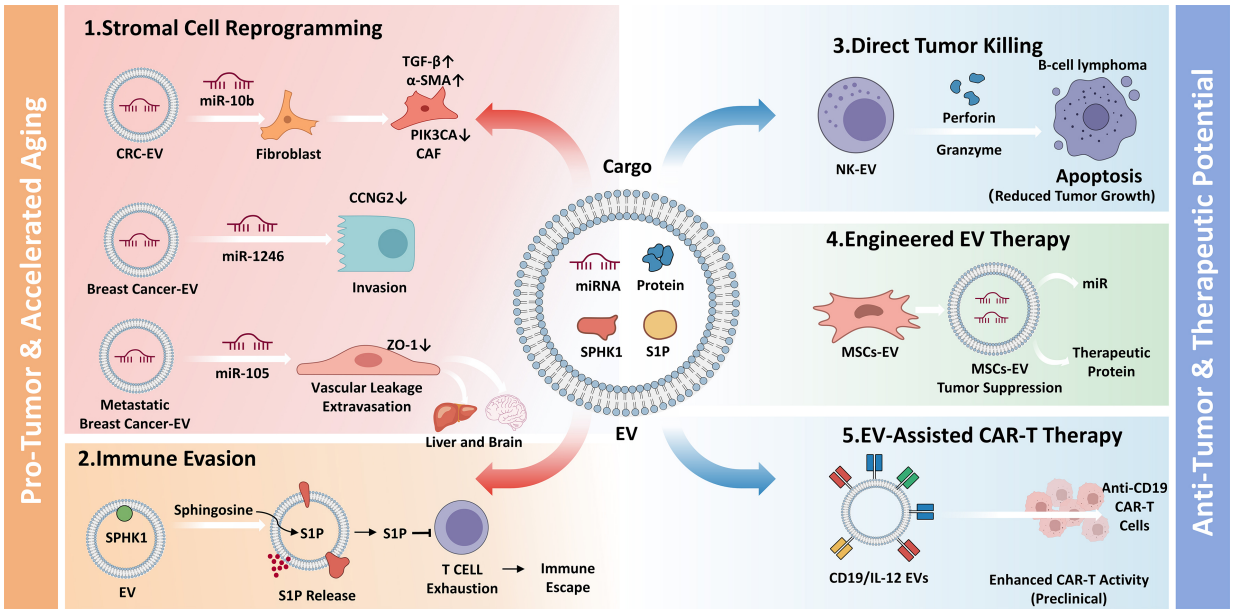


Figure 5. EV-mediated tumor remodeling and experimental antitumor strategies. Tumor-associated EVs can reshape stromal cells, support invasive behavior, alter vascular permeability, and suppress T-cell activity through miRNA transfer and lipid signaling[114,115,119,124]. Specifically, colorectal cancer EV miR-10b promotes fibroblast activation through PIK3CA downregulation[116]; breast cancer exosomal miR-1246 targets CCNG2[117], whereas secreted miR-105 compromises endothelial ZO-1-dependent barrier integrity[118]. The therapeutic examples depict NK cell-derived EV cytotoxicity[19], MSC EV delivery systems[125], and CD19/IL-12-bearing engineered HEK293T EVs that enhance CAR-T-cell activity[18]. These mechanisms originate from distinct experimental studies. They do not establish a universal causal link between tumor EV signaling and accelerated organismal aging. Upward and downward arrows indicate increased and decreased levels, respectively. EV: Extracellular vesicle; CAF: cancer-associated fibroblast; miR: microRNA; MSC: mesenchymal stem cell; NK: natural killer; CAR-T: chimeric antigen receptor T cell; IL-12: interleukin-12; SPHK1: sphingosine kinase 1; S1P: sphingosine-1-phosphate; TGF-β: transforming growth factor beta; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; CCNG2: cyclin G2; ZO-1: zonula occludens-1; α-SMA: alpha-smooth muscle actin; CRC: colorectal cancer.

zonula occludens-1 (ZO-1)-dependent barrier integrity[118]. These model-specific mechanisms complement broader evidence on EV-mediated cargo transfer[119].

Other experimental pathways link EVs to metabolism, immune checkpoints, and drug resistance. Cancer-associated fibroblast-derived exosomes enhance glycolysis and alter glutamine metabolism in recipient cancer cells[120]. Tumor-derived exosomes promote macrophage glycolysis and programmed death-ligand 1 (PD-L1) expression in pre-metastatic niches[121], while melanoma-derived exosomal PD-L1 suppresses CD8-positive T-cell function[122]. Transfer of the long noncoding RNA *lncARSR* propagates sunitinib resistance among renal cancer cells[123]. These findings derive from distinct experimental systems and do not establish a single mechanism common to all age-associated cancers.

EV membrane-associated sphingosine kinase 1 (SPHK1) converts sphingosine to sphingosine-1-phosphate (S1P), affecting membrane stability and cargo release and reducing T-cell cytotoxicity-marker expression in experimental systems[124]. Conversely, engineered CD19/IL-12-bearing EVs enhance chimeric antigen receptor T-cell (CAR-T-cell) activity[18], and natural killer (NK)-cell EV fractions show antitumor activity in experimental lymphoma systems[19]. MSC-based EV delivery strategies remain under investigation[125]. These reports support preclinical mechanisms, not established clinical superiority over cell-based therapies or validated age-specific treatment selection. Selectively inhibiting tumor-promoting EV activities while preserving antitumor functions remains unresolved [Figure 5].

Table 1 compares selected representative studies already discussed in this review. It illustrates differences in EV source attribution, subtype terminology, and preparation methods; it is not an exhaustive survey of all six

disease categories. Defined producer-cell systems support more direct investigation of cell-to-cell signaling, whereas bulk biofluid EV findings generally cannot establish the releasing cell or vesicle biogenesis pathway.

THERAPEUTIC ROLES OF EXTRACELLULAR VESICLES

The potential therapeutic applications of EVs are based on the pathological mechanisms described in Sections "Roles of extracellular vesicles in the aging microenvironment" and "Roles of extracellular vesicles in the mechanisms of age-related diseases". Knowledge of these pathways may guide the development of engineered EV-based interventions. Because chronic inflammation, impaired proteostasis, and mitochondrial dysfunction are interconnected, EV-based strategies may offer opportunities to modulate more than one of these pathways. The cancer immunotherapy examples in Section "Cancer" and Figure 5 also fall within the immune-modulation axis, although tumor-specific efficacy and safety require separate evaluation. The following sections organize selected interventions by their principal mechanistic target.

Inflammation and immune dysregulation

EV-based anti-inflammatory strategies may modulate macrophage polarization and profibrotic signaling.

In a rat model of hyperlipidemia, MSC-derived sEV-functionalized synthetic vascular grafts promoted endothelialization, altered macrophage polarization, and reduced calcification and thrombosis[126]. A separate pharmacological study found that extracellular signal-regulated kinase 1/2 (ERK1/2) inhibition increased miR-126-3p activity and modulated Dickkopf-related protein 1 (DKK1)/low-density lipoprotein receptor-related protein 6 (LRP6) and Wnt signaling to reduce vascular calcification[127]. The latter study identifies a signaling mechanism; it does not demonstrate an engineered EV treatment. In bone models, osteoclast-associated miR-214-3p signaling offers another candidate route for limiting pathological intercellular communication[87,88].

