

The Dual Role of Extracellular Vesicles in Aging and Age-Related Diseases: Pathophysiology and Therapeutic Potential

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Abstract: Aging is a complex biological process characterized by progressive loss of physiological integrity and represents the primary risk factor for numerous chronic disorders, including neurodegenerative diseases, diabetes mellitus, cardiovascular disease, and stroke. Increasing evidence indicates that chronic low-grade inflammation (“inflammaging”), genomic instability, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, and impaired intercellular communication collectively drive aging and age-related pathologies. Extracellular vesicles (EVs), a heterogeneous population of lipid bilayer-enclosed nanoparticles released by nearly all cell types, have emerged as critical regulators of these processes by mediating intercellular transfer of proteins, lipids, metabolites, and nucleic acids. In this review, we systematically synthesize current advances in EV biology within the context of aging and major age-related diseases, emphasizing their double-edged roles in disease pathogenesis and therapy. We discuss how senescent or diseased cell-derived EVs propagate inflammation, oxidative stress, genomic damage, mitochondrial dysfunction, and maladaptive immune responses, thereby accelerating tissue degeneration. Conversely, EVs derived from stem cells or young, healthy tissues exert therapeutic and rejuvenating effects by restoring redox balance, modulating immune polarization, enhancing mitochondrial function, regulating nutrient-sensing pathways, and promoting tissue repair and regeneration. Finally, we highlight the therapeutic potential of native and engineered EVs as diagnostic biomarkers and treatment modalities for aging and age-related diseases, while discussing key limitations, including rapid systemic clearance and targeting efficiency. Collectively, this review provides a comprehensive and therapy-oriented framework for understanding EVs as both drivers of aging-associated pathology and promising tools for anti-aging and regenerative medicine.

Keywords: extracellular vesicles, aging, neurodegenerative diseases, diabetes, cardiovascular disease, stroke

Introduction

Recent advances in socioeconomic development and medical technology have markedly extended human life expectancy. However, increased longevity has been accompanied by a growing burden of age-related diseases, including neurodegenerative disorders, diabetes mellitus, cardiovascular disease, and stroke.¹ As the global population ages, elucidating the molecular and cellular mechanisms that drive aging and its associated pathologies has become a central focus of biomedical research. Aging is defined as a progressive decline in physiological integrity across tissues and organs, ultimately increasing vulnerability to disease and mortality.² A hallmark feature of aging is chronic, low-grade, sterile inflammation termed “inflammaging” which is closely linked to the development of dementia, metabolic dysfunction, and cardiovascular failure.³ This persistent inflammatory state functions not only as a biomarker of biological aging but also as an active driver of tissue degeneration. To conceptualize the biological basis of aging, aging hallmarks have been

categorized into primary, antagonistic, and integrative processes.⁴ Primary hallmarks, including genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis, initiate cellular damage, whereas antagonistic hallmarks such as mitochondrial dysfunction, reactive oxygen species (ROS) accumulation, dysregulated nutrient sensing, and cellular senescence are initially compensatory but become deleterious when chronically activated.⁵ These processes converge to impair tissue regeneration and functional homeostasis.

Within this complex aging landscape, extracellular vesicles (EVs) build up's have emerged as critical mediators of intercellular communication and systemic regulation. EVs are lipid bilayer-enclosed particles that carry proteins, lipids, and nucleic acids derived from donor cells and are widely distributed in biological fluids.^{6,7} Due to their heterogeneity in biogenesis, size, cargo composition, and biological function, EVs participate in diverse physiological and pathological processes. While many recent reviews have summarized EV functions in individual diseases, the present review provides a distinct integrative perspective by examining EV biology across aging and four major age-related disease clusters: neurodegeneration, diabetes, cardiovascular disease, and stroke through a unified “double-edged sword” framework.⁵ Specifically, we contrast pathogenic versus protective EV cargos and contexts, and critically evaluate methodological challenges related to EV isolation and characterization, including the confounding contributions of non-vesicular extracellular nanoparticles (NVEPs) such as exomeres and supermeres.⁸ These factors may have led to misattribution of biological effects in earlier studies.

Understanding the multifaceted roles of EVs in biological aging is of substantial scientific and translational significance. EVs can propagate inflammatory signals, oxidative stress, and senescence-associated phenotypes, thereby accelerating age-related tissue dysfunction, yet they also hold promise as therapeutic agents capable of modulating immune responses, restoring cellular homeostasis, and promoting tissue repair. By systematically synthesizing current evidence and highlighting unresolved mechanistic questions, this review aims to clarify the dualistic nature of EVs in aging and age-related diseases. This integrated framework not only advances conceptual understanding of aging biology but also informs the rational development of EV-based diagnostics and regenerative medicine strategies.

Extracellular Vesicles

Biogenesis and Classification of EVs

The biogenesis of EVs begins with the inward budding of endosomal membranes, leading to the formation of multivesicular bodies (MVBs) that release small EVs (sEVs) through fusion with the plasma membrane.⁹ Based on their size and biogenesis pathways, EVs are generally classified into microvesicles (MVs, 50–10,000 nm) and sEVs (30–150 nm).^{10,11} Beyond their structural classification, EVs actively modulate gene expression and cellular behavior by transferring functional proteins, lipids, carbohydrates, and nucleic acids (including DNA, mRNA, and non-coding RNAs) to recipient cells through mechanisms such as endocytosis, membrane fusion, or receptor-mediated uptake.^{12–14} Through these interactions, EVs influence both local cellular microenvironments and systemic physiological processes throughout the organism.¹⁵

Pharmacokinetics and Systemic Clearance of EVs

Despite their critical roles, an important aspect of EV biology is often underestimated: their relatively short lifespan in systemic circulation. Numerous *in vivo* pharmacokinetic studies demonstrate that EVs are rapidly cleared following systemic administration. Some intravenously delivered sEV subtypes exhibit plasma half-lives of only a few minutes, with certain species displaying a half-life of approximately 2 minutes.^{16,17} Consistent with these findings, physiologically based pharmacokinetic (PBPK) modeling shows that administered EVs are quickly sequestered and phagocytosed by macrophages and the reticuloendothelial system (RES), resulting in rapid systemic elimination.^{18,19} More recent experimental investigations provide further support: for example, labeled murine plasma EVs (PS⁺ EVs) were found to have a circulating half-life of roughly 30 minutes before being rapidly removed from the bloodstream, although residual EVs persisted within splenic immune cells.²⁰ EV half-lives also vary substantially by cellular origin; human platelet derived EVs exhibit a longer circulation time of approximately 5.5 hours, yet still remain short-lived compared with many synthetic nanocarriers.²¹