Some EV populations have been reported to modulate profibrotic signaling. EV-associated miR-142-3p has been reported to downregulate transforming growth factor beta receptor 1 (TGFβ-R1) and influence profibrotic signaling[128]. Furthermore, EVs, as maintainers of endogenous mitochondrial homeostasis, protect damaged alveolar epithelium by stabilizing mtDNA and attenuating oxidative stress, suggesting an experimental alternative to broad immunosuppressive approaches[129]. These findings motivate investigation of more selective approaches to modulating inflammatory and fibrotic pathways.

Genetic engineering to modify parental cells has emerged as a new strategy for enhancing EV therapeutic efficacy. For instance, NELL1-modified MSC-EVs promote osteogenic differentiation through the SMAD2 pathway[130]; in the treatment of muscle atrophy, EV-delivered miR-29 simultaneously inhibits the YY1 and TGF-β pathways, suggesting a potential experimental approach to this condition[131].

Loss of proteostasis

Impaired proteostasis interacts with inflammation and provides another target for experimental EV-based interventions. EVs can be surface-engineered to enhance delivery to selected tissues, including experimental approaches targeting the central nervous system. For example, neuronal EVs genetically engineered to fuse the Fe65 protein on their surface exploit the affinity of Fe65 for amyloid precursor protein (APP) to achieve targeting, thereby delivering the autophagy inducer Corynoxine-B to enhance Aβ clearance in experimental models[132]. In PD treatment, engineered EVs displaying a dopamine transporter (DAT)-specific single-chain antibody fragment (scFv) on their surface have been used to deliver cargo to dopaminergic neurons and reduce abnormal α-syn aggregation in experimental models[133]. Furthermore, certain endogenous microglia-derived EVs exhibit natural Aβ aggregation inhibitory activity, suggesting a possible contribution to proteostasis maintenance[134].

EV-mediated immune modulation may influence the relationship between neuroinflammation and impaired proteostasis. MSC-EVs attenuate microglial pro-inflammatory phenotypes by inhibiting the NF-κB signaling pathway, thereby reducing Aβ and tau pathological burden and indirectly creating a microenvironment conducive to the restoration of neuronal protein metabolic functions[135]. Conversely, inhibiting pathological EV release [e.g., using neutral sphingomyelinase 2 (nSMase2) inhibitors] or interfering with their generation (e.g., silencing Selenoprotein P) can block the propagation of pro-inflammatory cargoes and attenuate tau-associated pathology in experimental systems[136,137]. Whether inhibiting pathological EV release preserves physiological EV functions requires further investigation.

EV-based interventions are being investigated both as cargo-delivery systems and as modulators of endogenous cellular responses. Mesenchymal stem cell-derived nanovesicle-coated poly(lactic-co-glycolic acid) nanoparticles (MSC-PLGA-NPs) have been shown to remodel lysosomal function and facilitate pathological protein clearance in experimental Alzheimer's disease models[138]. This EV-inspired hybrid formulation should be distinguished from isolated MSC-derived EVs. Moreover, *Gardenia jasminoides*-derived EV-enriched preparations attenuated rotenone-induced mitochondrial dysfunction and apoptosis in PC12 cells, accompanied by reduced p38 MAPK/p53 phosphorylation, and reduced dopaminergic neuron loss in *Caenorhabditis elegans* models[139]. However, these observations are limited to cell and nematode models and do not establish intact-vesicle delivery or therapeutic efficacy in mammals. The active components of these preparations remain unidentified, and possible contributions from co-isolated non-vesicular substances have not been excluded. Clinical studies would need to distinguish the contributions of vesicles, delivered drugs, and other formulation components to any observed benefit.

Mitochondrial dysfunction

Protein aggregation and inflammatory signaling can intersect with mitochondrial dysfunction. This hallmark of aging is closely linked to disturbances in proteostasis and inflammatory responses. EVs may influence mitochondrial homeostasis through several mechanisms. Experimental approaches include signaling cargoes that enhance autophagic clearance[133,140], mitochondria-enriched preparations for organelle transfer[141], and delivery of metabolic precursors[142]. Detection of mtDNA or mitochondrial proteins alone does not demonstrate transfer of intact, functional mitochondria.

In experimental aging models, some EV interventions promote mitochondrial quality control by enhancing mitophagy. For instance, engineered EVs derived from young mouse serum, by upregulating translocase of outer mitochondrial membrane 7 (TOMM7), activate PTEN-induced kinase 1 (PINK1)/Parkin-mediated mitophagy, reducing dysfunctional mitochondria in aged bone marrow mesenchymal stem cells (BMSCs) and improving features of the aged bone microenvironment[140]. Furthermore, β-nicotinamide mononucleotide (NMN)-loaded sEVs activate nicotinamide adenine dinucleotide (NAD^+)/sirtuin 3 (SIRT3)-associated mitophagy in experimental skin-aging models[142].

In degenerative lesions of the cardiovascular and musculoskeletal systems, EV-based strategies are expanding from molecular signaling approaches to experimental organelle transfer. Through co-delivery of SIRT3 and insulin, engineered EVs can activate the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway to enhance mitochondrial respiratory chain integrity[143]. For osteoarthritis, additional EV approaches have been investigated: MSC-EVs have been reported to maintain the AMPK-SIRT3 homeostasis of chondrocytes through heat shock protein 70 (Hsp70) molecules[144]. Separately, experimental studies indicate that mitochondria-enriched EVs (Mito-EVs) derived from synovial fluid MSCs can directly transfer healthy mitochondria into stressed chondrocytes, improving oxidative phosphorylation and reducing cartilage degeneration in experimental systems[141]. Functional mitochondrial transfer may expand the range of EV-based experimental therapeutic approaches. Together with approaches that activate mitophagy, mitochondrial transfer could provide complementary strategies for improving mitochondrial quality control [Figure 6].

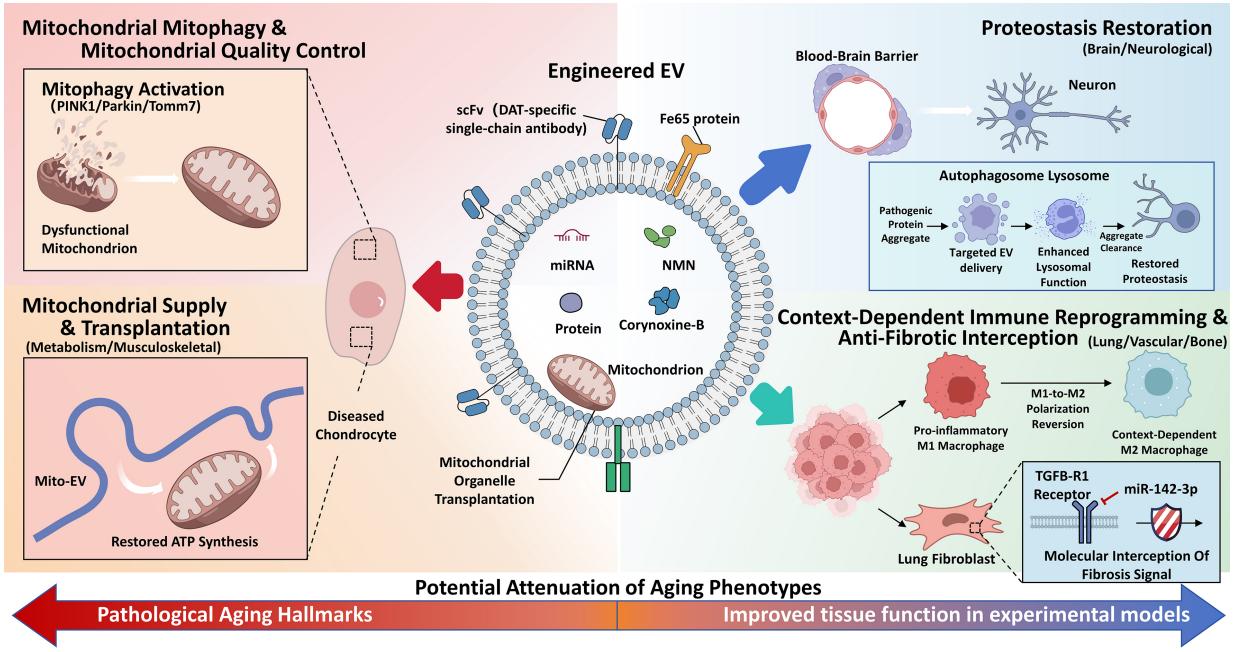


Figure 6. Representative EV-based strategies targeting interconnected aging mechanisms. This figure summarizes representative engineered and bioactive EV-based therapeutic strategies investigated in distinct preclinical studies. EV-based interventions may enhance TOMM7/PINK1/Parkin-associated mitophagy[140], facilitate mitochondrial transfer to chondrocytes[141], or deliver cargo to neurons to modulate autophagic and lysosomal pathways involved in protein clearance[132,133]. Other EV strategies affect context-dependent macrophage polarization and miR-142-3p/TGFβ-R1-associated fibrotic signaling[126,128]. Importantly, the M1-to-M2 transition depicted in the figure represents an experimental phenotypic shift and does not imply a uniformly anti-fibrotic or protective effect; M2 macrophages can exert either reparative or pro-fibrotic functions depending on the tissue microenvironment. The central cargo display is a composite schematic illustrating distinct products and studies; it does not depict a validated single EV product containing all illustrated cargoes. These examples do not demonstrate systemic rejuvenation in humans. EV: Extracellular vesicle; mito-EV: mitochondria-containing EV; miR: microRNA; scFv: single-chain variable fragment; DAT: dopamine transporter; APP: amyloid precursor protein; Aβ: amyloid-beta; Fe65: amyloid beta A4 precursor protein-binding family A member 1; Corynoxine-B: an autophagy inducer; NMN: nicotinamide mononucleotide; ATP: adenosine triphosphate; TOMM7: translocase of outer mitochondrial membrane 7; PINK1: PTEN-induced kinase 1; Parkin: PRKN E3 ubiquitin ligase; TGFβ-R1: transforming growth factor beta receptor 1; M1/M2: macrophage activation phenotypes.

These three therapeutic axes are interconnected. Mitochondrial reactive oxygen species and oxidized mtDNA can promote NLRP3 inflammasome activation[38,39], while mitochondria-enriched sEVs released by injured cardiac fibroblasts can contribute to inflammatory responses[58]. In Parkinson's disease models, pathological α-synuclein interferes with mitochondrial protein import[145], and mitochondrial oxidative stress can impair lysosomal function and promote α-synuclein accumulation[146]. Together, these findings illustrate reciprocal links among inflammation, proteostasis failure, and mitochondrial injury. EV-based approaches that modulate lysosomal function, mitophagy, or inflammatory signaling[133,140,142] may help interrupt different components of this cycle; however, coordinated efficacy and clinical benefit remain to be established [Figure 6].

CONCLUSION AND PROSPECTS

EV research provides a framework for studying how intracellular disturbances can affect other cells and tissues during aging. Beyond being passive byproducts, EVs can transport molecular signals associated with impaired proteostasis, mitochondrial dysfunction, and altered autophagy. The biological effects of EVs depend on their source, cargo, and recipient cells; the balance between harmful and protective signaling may contribute to differences in aging-associated outcomes and multimorbidity.

Three key limitations currently constrain clinical translation. First, EV heterogeneity across size, cargo, cellular origin, and functional state remains technically challenging to resolve at single-vesicle resolution. Second, the lack of standardized protocols for EV isolation, characterization, and quality control limits comparisons across studies and complicates regulatory development. Third, dose-response relationships, biodistribution, clearance kinetics, and immunogenicity need product-specific characterization during clinical development. Clinical investigations of EV-based therapeutics have expanded, and a 2026 review describes continuing regulatory and development barriers[147]. Translation requires disease-specific evaluation of safety and efficacy alongside reproducible dose definition, including particle number, biologically active cargo, functional potency, repeat dosing, and biodistribution; these measures are not interchangeable across EV products[148]. Manufacturing under good manufacturing practice (GMP) conditions also requires control of producer-cell identity, processing, batch consistency, purity, sterility and potency, together with product-specific regulatory classification and immune-safety assessment[7,149]. Representative clinical development programs include intravenously administered bone marrow MSC-derived EVs for acute respiratory distress syndrome (NCT05354141) and a topical platelet-derived exosome formulation for diabetic foot ulcers (NCT06319287)[147]. These registered programs illustrate different indications, EV sources and administration routes; registration alone does not establish efficacy. Study-specific doses, outcome data, and current recruitment status should be obtained from the relevant trial records before making clinical comparisons.

Addressing these challenges will require concerted methodological advances. Emerging single-vesicle analytical approaches may help resolve EV heterogeneity and identify distinct particle subpopulations. Standardization efforts, coordinated through bodies such as the International Society for Extracellular Vesicles (ISEV), can further support consensus guidance on isolation methods, characterization criteria, and reporting standards. Multi-target formulations are one possible research direction rather than an established improvement over single-cargo delivery. Future engineered EV platforms might combine mitophagy modulators, anti-inflammatory cargoes, and proteostasis-related agents, although the safety and efficacy of such multi-target strategies require direct evaluation.

Across disease areas, interpretation also depends on donor and participant age, sex, menopausal status, comorbidity, treatment exposure, and population background. Differences in these variables can affect both EV profiles and disease endpoints, as illustrated by the cardiovascular studies[69-71]. Their reporting and stratified evaluation should accompany replication in independent and more diverse populations. The narrative evidence assembled here does not establish comparable demographic coverage across all disease categories.

With continued mechanistic clarification and technical refinement, EV-based diagnostics and therapeutics may progress toward clinical applications. Further work is needed to determine which EV-associated pathways are therapeutically modifiable and clinically relevant to age-related diseases.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study: Zou WC
Drafted the manuscript: He WY
Revised the manuscript critically for important intellectual content: Wu RQ
Prepared figures and tables: Zeng HY
Provided administrative, technical, and material support: Yang J, Lai MQ, Li ZY, Zhang N
All authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version GPT-6, Instant mode, released 2026-10-07) was used solely for language editing, improving readability, and grammar correction. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

Financial support and sponsorship

This project was supported by the National Natural Science Foundation of China (32671036), the Hangzhou Normal University Scientific Research Start-up Fund (4255C50223204120), and the Natural Science Foundation of Zhejiang Province (LMS25C070003).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2026.