Strategies to Extend EV Circulation Time

Rapid clearance poses a major challenge for EV based signaling or therapeutic applications, as short circulation times limit their ability to sustain prolonged communication or maintain therapeutic concentrations. Consequently, EV based therapies may require frequent dosing or high administration levels. To overcome these limitations, several engineering strategies have been developed to extend EV circulation time. These include surface “camouflage” approaches, such as expressing CD47 or other “don’t-eat-me” signals to inhibit macrophage-mediated phagocytosis.²² PEGylation of the EV membrane with polyethylene glycol to reduce mononuclear phagocyte system (MPS) uptake;²² and local or targeted delivery strategies, such as encapsulating EVs within hydrogels to achieve sustained, site specific release.²³ These methods help prolong the circulation time of EVs.

Engineered EVs as Targeted Therapeutic Platforms

Building upon these insights, engineered EVs have emerged as highly adaptable therapeutic platforms and have achieved substantial advances in preclinical research. A notable example is the engineering of dendritic cell derived EVs expressing Lamp2b fused to the neuron-specific RVG peptide, enabling targeted delivery of siRNA to neuronal cells and producing effective gene knockdown.^{24,25} Similarly, red blood cell-derived EVs (RBCEVs) can be functionalized via enzyme-catalyzed coupling with targeting peptides or ligands such as the ET peptide for EGFR⁺ lung cancer cells and subsequently loaded with chemotherapeutic agents including paclitaxel (PTX). These engineered RBCEVs demonstrate superior tumor accumulation and enhanced therapeutic efficacy compared with unmodified EVs in EGFR⁺ lung cancer models.^{25,26} Collectively, these advancements underscore the versatility of engineered EVs as precise and powerful delivery vehicles for targeted therapeutic interventions.

Immunomodulatory Functions of EVs

In parallel, accumulating evidence indicates that EVs play crucial roles in modulating both innate and adaptive immune responses. They deliver bioactive ligands and nucleic acids that can reprogram immune cell behavior shifting macrophage polarization, modulating dendritic cell antigen presentation, and regulating T-cell activation. Notably, tumor or senescent cell derived EVs enriched in specific miRNAs or heat shock proteins (HSPs) tend to promote M1-like proinflammatory phenotypes, whereas mesenchymal stem cell (MSC)-derived EVs (MSC-EVs) generally induce an M2-like, tissue-repairing phenotype. This functional dichotomy has profound implications for immunopharmacology and the rational design of EV-based therapeutic strategies.^{8,27}

Noncanonical Biological Functions of EVs

In addition to mediating intercellular communication, EVs exert a variety of noncanonical biological functions that are increasingly recognized as fundamental to cellular and tissue homeostasis.⁷ Traditionally viewed as vehicles for intercellular signal exchange, EVs also act as regulators of intracellular quality control, biochemical microreactors, and mediators of extracellular matrix (ECM) remodeling. These alternative roles, though often overlooked, have profound implications for understanding tissue physiology, aging, and disease progression.^{28,29}

EVs as a Cellular Waste Disposal System

EV secretion constitutes an evolutionarily conserved mechanism for removing superfluous or harmful cellular components. Cells utilize EV mediated extrusion to eliminate misfolded proteins, oxidized lipids, cytoplasmic DNA fragments, and even damaged organelle remnants, thereby preventing intracellular stress and inflammation.^{30,31} This “excretory” function is particularly important in long lived or postmitotic cells such as neurons, which have limited capacity for proteasomal or lysosomal degradation. For example, DNA containing EVs have been shown to protect cells from cytosolic DNA accumulation and cGAS-STING mediated senescence associated inflammation.³² Similarly, tumor and senescent cells increase EV release as a compensatory response to oxidative or genotoxic stress, highlighting EV secretion as a stress adaptation strategy.³³

Matrix Vesicles as Nanoreactors for Biomineralization

A distinct subset of EVs, termed MVs, plays a pivotal role in the initiation of tissue mineralization. These nanosized vesicles, released mainly by osteoblasts, chondrocytes, and odontoblasts, concentrate calcium and phosphate ions through the activity of membrane-bound enzymes such as alkaline phosphatase (ALP), annexins, and PHOSPHO1.^{34,35} Within the confined lumen of MVs, these ions nucleate to form hydroxyapatite crystals, which subsequently propagate into the surrounding ECM.³⁶ Disruption of MV formation or composition leads to skeletal mineralization defects, as seen in hypophosphatasia.³⁷ Beyond bone, emerging evidence suggests that similar EV mediated mineralization contributes to ectopic calcification in vascular smooth muscle cells and other soft tissues, linking EVs to aging associated vascular pathology.^{38,39}

Interactions Between EVs and the Extracellular Matrix

EVs also function as dynamic mediators of ECM remodeling. They can directly bind to ECM components such as collagen, laminin, or fibronectin through integrins and tetraspanins, acting as localized delivery vehicles for proteases and signaling molecules.^{40,41} Many EVs carry matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and ECM modifying enzymes that regulate tissue stiffness, fibrosis, and cellular migration. For instance, cancer derived EVs rich in MMP-2 and MMP-9 degrade the ECM to facilitate tumor invasion and metastasis, whereas fibroblast or stem cell derived EVs can promote ECM regeneration and wound healing.⁴² Moreover, the ECM itself can serve as a reservoir for EVs, providing a structural niche that stabilizes their bioactive cargo and enables sustained paracrine signaling.⁴³