REFERENCES

1. Freihat O, Sipos D, Aamir M, Kovacs A. Global burden and future projections of non-communicable diseases (2000-2050): progress toward SDG 3.4 and disparities across regions and risk factors. *PLoS One.* 2025;20:e0336036. DOI PubMed PMC
2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell.* 2023;186:243-78. DOI PubMed
3. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol.* 2018;14:576-90. DOI PubMed
4. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol.* 2010;5:99-118. DOI PubMed PMC
5. Putri PHL, Alamudi SH, Dong X, Fu Y. Extracellular vesicles in age-related diseases: disease pathogenesis, intervention, and biomarker. *Stem Cell Res Ther.* 2025;16:263. DOI PubMed PMC
6. Shimizu Y, Inoue Y, Matsuura N, et al. Mesenchymal stromal cell-derived extracellular vesicles in regenerative medicine: standardisation, bioengineering and clinical translation. *Regen Ther.* 2026;31:101058. DOI PubMed PMC
7. Welsh JA, Goberdhan DCI, O'Driscoll L, et al. ; MISEV Consortium. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles.* 2024;13:e12404. DOI PubMed PMC
8. Cai Y, Chen T, Cai Y, et al. Surface protein profiling and subtyping of extracellular vesicles in body fluids reveals non-CSF biomarkers of Alzheimer's disease. *J Extracell Vesicles.* 2024;13:e12432. DOI PubMed PMC
9. Chen X, Chen S, Pang J, et al. Hepatic steatosis aggravates atherosclerosis via small extracellular vesicle-mediated inhibition of cellular cholesterol efflux. *J Hepatol.* 2023;79:1491-501. DOI PubMed
10. Xie L, Chen J, Hu H, et al. Engineered M2 macrophage-derived extracellular vesicles with platelet membrane fusion for targeted therapy of atherosclerosis. *Bioact Mater.* 2024;35:447-60. DOI PubMed PMC
11. Camino T, Lago-Baameiro N, Bravo SB, et al. Human obese white adipose tissue sheds depot-specific extracellular vesicles and reveals candidate biomarkers for monitoring obesity and its comorbidities. *Transl Res.* 2022;239:85-102. DOI PubMed
12. Aparicio P, Navarrete-Villanueva D, Gómez-Cabello A, et al. Proteomic profiling of human plasma extracellular vesicles identifies PF4 and C1R as novel biomarker in sarcopenia. *J Cachexia Sarcopenia Muscle.* 2024;15:1883-97. DOI PubMed PMC
13. Lin L, Guo Z, He E, et al. SIRT2 regulates extracellular vesicle-mediated liver-bone communication. *Nat Metab.* 2023;5:821-41. DOI PubMed PMC
14. Sun W, Zhao C, Li Y, et al. Osteoclast-derived microRNA-containing exosomes selectively inhibit osteoblast activity. *Cell Discov.* 2016;2:16015. DOI PubMed PMC
15. Huo C, Li Y, Qiao Z, et al. Comparative proteomics analysis of microvesicles in human serum for the evaluation of osteoporosis. *Electrophoresis.* 2019;40:1839-47. DOI PubMed

16. Carpi S, Polini B, Nieri D, et al. Extracellular vesicles induce nuclear factor-κB activation and interleukin-8 synthesis through miRNA-191-5p contributing to inflammatory processes: potential implications in the pathogenesis of chronic obstructive pulmonary disease. *Biomolecules.* 2024;14:1030. DOI PubMed PMC
17. Enomoto T, Shirai Y, Takeda Y, et al. SFTPB in serum extracellular vesicles as a biomarker of progressive pulmonary fibrosis. *JCI Insight.* 2024;9:e177937. DOI PubMed PMC
18. Zhang Y, Huang M, Zhang S, et al. Improving CAR-T cell function through a targeted cytokine delivery system utilizing car target-modified extracellular vesicles. *Exp Hematol Oncol.* 2025;14:110. DOI PubMed PMC
19. Cecchetti S, Federici C, Canese R, et al. NK cells-derived extracellular vesicles potency in the B cell lymphoma biotherapy. *Front Immunol.* 2024;15:1503857. DOI PubMed PMC
20. Wallis R, Josipovic N, Mizen H, et al. Isolation methodology is essential to the evaluation of the extracellular vesicle component of the senescence-associated secretory phenotype. *J Extracell Vesicles.* 2021;10:e12041. DOI PubMed PMC
21. Chen X, Luo Y, Zhu Q, et al. Small extracellular vesicles from young plasma reverse age-related functional declines by improving mitochondrial energy metabolism. *Nat Aging.* 2024;4:814-38. DOI PubMed PMC
22. Xiao L, Zhang Z, Li T, et al. Small extracellular vesicles from human amniotic membrane mesenchymal stem cells rejuvenate senescent β cells and cure age-related diabetes in mice. *Aging Cell.* 2026;25:e70327. DOI PubMed PMC
23. Bonavina G, Mamillapalli R, Krikun G, Zhou Y, Gawde N, Taylor HS. Bone marrow mesenchymal stem cell-derived exosomes shuttle microRNAs to endometrial stromal fibroblasts that promote tissue proliferation /regeneration/ and inhibit differentiation. *Stem Cell Res Ther.* 2024;15:129. DOI PubMed PMC
24. Yin Y, Chen H, Wang Y, Zhang L, Wang X. Roles of extracellular vesicles in the aging microenvironment and age-related diseases. *J Extracell Vesicles.* 2021;10:e12154. DOI PubMed PMC
25. Iorio R, Petricca S, Di Emidio G, Falone S, Tatone C. Mitochondrial extracellular vesicles (mitoEVs): emerging mediators of cell-to-cell communication in health, aging and age-related diseases. *Ageing Res Rev.* 2024;101:102522. DOI PubMed
26. Hernandez P, Rackles E, Alboniga OE, et al. Metabolic profiling of brain tissue and brain-derived extracellular vesicles in Alzheimer's disease. *J Extracell Vesicles.* 2025;14:e70043. DOI PubMed PMC
27. Cai H, Pang Y, Wang Q, et al. Proteomic profiling of circulating plasma exosomes reveals novel biomarkers of Alzheimer's disease. *Alzheimers Res Ther.* 2022;14:181. DOI PubMed PMC
28. Wu CC, Tsantilas KA, Park J, et al. Enrichment of extracellular vesicles using Mag-Net for the analysis of the plasma proteome. *Nat Commun.* 2025;16:5447. DOI PubMed PMC
29. Kumar A, Su Y, Sharma M, et al. MicroRNA expression in extracellular vesicles as a novel blood-based biomarker for Alzheimer's disease. *Alzheimers Dement.* 2023;19:4952-66. DOI PubMed PMC
30. Kluge A, Bunk J, Schaeffer E, et al. Detection of neuron-derived pathological α-synuclein in blood. *Brain.* 2022;145:3058-71. DOI PubMed
31. Yan S, Jiang C, Janzen A, et al. Neuronally derived extracellular vesicle α-synuclein as a serum biomarker for individuals at risk of developing Parkinson disease. *JAMA Neurol.* 2024;81:59-68. DOI PubMed PMC
32. Yanagawa K, Kuma A, Hamasaki M, et al. The rubicon-WIPI axis regulates exosome biogenesis during ageing. *Nat Cell Biol.* 2024;26:1558-70. DOI PubMed
33. Palumbos SD, Popolow J, Goldsmith J, Holzbaur ELF. Autophagic stress activates distinct compensatory secretory pathways in neurons. *Proc Natl Acad Sci U S A.* 2025;122:e2421886122. DOI PubMed PMC
34. Xiao Y, Liang J, Witwer KW, Zhang Y, Wang Q, Yin H. Extracellular vesicle-associated microRNA-30b-5p activates macrophages through the SIRT1/ NF-κB pathway in cell senescence. *Front Immunol.* 2022;13:955175. DOI PubMed PMC
35. Lazo S, Noren Hooten N, Green J, et al. Mitochondrial DNA in extracellular vesicles declines with age. *Aging Cell.* 2021;20:e13283. DOI PubMed PMC
36. Borghesan M, Fafián-Labora J, Eleftheriadou O, et al. Small extracellular vesicles are key regulators of non-cell autonomous intercellular communication in senescence via the interferon protein IFITM3. *Cell Rep.* 2019;27:3956-71.e6. DOI PubMed PMC
37. Li J, Wang X, Yao Z, et al. NLRP3-dependent crosstalk between pyroptotic macrophage and senescent cell orchestrates trauma-induced heterotopic ossification during aberrant wound healing. *Adv Sci.* 2023;10:e2207383. DOI PubMed PMC
38. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature.* 2011;469:221-5. DOI PubMed
39. Shimada K, Crother TR, Karlin J, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity.* 2012;36:401-14. DOI PubMed PMC
40. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci.* 2000;908:244-54. DOI PubMed