EV Isolation, Characterization

Emerging Standards and Advanced Characterization Technologies

Efficient isolation of EVs remains technically challenging due to the frequent co-isolation of abundant non-vesicular components (Table 1). Conventional ultracentrifugation and polymer-based precipitation methods often co-purify albumin, apolipoproteins (ApoA1 and ApoB), Argonaute-2 (Ago2) ribonucleoprotein complexes, and vault particles, resulting in contaminated proteomic and transcriptomic profiles and potential misinterpretation of EV-associated functions.⁴⁴ To overcome these limitations, advanced separation strategies have been developed. Asymmetric flow field-flow fractionation (AF4) enables high-resolution, label-free separation of EV subpopulations from NVEPs, including exomeres and supermeres, and has been validated for distinguishing lipoprotein-bound miRNAs from bona fide EV cargo.^{45,46} In addition, combining density gradient ultracentrifugation with size-exclusion chromatography (SEC) significantly improves EV purity, with SEC-isolated EVs retaining higher biological activity compared with

Table 1 Summary of EV Subtypes, Isolation, and Characterization Methods

Type	Isolation/Enrichment Methods	Characterization/Validation Techniques	Ref.
sEVs	Differential ultracentrifugation; Tangential Flow Filtration (TFF); Density Gradient + SEC; Immunoaffinity capture (CD63/CD9/CD81)	Cryo-electron microscopy/tomography. Single particle tracking. Multi-omic profiling. Machine learning-based classification. Negative marker assessment (ApoA1, ApoB, MVP, Ago2)	[44,46,49]
Exomeres	AF4 fractionation ± MALS or NTA	Cryo-electron microscopy. Multi-omic profiling. Machine learning classification	[50]
Supermeres	AF4 fractionation ± MALS or NTA; density gradient validation	Cryo-electron microscopy; Proteomics.	[46,50]
General NVEPs	AF4; SEC; Exclusion from immunoaffinity capture	Nuclease/proteinase protection assays Cryo-EM. Cargo composition analysis; Machine learning-based differentiation	[45,46]

ultracentrifugation alone.⁴⁷ Immunoaffinity capture approaches targeting canonical EV markers (CD63, CD9, and CD81), while simultaneously assessing negative markers such as ApoA1, ApoB, major vault protein (MVP), and Ago2, are now explicitly recommended in the MISEV 2023 guidelines to enhance isolation specificity and experimental rigor.⁴⁸

EV Characterization and Discrimination from Non-Vesicular Nanoparticles

Beyond isolation, rigorous characterization is essential to distinguish membrane-enclosed EVs from non-vesicular extracellular nanomaterials. High-resolution imaging techniques, particularly cryo-electron tomography and single-particle tracking, provide nanometer-scale visualization of vesicular membranes and enable discrimination between EVs and proteinaceous particles such as vaults.⁵¹ These approaches offer direct structural evidence supporting accurate classification of extracellular nanoparticles. Furthermore, emerging characterization strategies integrating multi-omic profiling with machine learning-based classification algorithms allow differentiation of EV and NVEP subtypes based on cargo composition and molecular signatures.⁵² The establishment of standardized reference materials and quantitative purity indices, as emphasized in the MISEV 2023 guidelines, is critical for improving reproducibility and for redefining experimental frameworks used to assess EV-mediated intercellular communication.⁵³

Integrated Workflow for sEV NVEP Separation and Validation

The separation workflow for sEVs from exomeres and supermeres generally involves multiple sequential steps. Preprocessing removes cells and large debris via low-speed centrifugation followed by 0.22µm filtration. Initial enrichment of vesicles is achieved through differential ultracentrifugation or tangential flow filtration (TFF) to eliminate large volume proteins and lipids.⁴⁹ High-resolution fractionation using AF4 coupled with multi-angle light scattering (MALS) or online nanoparticle tracking analysis (NTA) enables separation of 30~40 nm exomeres from 60~120 nm sEVs. Subsequent density gradient ultracentrifugation or SEC can validate the membranous vesicle fraction according to buoyant density and assess potential contamination with negative markers (ApoA1/ApoB, MVP, Ago2).⁵⁰ Orthogonal verification includes cryo-electron microscopy to confirm vesicular membrane integrity, comparative proteomics, and nuclease/proteinase protection assays to determine whether cargo is membrane-protected. Finally, functional validation can be performed by immunoaffinity enrichment of sEVs (CD63/CD9/CD81) with parallel comparison to exomere or supermere-enriched fractions, enabling accurate attribution of observed biological effects.⁴⁶

Aging and EVs

Targeted Therapeutic Interventions

EVs are pivotal mediators of the aging process through their capacity to transfer bioactive molecules between cells. Senescent cells exhibit increased EV secretion, and these vesicles often carry pro-senescent cargos, including inflammatory cytokines, miRNAs, and damaged proteins, which propagate cellular dysfunction to neighboring cells and tissues, thereby amplifying age-associated inflammation and tissue degeneration.^{54–56} This EV-mediated signaling contributes to the senescence-associated secretory phenotype (SASP) and exacerbates organ decline. Conversely, EVs derived from non-senescent cells, particularly stem or progenitor cells, are enriched in anti-inflammatory and antioxidant molecules, which mitigate oxidative stress, modulate immune responses, and promote tissue repair.^{57–60} These EVs can attenuate the pro-inflammatory environment established by senescent cells, reduce SASP activity, and restore homeostasis in aging tissues. In addition, EVs influence mitochondrial function, proteostasis, and extracellular matrix remodeling, further impacting the systemic aging process.^{58,60} Importantly, the dual role of EVs accelerating or decelerating aging—depends on their cellular source and molecular cargo, highlighting their potential as both biomarkers and therapeutic targets in age-related pathologies. The dynamic regulation of EV composition with age underscores their critical function in orchestrating intercellular communication that shapes organismal aging. (Table 2).

Table 2 Role of EVs in Aging

Effect	EVs cargos	Mechanism of Action	Ref
Promote Aging	ATM miR-21-5p, miR-217 miR-23b-3p, miR-494-3p	Inhibition and gene depletion and reversal of the aging process Down-regulation of DNMT1, SIRT1 in young cells Increased mitochondrial ROS cause damage and induce subsequent lung epithelial cell senescence	[61] [62] [63]
Delay Aging	ATR DNMT1, SIRT1 eNAMPT	Induces the NF-κB signaling pathway, which contributes to SASP Maintaining patterns of genetic methylation and ensuring genomic integrity through mitosis. Enhanced NAD synthesis	[1] [64] [65]

EVs and Cellular Senescence Hallmarks

Genomic Instability

The slow buildup of genetic damage over time is a typical aspect of aging.⁶⁶ An increased accumulation of DNA damage is the cause of some premature aging disorders, including Werner syndrome and Bloom syndrome.⁶⁷ The stability and integrity of DNA are continuously endangered as humans age by both internal and external sources, such as spontaneous hydrolysis, ROS, and mistakes in DNA replication, as well as by physical, chemical, and biological agents.⁶⁸ According to certain research, EVs may also help maintain the stability of DNA as it ages. Signals of DNA damage are transferred between cells by EVs. The senescence cascade is accelerated when senescent cells release EVs that include damaged DNA fragments, γ-H2AX proteins, or cGAS-STING activators. These EVs can cause chromosomal abnormalities or trigger stress responses in neighboring cells.⁶⁹ The aging process is accelerated in this case by EVs.