41. Palmulli R, Jackson HK, Edgar JR. Tethered exosomes containing the matrix metalloproteinase MT1-MMP contribute to extracellular matrix degradation. *J Extracell Vesicles.* 2025;14:e70122. DOI PubMed PMC
42. Siametis A, Garinis GA. From genome to geroscience: how DNA damage shapes systemic decline. *Bioessays.* 2025;47:e70051. DOI PubMed PMC
43. Yushkov B, Chereshnev V, Korneva E, Yushkova V, Sarapultsev A. Stem-cell niches in health and disease: microenvironmental determinants of regeneration and pathology. *Cells.* 2025;14:981. DOI PubMed PMC
44. Jiang S, Kang S, Kwon O, et al. Small extracellular vesicles derived from damaged muscle aggravate kidney injury progression. *J Cachexia Sarcopenia Muscle.* 2025;16:e13861. DOI PubMed PMC
45. Zeng ZL, Zhao ZB, Yuan Q, et al. Hepatic steatosis aggravates vascular calcification via extracellular vesicle-mediated osteochondrogenic switch of vascular smooth muscle cells. *Adv Sci.* 2025;12:e2408660. DOI PubMed PMC
46. Mattson MP, Arumugam TV. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. *Cell Metab.* 2018;27:1176-99. DOI PubMed PMC
47. Kalia LV, Lang AE. Parkinson's disease. *Lancet.* 2015;386:896-912. DOI PubMed
48. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet.* 2021;397:1577-90. DOI PubMed PMC
49. Sardar Sinha M, Ansell-Schultz A, Civitelli L, et al. Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers. *Acta Neuropathol.* 2018;136:41-56. DOI PubMed PMC
50. Fowler SL, Behr TS, Turkes E, et al. Tau filaments are tethered within brain extracellular vesicles in Alzheimer's disease. *Nat Neurosci.* 2025;28:40-8. DOI PubMed PMC
51. González-Molina LA, Villar-Vesga J, Henao-Restrepo J, et al. Extracellular vesicles from 3xTg-AD mouse and Alzheimer's disease patient astrocytes impair neuroglial and vascular components. *Front Aging Neurosci.* 2021;13:593927. DOI PubMed PMC
52. You Y, Muraoka S, Jedrychowski MP, et al. Human neural cell type-specific extracellular vesicle proteome defines disease-related molecules associated with activated astrocytes in Alzheimer's disease brain. *J Extracell Vesicles.* 2022;11:e12183. DOI PubMed PMC
53. Xie J, Van Hoecke L, Van Wonterghem E, et al. The gut-brain axis in Alzheimer's disease is shaped by commensal gut microbiota derived extracellular vesicles. *Gut Microbes.* 2025;17:2501193. DOI PubMed PMC
54. Faleeva M, Ahmad S, Theofilatos K, et al. Sox9 accelerates vascular aging by regulating extracellular matrix composition and stiffness. *Circ Res.* 2024;134:307-24. DOI PubMed PMC
55. Gan L, Zhao J, Yao P, et al. Adipocyte-derived small extracellular vesicles exacerbate diabetic ischemic heart injury by promoting oxidative stress and mitochondrial-mediated cardiomyocyte apoptosis. *Redox Biol.* 2025;79:103443. DOI PubMed PMC
56. Zhao J, Cheng W, Dai Y, et al. Excessive accumulation of epicardial adipose tissue promotes microvascular obstruction formation after myocardial ischemia/reperfusion through modulating macrophages polarization. *Cardiovasc Diabetol.* 2024;23:236. DOI PubMed PMC
57. Sun P, Wang C, Mang G, et al. Extracellular vesicle-packaged mitochondrial disturbing miRNA exacerbates cardiac injury during acute myocardial infarction. *Clin Transl Med.* 2022;12:e779. DOI PubMed PMC
58. Zhao Y, Hu Y, Wang Y, et al. Cardiac fibroblast-derived mitochondria-enriched sEVs regulate tissue inflammation and ventricular remodeling post-myocardial infarction through NLRP3 pathway. *Pharmacol Res.* 2025;214:107676. DOI PubMed
59. Zhang Y, Li X, Dai Y, et al. Neutrophil N1 polarization induced by cardiomyocyte-derived extracellular vesicle miR-9-5p aggravates myocardial ischemia/reperfusion injury. *J Nanobiotechnology.* 2024;22:632. DOI PubMed PMC
60. Senesi G, Lodrini AM, Mohammed S, et al. miR-24-3p secreted as extracellular vesicle cargo by cardiomyocytes inhibits fibrosis in human cardiac microtissues. *Cardiovasc Res.* 2025;121:143-56. DOI PubMed PMC
61. Ribeiro-Rodrigues TM, Laundos TL, Pereira-Carvalho R, et al. Exosomes secreted by cardiomyocytes subjected to ischaemia promote cardiac angiogenesis. *Cardiovasc Res.* 2017;113:1338-50. DOI PubMed
62. Ong SG, Lee WH, Huang M, et al. Cross talk of combined gene and cell therapy in ischemic heart disease: role of exosomal microRNA transfer. *Circulation.* 2014;130:S60-9. DOI PubMed PMC
63. Gollmann-Tepeköylü C, Pölzl L, Graber M, et al. miR-19a-3p containing exosomes improve function of ischaemic myocardium upon shock wave therapy. *Cardiovasc Res.* 2020;116:1226-36. DOI PubMed
64. Wei G, Li C, Jia X, et al. Extracellular vesicle-derived CircWhsc1 promotes cardiomyocyte proliferation and heart repair by activating TRIM59/STAT3/Cyclin B2 pathway. *J Adv Res.* 2023;53:199-218. DOI PubMed PMC
65. Guo D, Yang X, Yu R, et al. Macrophage-derived extracellular vesicles represent a promising endogenous iron-chelating therapy for iron overload and cardiac injury in myocardial infarction. *J Nanobiotechnology.* 2024;22:527. DOI PubMed PMC
66. Xiao X, Xu M, Yu H, et al. Mesenchymal stem cell-derived small extracellular vesicles mitigate oxidative stress-induced senescence in endothelial cells via regulation of miR-146a/Src. *Signal Transduct Target Ther.* 2021;6:354. DOI PubMed PMC
67. Wang F, Long G, Zhao C, et al. Plasma microRNA-133a is a new marker for both acute myocardial infarction and underlying coronary artery stenosis. *J Transl Med.* 2013;11:222. DOI PubMed PMC