Telomere Attrition

DNA damage accumulates with age, impacting the genome nearly randomly, but there are specific chromosomal areas, such as telomeres, that are particularly sensitive to age-related degeneration.⁷⁰ Replicative DNA polymerase is incapable of fully replicating the termini of linear DNA molecules, a function reserved for specialized DNA polymerases known as telomerase.⁷¹ Telomeres can be seen as DNA breaks that evade detection by the DNA repair system due to the establishment of a specialized nucleoprotein complex known as shelterin.⁷¹ This introduces an additional characteristic of telomeres: they not only progressively shorten in the absence of telomerase, but even in its presence, external DNA damage to telomeres becomes imperceptible to DNA repair processes due to the presence of shelterin. Consequently, DNA damage at telomeres induces persistent DNA damage, resulting in detrimental cellular effects, including senescence.⁷² Likewise, EVs can impact cellular senescence by influencing telomeres, as they contribute to telomere attrition through modulation of telomerase activity and regulation of telomere-protective protein expression. For instance, EVs sourced from youthful stem cells can be augmented with miRNAs that enhance TERT expression, hence extending telomeres and decelerating the aging process in senescent cells.⁷³

Epigenetic Alterations

Epigenetic modifications influence the trajectory of life.⁷⁴ Epigenetic modifications encompass altered DNA methylation patterns, post-translational histone modifications, and chromatin reorganization. Age-associated epigenetic signatures include elevated acetylation of histone H4K16, increased trimethylation of H4K20 or H3K4, and reduced methylation of H3K9 or trimethylation of H3K27.^{72,75} Emerging evidence indicates that senescence-associated EVs are enriched in miRNAs capable of regulating epigenetic machinery in recipient cells. For example, researcher demonstrated that EVs released from senescent fibroblasts are enriched in miR-29 family members, which directly target DNA methyltransferases DNMT3A and DNMT3B, leading to global DNA hypomethylation in neighboring cells.^{62,76,77} Similarly, researchers have reported that miR-34a is selectively packaged into EVs derived from senescent endothelial cells and suppresses SIRT1 and class I histone deacetylases, thereby promoting histone hyperacetylation and chromatin relaxation in recipient cells.^{77,78} In addition, EV-associated miR-34a has been shown to indirectly influence histone methylation by modulating EZH2-dependent H3K27 trimethylation, reinforcing senescence-associated transcriptional programs.⁷⁹

Through EV-mediated transfer of epigenetically active miRNAs, senescent cells can reprogram the chromatin landscape of surrounding cells, amplify senescence signaling, and ultimately accelerate the aging process.

Loss of Proteostasis

Aging and certain age-related disorders are linked to protein homeostasis or its impairment.⁸⁰ All cells employ several quality control systems to preserve the integrity and functionality of their proteome.⁸¹ Protein systems operate in a coordinated fashion to either repair the structure of misfolded polypeptides or to eliminate and degrade them entirely, thus limiting the buildup of damaged components and maintaining the ongoing replenishment of intracellular proteins.⁸² Persistent production of unfolded, misfolded, or aggregated proteins can result in the onset of various age-related disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD).⁸⁰ EVs are intended to function as a mechanism for maintaining protein homeostasis by eliminating improperly folded proteins or aggregates (eg, A β , α -synuclein). Nonetheless, over the aging process, this role becomes overburdened, resulting in the dissemination of pathogenic proteins via EVs and intensifying protein stress in adjacent cells.⁸³

Deregulated Nutrient Sensing

The mammalian growth axis comprises growth hormone (GH) synthesized by the anterior pituitary gland and its secondary mediator, insulin-like growth factor (IGF-1), produced by various cell types, particularly hepatocytes, in response to GH. The intracellular signaling pathway activated by IGF-1 is identical to that triggered by insulin, which notifies the cell of glucose availability. Consequently, IGF-1 and insulin signaling are collectively termed the "insulin and IGF-1 signaling" (IIS) pathway. The IIS pathway represents the most conserved mechanism for regulating senescence throughout evolution. Its various targets encompass the FOXO family of transcription factors and the mTOR complex, both of which play roles in senescence and have been preserved across evolutionary history.⁸⁴ Genetic polymorphisms or mutations that diminish the function of growth hormone (GH), the IGF-1 receptor (IGF-1R), the insulin receptor, or downstream intracellular effectors such as AKT, mTOR, and FOXO have been linked to increased longevity in humans and model organisms. This underscores the significant role of nutritional and bioenergetic pathways in influencing lifespan.^{84,85} Research indicates that miRNAs transported by EVs, such as miR-100, facilitate the autophagy process in hepatocellular carcinoma cells by directly suppressing the expression of mTOR and IGF-1R.⁸⁶ miR-21 has been identified as an activator in various cancers through the inhibition of PTEN expression and the activation of the PI3K/Akt signaling pathway, which influences cell proliferation and survival.⁸⁷ These pathways serve as critical components in the regulation of aging and lifespan. Abnormal EV-mediated signaling may disrupt nutrient perception balance and expedite metabolic aging.

Mitochondrial Dysfunction

With aging, the efficiency of the respiratory chain declines, resulting in decreased ATP production.⁸⁸ This progressive mitochondrial dysfunction is associated with increased ROS production, which exacerbates mitochondrial damage and overall cellular injury.⁸⁹ Oxidative stress is a significant factor in aging and related diseases.⁹⁰ As aging advances, the regulation of cellular defense mechanisms deteriorates, leading to the accumulation of oxidative damage in essential macromolecules, including lipids, proteins, and DNA.⁹¹ Mitochondrial damage prompts the release of specific EVs enriched in oxidized DNA, N-formyl peptides, and ROS-generating enzymes, which induce oxidative stress and metabolic disorders in neighboring cells. Conversely, EVs from healthy sources may help restore mitochondrial membrane potential and ATP levels.⁹²

Cellular Senescence

A fundamental component of cellular senescence is the SASP, comprising immunomodulators, pro-inflammatory cytokines, growth factors, chemokines, and proteases that exert effects on neighboring cells in a non-autonomous fashion.⁹³ Within the SASP, EVs experience substantial alterations in senescent cells. These modifications are predominantly induced by permanent DNA damage that accumulates with age, resulting in heightened sphingomyelinase and

ceramide activity, Golgi enlargement, and endoplasmic reticulum stress. Consequently, inflammation intensifies, whereas autophagy diminishes.^{32,69,94} Moreover, senescent EVs are abundant in SASP components (such as IL-6, IL-1 β , MCP-1) and microRNAs (miRNA)(including miR-146a, miR-21), which enhance inflammatory signaling within the tissue microenvironment and prompt adjacent cells to adopt a senescent phenotype, thereby producing a “paracrine senescence” effect.^{95,96}

Stem Cell Exhaustion

The diminished regenerative capacity of tissues is a prominent characteristic of aging, with analogous functional decline observed in nearly all adult stem cell compartments.⁹⁷ Research involving aged mice indicates that hematopoietic stem cells (HSCs) exhibit a general reduction in cell cycle activity, resulting in fewer cell divisions compared to their younger counterparts.⁹⁸ EVs have been identified as regulators of stem cell self-renewal and directed differentiation. miRNAs, such as miR-125b, present in aged EVs, down-regulate essential stem cell transcription factors like Sox2 and Oct4, thereby impairing the maintenance of stemness.⁹⁹ Conversely, embryonic stem cell-derived EVs (ESC-EVs) have been shown to preserve the stem cell characteristics of ESCs, consistently express stemness genes, and maintain their pluripotency and capacity to generate chimeric mice under differentiation-inducing culture conditions.¹⁰⁰

Altered Intercellular Communication

Aging encompasses alterations in intercellular communication, including endocrine, neuroendocrine, and neuronal changes, alongside cell-autonomous modifications.^{101–103} Consequently, heightened inflammatory responses, diminished immune surveillance of pathogens and precancerous cells, alterations in the composition of the pericellular and extracellular milieu, and dysregulation of neurohormonal signaling (eg, renin-angiotensin, adrenergic, and insulin-IGF1 pathways) typically occur during senescence, impacting both the mechanical properties and functional performance of tissues. Research indicates that senescence-associated EVs may influence the NF- κ B signaling pathway by transporting certain miRNAs, including miR-766-3p. The decrease of miR-766-3p in EVs produced from senescent cells resulted in heightened NF- κ B activity, which facilitated the secretion of pro-inflammatory cytokines and intensified the inflammatory response.¹⁰⁴ Furthermore, EVs may influence innate immune responses through interactions with Toll-like receptors (TLRs). TLR4 is a crucial pattern-recognition receptor that identifies various pathogen-associated or damage-associated molecular patterns (PAMPs or DAMPs) and activates transcription factors, such as NF- κ B, via MyD88- or TRIF-dependent pathways, thereby promoting the expression of pro-inflammatory cytokines.¹⁰⁵ Research indicates that senescence-associated EVs may affect immunological clearance by altering the polarization state of macrophages. Research indicates that EVs originating from MSCs can promote macrophage polarization towards the anti-inflammatory M2 phenotype, therefore influencing the inflammatory response.¹⁰⁶

Role of EVs in Delaying Aging

Anti-Aging Effects of Young and Stem Cell-Derived EVs

EVs are linked to aging, although they possess the capacity to alleviate its impacts. Recent research indicates that young sEVs can counteract degenerative changes and age-related dysfunction.¹⁰⁷ By administering sEVs derived from young mouse plasma into older mice via intravenous injection, scientists successfully extended lifespan, mitigated senescent traits, and enhanced functional decline across various tissues.¹⁰⁷ Mechanistic analyses reveal that these sEVs promote PGC-1 α expression both in vitro and in vivo through their miRNA cargo, leading to improved mitochondrial function and a reduction in age-related mitochondrial impairments.¹⁰⁷ Another study found that EVs derived from neonatal umbilical cord MSC (UC-MSCs) had anti-aging effects. These UC-EVs rejuvenate aging bone marrow-derived MSCs (AB-MSCs) by reducing the expression of aging markers, enhancing self-renewal, and lengthening telomeres. This regenerative effect is partly mediated by the transfer of proliferating cell nuclear antigen (PCNA).¹⁰⁸ UC-EVs promote bone formation, wound healing, and angiogenesis. In aged mice, their administration also reduced bone and kidney degeneration.¹⁰⁸

EVs in Oxidative Stress Regulation and SASP Modulation

EVs are essential for sustaining cellular redox balance through the effective transfer of antioxidant molecules, thereby offering protection against oxidative damage in instances of acute injury and the aging process.¹⁰⁹ Studies indicate that exposure of primary mouse keratinocytes to SASP conditions results in a transient elevation of stem cell markers and improved regenerative capacity *in vivo*. The phosphatidylinositol 3-kinase-related kinase (PIKK) superfamily, which encompasses adipose tissue macrophage (ATM) kinases, ATR kinases, and DNA-PKcs kinases, is crucial for senescence and the activation of SASP genes, especially prior to NF- κ B signaling in the context of DNA damage-induced senescence.¹¹⁰ Inhibition or genetic depletion of ATM effectively blocks NF- κ B activation, reduces levels of inflammatory cytokines, and reverses senescence.⁶¹