68. Lee TL, Shen WC, Chen YC, et al. Mir221- and Mir222-enriched adsc-exosomes mitigate PM exposure-exacerbated cardiac ischemia-reperfusion injury through the modulation of the BNIP3-MAP1LC3B-BBC3/PUMA pathway. *Autophagy.* 2025;21:374-93. DOI PubMed PMC
69. Khan ZA, Janssen I, Mazzarelli JK, et al. Serial studies in subclinical atherosclerosis during menopausal transition (from the Study of Women's Health Across the Nation). *Am J Cardiol.* 2018;122:1161-8. DOI PubMed PMC
70. Karvinen S, Korhonen TM, Sievänen T, et al. Extracellular vesicles and high-density lipoproteins: exercise and oestrogen-responsive small RNA carriers. *J Extracell Vesicles.* 2023;12:e12308. DOI PubMed PMC
71. Kargl CK, Sterczala AJ, Santucci D, et al. Circulating extracellular vesicle characteristics differ between men and women following 12 weeks of concurrent exercise training. *Physiol Rep.* 2024;12:e16016. DOI PubMed PMC
72. Wei D, Zhan W, Gao Y, et al. RAB31 marks and controls an ESCRT-independent exosome pathway. *Cell Res.* 2021;31:157-77. DOI PubMed PMC
73. Kovácsházi C, Hambalkó S, Sayour NV, et al. Effect of hypercholesterolemia on circulating and cardiomyocyte-derived extracellular vesicles. *Sci Rep.* 2024;14:12016. DOI PubMed PMC
74. Wang J, Li L, Zhang Z, et al. Extracellular vesicles mediate the communication of adipose tissue with brain and promote cognitive impairment associated with insulin resistance. *Cell Metab.* 2022;34:1264-79.e8. DOI PubMed
75. Zhou Z, Mahdi A, Tratsiakovich Y, et al. Erythrocytes from patients with type 2 diabetes induce endothelial dysfunction via arginase I. *J Am Coll Cardiol.* 2018;72:769-80. DOI PubMed
76. Li X, Zhao W, Peng L, et al. Elevated serum extracellular vesicle arginase 1 in type 2 diabetes mellitus: a cross-sectional study in middle-aged and elderly population. *BMC Endocr Disord.* 2022;22:62. DOI PubMed PMC
77. Zhang H, Yan Z, Zhu J, et al. Extracellular mitochondrial-derived vesicles affect the progression of diabetic foot ulcer by regulating oxidative stress and mitochondrial dysfunction. *Adv Sci.* 2025;12:e2407574. DOI PubMed PMC
78. Chen C, Liang Z, He Y, et al. Bacteroides fragilis exacerbates T2D vascular calcification by secreting extracellular vesicles to induce M2 macrophages. *Adv Sci.* 2025;12:e2410495. DOI PubMed PMC
79. Barreiro K, Karttunen J, Valo E, et al. Selected miRNAs in urinary extracellular vesicles show promise for early and specific diagnostics of diabetic kidney disease. *J Extracell Biol.* 2025;4:e70089. DOI PubMed PMC
80. Lou NJ, Ni YH, Jia HY, et al. Urinary microvesicle-bound uromodulin: a potential molecular biomarker in diabetic kidney disease. *J Diabetes Res.* 2017;2017:3918681. DOI PubMed PMC
81. Jin Y, Sun G, Chen B, et al. Delivering miR-23b-3p by small extracellular vesicles to promote cell senescence and aberrant lipid metabolism. *BMC Biol.* 2025;23:41. DOI PubMed PMC
82. Phu TA, Ng M, Vu NK, Gao AS, Raffai RL. ApoE expression in macrophages communicates immunometabolic signaling that controls hyperlipidemia-driven hematopoiesis & inflammation via extracellular vesicles. *J Extracell Vesicles.* 2023;12:e12345. DOI PubMed PMC
83. Ma P, Wu J, Zhou R, et al. Glucocorticoid-induced muscle satellite cell-derived extracellular vesicles mediate skeletal muscle atrophy via the miR-335-5p/MAPK11/iNOS pathway. *Biomolecules.* 2025;15:1072. DOI PubMed PMC
84. Song J, Liu J, Cui C, et al. Mesenchymal stromal cells ameliorate diabetes-induced muscle atrophy through exosomes by enhancing AMPK/ULK1-mediated autophagy. *J Cachexia Sarcopenia Muscle.* 2023;14:915-29. DOI PubMed PMC
85. Shao X, Gong W, Wang Q, et al. Atrophic skeletal muscle fibre-derived small extracellular vesicle miR-690 inhibits satellite cell differentiation during ageing. *J Cachexia Sarcopenia Muscle.* 2022;13:3163-80. DOI PubMed PMC
86. Song J, Yang M, Xia L, et al. Aptamer-conjugated exosomes ameliorate diabetes-induced muscle atrophy by enhancing SIRT1/FoxO1/3a-mediated mitochondrial function. *J Cachexia Sarcopenia Muscle.* 2025;16:e13717. DOI PubMed PMC
87. Fang F, Yang J, Wang J, et al. The role and applications of extracellular vesicles in osteoporosis. *Bone Res.* 2024;12:4. DOI PubMed PMC
88. Li D, Liu J, Guo B, et al. Osteoclast-derived exosomal miR-214-3p inhibits osteoblastic bone formation. *Nat Commun.* 2016;7:10872. DOI PubMed PMC
89. Uenaka M, Yamashita E, Kikuta J, et al. Osteoblast-derived vesicles induce a switch from bone-formation to bone-resorption in vivo. *Nat Commun.* 2022;13:1066. DOI PubMed PMC
90. Lee KS, Lee J, Kim HK, et al. Extracellular vesicles from adipose tissue-derived stem cells alleviate osteoporosis through osteoprotegerin and miR-21-5p. *J Extracell Vesicles.* 2021;10:e12152. DOI PubMed PMC
91. Zhi F, Ding Y, Wang R, Yang Y, Luo K, Hua F. Exosomal hsa_circ_0006859 is a potential biomarker for postmenopausal osteoporosis and enhances adipogenic versus osteogenic differentiation in human bone marrow mesenchymal stem cells by sponging miR-431-5p. *Stem Cell Res Ther.* 2021;12:157. DOI PubMed PMC
92. Shi H, Jiang X, Xu C, Cheng Q. MicroRNAs in serum exosomes as circulating biomarkers for postmenopausal osteoporosis. *Front Endocrinol.* 2022;13:819056. DOI PubMed PMC