EV-Mediated Signaling in Anti-Aging Pathways

EVs facilitate the attenuation of aging through cellular communication pathways. Adult mouse myoblasts and primary human myotubes subjected to hydrogen peroxide produce EVs containing miR-34a, which suppresses SIRT1, leading to the senescence and apoptosis of bone marrow MSC (BMSCs).⁷⁷ EVs derived from MSC (MSC-EVs) can stimulate genes associated with anti-aging, stem cell proliferation, and osteogenic differentiation. Fzd9, Wnt4, Sox9, Wnt2b, Wnt6, and Wnt10b are associated with the Wnt signaling system, which has been demonstrated to promote MSC self-renewal and differentiation while inhibiting bone aging.^{111–113} Pfkfb3, Nos, and Cpt1b are linked to the Sirtuin signaling system, facilitating cell cycle progression, suppressing apoptosis, and postponing cellular senescence.^{114,115} Hmga2, Fgf21, Met, and Tbx2 have been identified as factors that inhibit senescence and enhance stem cell proliferation.^{116,117} Bone marrow-derived MSC-EVs can diminish the synthesis of inflammatory cytokines, including interleukin 6 (IL-6) and prostaglandin E2 (PGE2), along with oxidative stress, thereby decelerating the aging process.^{108,118}

Central Nervous System EVs and Longevity

Research demonstrates that the quantity of EVs produced by hypothalamic neural stem/progenitor (NSS) cells in cerebrospinal fluid (CSF) diminishes with advancing age.¹¹⁹ The direct distribution of healthy NSS-EVs to the central region can modulate aging by providing sEVs that contain miRNAs. Extracellular nicotinamide phosphoribosyl transferase (eNAMPT) in EVs has been demonstrated to prolong longevity and enhance physical activity in aged mice. This method entails the transport of eNAMPT-containing EVs to target cells, thereby augmenting the production of nicotinamide adenine dinucleotide (NAD), which is pivotal in the regulation of aging.⁶⁵ Furthermore, therapies based on EVs and drug delivery applications have been suggested as alternate treatment modalities. In contrast to conventional liposomes, EVs have benefits including reduced toxicity, the incorporation of membrane proteins, and an absence of immunogenic effects.¹²⁰

Herbal/Plant-Derived Vesicles in Anti-Aging and Age-Related Diseases

Recent studies have highlighted the potential of plant- or herbal-derived extracellular vesicles (PDEVs) as novel bioactive agents in aging and age-related diseases. PDEVs are lipid bilayer vesicles naturally secreted by plants, carrying proteins, miRNAs, lipids, and secondary metabolites that can interact with mammalian cells.^{121,122} These vesicles have demonstrated antioxidant, anti-inflammatory, and immunomodulatory properties, suggesting a capacity to mitigate aging-related cellular stress and tissue degeneration. For instance, ginger-derived EVs have been shown to reduce oxidative stress and inflammatory responses in intestinal and hepatic tissues, while grapefruit and lemon-derived vesicles exhibit anti-inflammatory effects on macrophages and endothelial cells.¹²³ Mechanistically, PDEVs can modulate key pathways involved in aging, such as NF- κ B, Nrf2, and mTOR signaling, thereby influencing oxidative stress, senescence, and immune homeostasis.^{124,125} Moreover, PDEVs offer advantages as therapeutics, including high biocompatibility, low immunogenicity, oral bioavailability, and intrinsic targeting properties, making them promising candidates for mitigating age-related pathologies such as neurodegeneration, metabolic dysfunction, and cardiovascular diseases.¹²⁶ However, challenges remain in standardizing isolation, quantifying bioactive cargo, and ensuring reproducible dosing for translational applications.

EVs and Aging-Related Diseases

Extracellular Vesicles in Neurodegenerative Diseases

Neurodegenerative diseases become more common with advancing age, as non-dividing neurons are more vulnerable to systemic and cellular senescence. These disorders pose a considerable challenge to human health, with their prevalence increasing partly due to an aging population.¹²⁷ Neurodegenerative diseases include various conditions such as AD, PD, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and spinocerebellar ataxia (SCA). Each of these disorders possesses unique underlying causes and impacts various functions, including memory, cognition, motor control, speech, and respiration.^{128,129} AD and PD are intricately associated with aging and are predominantly caused by the buildup of insoluble, misfolded proteins in particular areas of the brain. The existence of these neurotoxic proteins in EVs is significantly linked to age-related deficits in autophagy and lysosomal functionality.^{130–133} EVs serve a dual function in neurodegeneration: they may promote the dissemination of pathogenic proteins associated with disease advancement, while simultaneously providing potential therapeutic and protective advantages (Table 3). Furthermore, EVs are increasingly utilized in the detection and treatment of neurodegenerative disorders, functioning as biomarkers and targeted delivery systems for therapeutic medicines (Figure 1).

Diagnostic Potential

Circulating EVs carry disease-specific cargos such as A β , phosphorylated tau, and α -synuclein, which serve as early biomarkers for AD, PD, and related disorders. Their accessibility in biofluids, including plasma and cerebrospinal fluid (CSF), provides a minimally invasive diagnostic approach.¹⁴⁵

In AD, neuron-derived EVs (NDEVs) in plasma transport synaptic proteins, which decline as the disease progresses. Reduced excitatory synaptic proteins in NDEVs correlate with cognitive decline and illness severity.¹⁴⁶ sEVs also contain elevated tau isoforms (total tau, P-T181-tau, P-S396-tau) and A β 1-42, detectable 1–10 years before diagnosis, highlighting their predictive potential.¹⁴⁷ In addition, altered miRNA and lncRNA profiles contribute to biomarker panels: miR-135a and miR-384 increase, while miR-193b, miR-342-3p, miR-212, and miR-132 decline in AD sEVs.^{148–150} The lncRNA BACE1-AS shows disease-specific fluctuations, reinforcing its diagnostic value.¹⁵¹

In PD, sEVs traverse the blood–brain barrier, with α -syn markedly elevated in CNS-derived vesicles, correlating with severity.¹⁵² LRRK2 protein in urinary or CSF-derived sEVs has also been proposed as a biomarker.¹⁵³ Moreover, CSF-

Table 3 Role of EVs in Neurodegenerative Diseases

EV Sources	Target Cells or Tissues	EVs Cargos	Mechanism of Action	Ref.
Neuron CSF Plasma	Microtubule, microglia, mitochondrial synaptic, distant brain regions, neuron, neurites	A β 1-42,	Induced apoptosis in neuronal cells	[134]
		p-tau		
		α syn	Forms aggregates in normal neurons and induces receptor cell death	[135]
		LRRK2	Leads to late-onset Parkinson's disease	[136]
Stem-cell Astrocyte	Neuron, synaptic, axon, neurovascular, immune cells, microglia	mHTT	Physical blockage of axonal transport occurs leading to cell death.	[137]
		mSOD1	Leads to the formation of misfolded SOD1 protein aggregates and neurodegeneration	[138]
		TDP-43	Leads to mislocalization of the corresponding proteins	[139]
		FGF-2	Promotes cell proliferation, survival, migration and differentiation, and axon regeneration	[140]
		VEGF	Promotes angiogenesis, neurogenesis, synaptogenesis and synaptic plasticity in the brain	[141]
		Apo-D	Autocrine protection against oxidative stress	[142]
		HSP70	Mediates protective effects on neurons against physical trauma or toxicity	[143]
		EAAT	Glutamate removal from synapses preserves neuronal homeostasis.	[144]

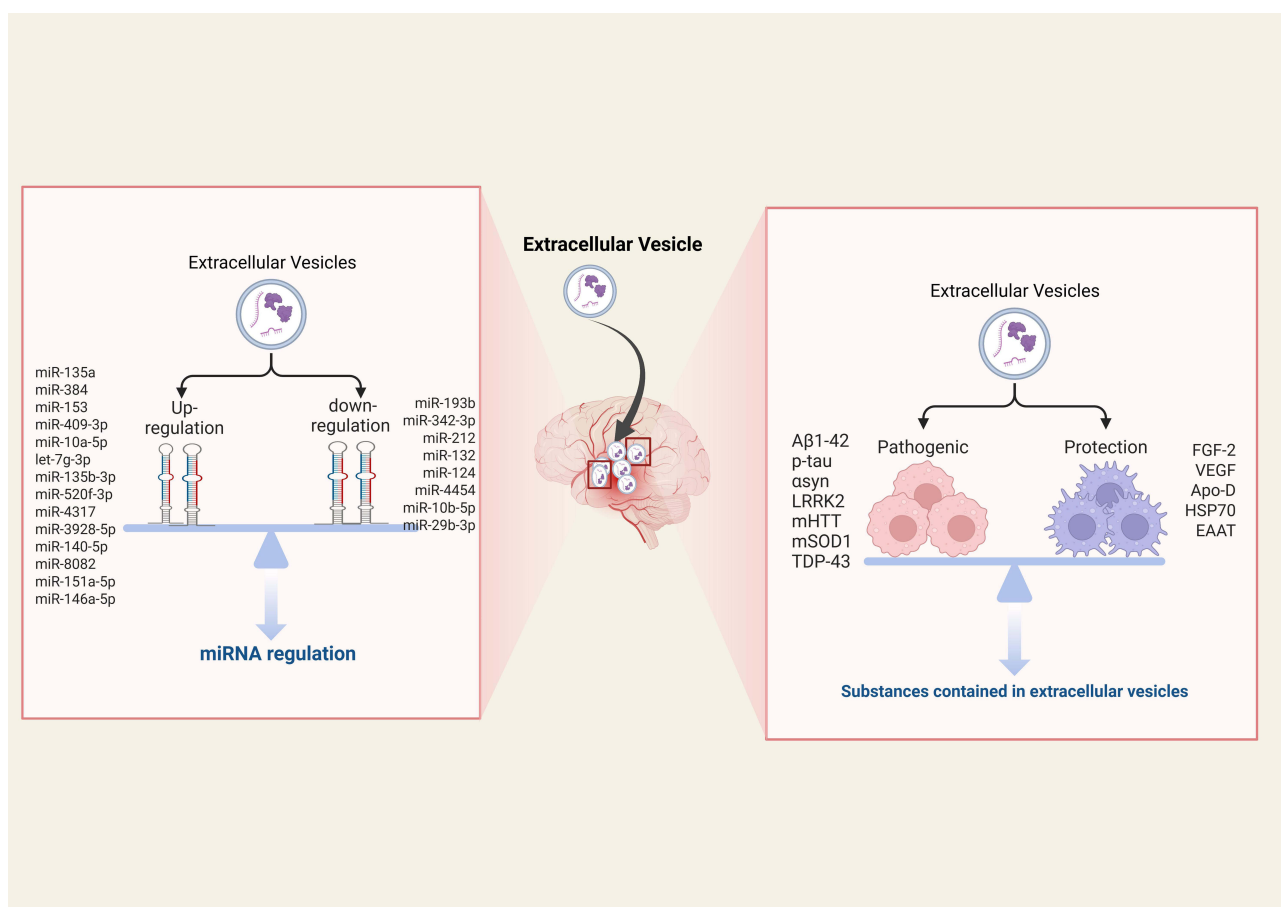


Figure 1 Neurodegenerative diseases are closely influenced by EV cargo, including pathogenic proteins and dysregulated miRNAs. The left panel shows the list of dysregulated miRNAs, while the right panel categorizes EV cargo into pathogenic and protective groups.

derived sEVs exhibit distinct miRNA profiles: 16 upregulated and 11 downregulated miRNAs, including reduced miR-1 and miR-19b-3p and elevated miR-153, miR-409-3p, miR-10a-5p, and let-7g-3p, all linked to disease monitoring.¹⁵⁴

In Huntington's disease (HD), CSF and plasma EVs show widespread miRNA alterations, with miR-135b-3p, miR-520f-3p, and miR-4317 increased, and miR-124 decreased in brain tissue, reflecting disease progression.^{155,156} For amyotrophic lateral sclerosis (ALS), sEV-derived TDP-43 levels rise during early disease, astrocyte-derived EVs (ASEVs) transport IL-6 correlated with progression rate, and several miRNAs (miR-151a-5p, miR-146a-5p, miR-4454, miR-10b-5p, miR-29b-3p) are dysregulated.^{157–159}

Although SCA research is less extensive, EV-based biomarkers have been suggested, with altered miRNAs (miR-9, miR-181a, miR-494, miR-7014) and reduced neurofilament light chain (NFL) and myelin basic protein indicating axonal injury.^{139,160,161} Together, these studies highlight EVs as a unifying, minimally invasive biomarker platform across neurodegenerative diseases.