93. Wang Q, Shen X, Chen Y, Chen J, Li Y. Osteoblasts-derived exosomes regulate osteoclast differentiation through miR-503-3p/Hpse axis. *Acta Histochem.* 2021;123:151790. DOI PubMed
94. Yu L, Hu M, Cui X, et al. M1 macrophage-derived exosomes aggravate bone loss in postmenopausal osteoporosis via a microRNA-98/DUSP1/JNK axis. *Cell Biol Int.* 2021;45:2452-63. DOI PubMed
95. Davis C, Dukes A, Drewry M, et al. MicroRNA-183-5p increases with age in bone-derived extracellular vesicles, suppresses bone marrow stromal (Stem) cell proliferation, and induces stem cell senescence. *Tissue Eng Part A.* 2017;23:1231-40. DOI PubMed PMC
96. Chen CY, Wang Z, Hong CG, et al. Brain neuron-derived WDFY1 induces bone loss. *Nat Aging.* 2026;6:329-48. DOI PubMed
97. He S, Chen D, Hu M, et al. Bronchial epithelial cell extracellular vesicles ameliorate epithelial-mesenchymal transition in COPD pathogenesis by alleviating M2 macrophage polarization. *Nanomedicine.* 2019;18:259-71. DOI PubMed
98. Devulder JV, Baker JR, Fenwick PS, Odqvist L, Donnelly LE, Barnes PJ. Chronic obstructive pulmonary disease airway epithelial cell-derived extracellular vesicles spread cellular senescence via microRNA-34a. *Am J Respir Cell Mol Biol.* 2025;73:210-20. DOI PubMed PMC
99. Wang R, Zhu Z, Peng S, et al. Exosome microRNA-125a-5p derived from epithelium promotes M1 macrophage polarization by targeting IL1RN in chronic obstructive pulmonary disease. *Int Immunopharmacol.* 2024;137:112466. DOI PubMed
100. Genschmer KR, Russell DW, Lal C, et al. Activated PMN exosomes: pathogenic entities causing matrix destruction and disease in the lung. *Cell.* 2019;176:113-26.e15. DOI PubMed PMC
101. Barnes PJ, Baker J, Donnelly LE. Cellular senescence as a mechanism and target in chronic lung diseases. *Am J Respir Crit Care Med.* 2019;200:556-64. DOI PubMed
102. Zhang M, Xue X, Lou Z, Lin Y, Li Q, Huang C. Exosomes from senescent epithelial cells activate pulmonary fibroblasts via the miR-217-5p/Sirt1 axis in paraquat-induced pulmonary fibrosis. *J Transl Med.* 2024;22:310. DOI PubMed PMC
103. Peng Y, Mei S, Qi X, et al. PGC-1α mediates migrasome secretion accelerating macrophage-myofibroblast transition and contributing to sepsis-associated pulmonary fibrosis. *Exp Mol Med.* 2025;57:759-74. DOI PubMed PMC
104. Fujita Y, Fujimoto S, Miyamoto A, et al. Fibroblast-derived extracellular vesicles induce lung cancer progression in the idiopathic pulmonary fibrosis microenvironment. *Am J Respir Cell Mol Biol.* 2023;69:34-44. DOI PubMed
105. Ali S, Malloci M, Safiedeen Z, et al. ; Metabol study Group. LPS-enriched small extracellular vesicles from metabolic syndrome patients trigger endothelial dysfunction by activation of TLR4. *Metabolism.* 2021;118:154727. DOI PubMed
106. Wang J, Wu W, Wen T, et al. Extracellular vesicle-bound S100A8/A9 is differentially expressed in septic shock and prompts acute lung injury. *Respir Res.* 2025;26:107. DOI PubMed PMC
107. Hsu AY, Huang Q, Pi X, et al. Neutrophil-derived vesicles control complement activation to facilitate inflammation resolution. *Cell.* 2025;188:1623-41.e26. DOI PubMed PMC
108. Eckhardt CM, Gambazza S, Bloomquist TR, et al. Extracellular vesicle-encapsulated microRNAs as novel biomarkers of lung health. *Am J Respir Crit Care Med.* 2023;207:50-9. DOI PubMed PMC
109. Li G, Wang B, Ding X, Zhang X, Tang J, Lin H. Plasma extracellular vesicle delivery of miR-210-3p by targeting ATG7 to promote sepsis-induced acute lung injury by regulating autophagy and activating inflammation. *Exp Mol Med.* 2021;53:1180-91. DOI PubMed PMC
110. Gao M, Yu T, Liu D, et al. Sepsis plasma-derived exosomal miR-1-3p induces endothelial cell dysfunction by targeting SERP1. *Clin Sci.* 2021;135:347-65. DOI PubMed PMC
111. Wang B, Gu C, Zhang Y, et al. MiR-27a-5p deficiency in plasma exosomes derived from obese individuals exacerbates ventilator-induced lung injury in vitro and in vivo. *J Transl Med.* 2025;23:1264. DOI PubMed PMC
112. López-Otín C, Pietrocola F, Roiz-Valle D, Galluzzi L, Kroemer G. Meta-hallmarks of aging and cancer. *Cell Metab.* 2023;35:12-35. DOI PubMed
113. Cocks A, Martinez-Rodriguez V, Del Vecchio F, et al. Diverse roles of EV-RNA in cancer progression. *Semin Cancer Biol.* 2021;75:127-35. DOI PubMed PMC
114. Cheng L, Hill AF. Therapeutically harnessing extracellular vesicles. *Nat Rev Drug Discov.* 2022;21:379-99. DOI PubMed
115. Moeng S, Son SW, Lee JS, et al. Extracellular vesicles (EVs) and pancreatic cancer: from the role of EVs to the interference with EV-mediated reciprocal communication. *Biomedicines.* 2020;8:267. DOI PubMed PMC
116. Dai G, Yao X, Zhang Y, et al. Colorectal cancer cell-derived exosomes containing miR-10b regulate fibroblast cells via the PI3K/Akt pathway. *Bull Cancer.* 2018;105:336-49. DOI PubMed
117. Li XJ, Ren ZJ, Tang JH, Yu Q. Exosomal microRNA MiR-1246 promotes cell proliferation, invasion and drug resistance by targeting CCNG2 in breast cancer. *Cell Physiol Biochem.* 2017;44:1741-8. DOI PubMed
118. Zhou W, Fong MY, Min Y, et al. Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. *Cancer Cell.* 2014;25:501-15. DOI PubMed PMC

119. Chen S, Iannotta D, O'Mara ML, Goncalves JP, Wolfram J. Extracellular vesicle lipids in cancer immunoevasion. *Trends Cancer.* 2023;9:883-6. DOI PubMed
120. Zhao H, Yang L, Baddour J, et al. Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism. *Elife.* 2016;5:e10250. DOI PubMed PMC
121. Morrissey SM, Zhang F, Ding C, et al. Tumor-derived exosomes drive immunosuppressive macrophages in a pre-metastatic niche through glycolytic dominant metabolic reprogramming. *Cell Metab.* 2021;33:2040-58.e10. DOI PubMed PMC
122. Chen G, Huang AC, Zhang W, et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature.* 2018;560:382-6. DOI PubMed PMC
123. Qu L, Ding J, Chen C, et al. Exosome-transmitted lncARSR promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA. *Cancer Cell.* 2016;29:653-68. DOI PubMed
124. Cheng X, Henick BS, Cheng K. Anticancer therapy targeting cancer-derived extracellular vesicles. *ACS Nano.* 2024;18:6748-65. DOI PubMed
125. Hwang WL, Huang SW, Hsiao AC, et al. Harnessing engineered mesenchymal stem cell-derived extracellular vesicles for innovative cancer treatments. *Stem Cell Res Ther.* 2025;16:648. DOI PubMed PMC
126. Wei Y, Wu Y, Zhao R, et al. MSC-derived sEVs enhance patency and inhibit calcification of synthetic vascular grafts by immunomodulation in a rat model of hyperlipidemia. *Biomaterials.* 2019;204:13-24. DOI PubMed
127. Zeng P, Yang J, Liu L, et al. ERK1/2 inhibition reduces vascular calcification by activating miR-126-3p-DKK1/LRP6 pathway. *Theranostics.* 2021;11:1129-46. DOI PubMed PMC
128. Guiot J, Cambier M, Boeckx A, et al. Macrophage-derived exosomes attenuate fibrosis in airway epithelial cells through delivery of antifibrotic miR-142-3p. *Thorax.* 2020;75:870-81. DOI PubMed PMC
129. Zhao M, Liu S, Wang C, et al. Mesenchymal stem cell-derived extracellular vesicles attenuate mitochondrial damage and inflammation by stabilizing mitochondrial DNA. *ACS Nano.* 2021;15:1519-38. DOI PubMed
130. Lan Y, Xie H, Jin Q, et al. Extracellular vesicles derived from neural EGFL-Like 1-modified mesenchymal stem cells improve acellular bone regeneration via the miR-25-5p-SMAD2 signaling axis. *Bioact Mater.* 2022;17:457-70. DOI PubMed PMC
131. Wang H, Wang B, Zhang A, et al. Exosome-mediated miR-29 transfer reduces muscle atrophy and kidney fibrosis in mice. *Mol Ther.* 2019;27:571-83. DOI PubMed PMC
132. Iyaswamy A, Thakur A, Guan XJ, et al. Fe65-engineered neuronal exosomes encapsulating corynoxine-B ameliorate cognition and pathology of Alzheimer's disease. *Signal Transduct Target Ther.* 2023;8:404. DOI PubMed PMC
133. Shie MY, Chen MC, Chen Y, et al. Engineered extracellular vesicles-mediated curcumin delivery in brain microenvironment modulating lysosomes, mitochondria, and microglia reprogram for parkinson's disease therapy. *J Nanobiotechnology.* 2025;24:46. DOI PubMed PMC
134. Wang C, Yang Y, Zhang X, et al. Secreted endogenous macrosomes reduce Aβ burden and ameliorate Alzheimer's disease. *Sci Adv.* 2023;9:eade0293. DOI PubMed PMC
135. Zhang J, He S, Xiao Q, et al. Engineered mesenchymal stem cell-derived extracellular vesicles overexpressing miR-146a alleviate neuroinflammation in Alzheimer's disease. *Neural Regen Res.* 2026;21:4989-99. DOI PubMed PMC
136. Bodart-Santos V, Ruan Z, Melvin BC, Pandey I, Ikezu S, Ikezu T. Selenoprotein P is a target for regulating extracellular vesicle biogenesis and secretion from activated microglia in vivo. *Cell Rep.* 2024;43:115025. DOI PubMed PMC
137. Tallon C, Bell BJ, Sharma A, et al. Dendrimer-conjugated nSMase2 inhibitor reduces Tau propagation in mice. *Pharmaceutics.* 2022;14:2066. DOI PubMed PMC
138. Gu Y, Hao M, Wang L, et al. Mesenchymal stem cell-derived nanovesicles coated PLGA nanoparticle (MSC-PLGA-NPs) remodel lysosomal function to clear pathological proteins in Alzheimer's disease models. *Nanomedicine.* 2026;21:213-227. DOI PubMed PMC
139. Chen W, Wang H, Ye X, et al. Gardenia-derived extracellular vesicles exert therapeutic effects on dopaminergic neuron apoptosis-mediated Parkinson's disease. *NPJ Parkinsons Dis.* 2025;11:200. DOI PubMed PMC
140. Zheng J, Ren Y, Ke J, et al. Engineered extracellular vesicles derived from juvenile mice enhance mitochondrial function in the aging bone microenvironment and achieve rejuvenation. *ACS Nano.* 2025;19:13952-67. DOI PubMed
141. Li X, Lu W, Ni L, Su J, Wang D, Deng Z. Mitochondria-rich extracellular vesicles derived from the culture supernatant of human synovial Fluid-derived mesenchymal stem cells Inhibited senescence of Stressed/inflammatory Licensed chondrocytes and Delayed Osteoarthritis progression. *Int Immunopharmacol.* 2025;147:113954. DOI PubMed
142. Sun Z, Li J, Zheng Y, et al. Small extracellular vesicles derived from mesenchymal stromal cells loaded with β-nicotinamide mononucleotide activate NAD^+/SIRT3 signaling pathway-mediated mitochondrial autophagy to delay skin aging. *Stem Cell Res Ther.* 2025;16:339. DOI PubMed PMC
143. Yang J, Yun X, Zheng W, et al. Nanoscale engineered exosomes for dual delivery of Sirtuin3 and insulin to ignite mitochondrial recovery in myocardial ischemia-reperfusion. *J Nanobiotechnology.* 2025;23:439. DOI PubMed PMC

144. Liu S, Mou J, Xiong Z, et al. Interferon-γ-induced mesenchymal stem cell exosomes attenuate chondrocyte senescence and osteoarthritis progression by Hsp70. *ACS Nano.* 2025;19:40932-50. DOI PubMed
145. Di Maio R, Barrett PJ, Hoffman EK, et al. α-Synuclein binds to TOM20 and inhibits mitochondrial protein import in Parkinson's disease. *Sci Transl Med.* 2016;8:342ra78. DOI PubMed PMC
146. Burbulla LF, Song P, Mazzulli JR, et al. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. *Science.* 2017;357:1255-61. DOI PubMed PMC
147. Chaudhari AP, Budayr OM, Bonacquisti EE, et al. The status of extracellular vesicles as drug carriers and therapeutics. *Nat Rev Bioeng.* 2026;4:301-18. DOI PubMed PMC
148. Gupta D, Zickler AM, El Andaloussi S. Dosing extracellular vesicles. *Adv Drug Deliv Rev.* 2021;178:113961. DOI PubMed
149. Terai S, Asonuma M, Hoshino A, et al. Guidance on the clinical application of extracellular vesicles. *Regen Ther.* 2025;29:43-50. DOI PubMed PMC

Disclaimer/Publisher's Note: All statements, opinions, and data contained in this publication are solely those of the individual author(s) and contributor(s) and do not necessarily reflect those of OAE and/or the editor(s). OAE and/or the editor(s) disclaim any responsibility for harm to persons or property resulting from the use of any ideas, methods, instructions, or products mentioned in the content.


© The Author(s) 2026. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.