Pathogenic Mechanisms

EVs participate in the propagation of toxic proteins (Aβ oligomers, p-tau, α-syn) across neuronal networks, amplifying neurodegeneration. They also induce neuroinflammation through microglia activation and mitochondrial dysfunction, aggravating disease progression.¹⁶²

In AD, these pathogenic cargos impair proteostasis, as Aβ1-42 resists degradation via the proteasome and autophagy, and hyperphosphorylated tau disrupts microtubule stabilization, accelerating synaptic loss.^{134,163–167} EV-mediated Aβ and tau transfer may also seed pathology in distant brain regions. In PD, degeneration of dopaminergic neurons in the substantia nigra is linked to EV-facilitated α-syn aggregation into Lewy bodies and neurites.^{135,168,169} Mutant LRRK2,

detectable in EVs, further amplifies pathology through kinase dysregulation.^{136,152} In HD, expanded CAG repeats in the IT15 gene generate mHTT with elongated polyQ tracts. EVs mediate intercellular mHTT transfer, as shown by fibroblast-derived EVs inducing HD-like pathology in mice.^{137,170–177} In ALS, multiple misfolded proteins (SOD1, TDP-43, FUS) spread via EVs, initiating neuroinflammatory cascades and glial-mediated toxicity. Mutant SOD1 within EVs disrupts neuromuscular junctions through PKC θ activation, impairing mitochondrial function and synaptic transmission.^{148,178–180} EVs secreted by injured neurons can activate signaling cascades that promote neuroinflammation, glial-mediated toxicity, and prion-like protein propagation. Mutant SOD1 (G93A) in muscle tissue disrupts neuronal integrity; when incorporated into EVs, it impairs neuromuscular junctions via a protein kinase C θ (PKC θ)-dependent mechanism, resulting in mitochondrial dysfunction, altered redox signaling, and defective acetylcholine receptor (AChR) transmission.¹⁸¹ These findings highlight the dual role of EVs in both propagating toxic proteins and amplifying neurotoxic signaling within the ALS microenvironment. In SCA, polyQ-extended proteins misfold and aggregate, causing neuronal death.^{182,183} These findings suggest that EVs not only act as carriers of toxic proteins but also activate microglia, trigger oxidative stress, and perturb mitochondrial homeostasis, reinforcing their role in disease amplification. Importantly, EVs embody a convergent mechanism across distinct diseases, linking protein misfolding, neuroinflammation, and intercellular communication into a shared pathological axis.

Protective/Therapeutic Roles

EVs not only convey pathogenic signals but also transport a wide range of protective cargos that can be therapeutically exploited. Stem cell-derived EVs are particularly enriched in growth factors such as fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), and apolipoprotein D (ApoD), which act through interconnected signaling pathways to promote neuroprotection and tissue homeostasis.¹⁸⁴ FGF-2 delivered via EVs binds to fibroblast growth factor receptors (FGFRs) on recipient neurons, activating downstream MAPK/ERK and PI3K/AKT signaling cascades. These pathways stimulate neuronal proliferation, axonal regeneration, and hippocampal neurogenesis, thereby facilitating functional recovery following injury or during age-related decline.^{140,185–189} In parallel, VEGF-containing EVs engage VEGF receptors (VEGFRs) to enhance angiogenesis, neurogenesis, synaptogenesis, and synaptic plasticity, ultimately improving neurovascular coupling and neuronal resilience under pathological stress conditions.^{141,190–193} The coordinated activation of FGF-2/FGFR and VEGF/VEGFR signaling ensures synchronized neurogenic and angiogenic responses, amplifying tissue repair and maintaining neural homeostasis.

ApoD transported by EVs further complements these growth factor-mediated effects by attenuating oxidative stress. Through scavenging ROS and stabilizing lipid membranes, ApoD reduces oxidative damage and preserves neuronal viability.¹⁴² In combination with FGF-2 and VEGF signaling, ApoD contributes to the maintenance of synaptic integrity and neuronal survival, particularly in the context of aging and neurodegenerative disorders.^{194,195}

In addition to growth factors and antioxidants, EVs carry molecular chaperones that mitigate proteotoxic stress. HSPs, especially HSP70, stabilize misfolded proteins, inhibit apoptotic signaling via interactions with Bcl-2 family members, and modulate immune responses through activation of TLR2/4 and CD94 on microglia. These actions collectively reduce cellular stress and neuroinflammation, acting synergistically with growth factor- and antioxidant-mediated pathways.^{143,196} Similarly, EV-associated excitatory amino acid transporters (EAATs) prevent glutamate-induced excitotoxicity by clearing excess synaptic glutamate, thereby complementing other neuroprotective mechanisms.¹⁴⁴

Additional EV cargos, including functional prion protein (PrP) and synaptic proteins such as synaptophysin 1, further reinforce neuronal resilience. PrP protects neurons against oxidative stress, ischemia, and metabolic perturbations, whereas synaptophysin 1 facilitates the release of neurotrophic factors and supports synaptic formation, plasticity, and adaptive responses under stress conditions.^{197–199} Collectively, these protective EV cargos operate through coordinated and overlapping signaling networks that integrate growth factor signaling, redox control, protein quality maintenance, and synaptic support to counteract aging-associated and disease-related neuronal dysfunction.

Beyond soluble proteins and RNAs, increasing evidence suggests that EV-mediated mitochondrial transfer represents an additional compensatory or therapeutic mechanism, particularly in ALS. Hayakawa et al demonstrated that astrocytes can donate mitochondria to neurons via EV-like structures not only after stroke but also in neurodegenerative settings, including ALS models, where mitochondrial transfer exerted neuroprotective effects.²⁰⁰ Consistently, MSC-EVs have

been shown to transport mitochondrial components and enhance mitochondrial bioenergetics in recipient cells, thereby reducing oxidative stress and apoptosis—processes central to ALS pathology.²⁰¹ Together, these findings indicate that harnessing EVs for the targeted delivery of healthy mitochondria or mitochondrial components may represent a promising therapeutic avenue for ALS.

Extracellular Vesicles in Diabetes Mellitus

DM is a prevalent disorder that is increasingly common worldwide. It is characterized by persistently elevated blood glucose levels resulting from either the body's resistance to insulin or inadequate insulin secretion. DM is generally categorized into two primary types: type 1 diabetes (T1D) and type 2 diabetes (T2D). T2D constitutes the primary variant of DM, comprising over 90% of global cases, while T1D represents over 10%.^{202,203} Disproportionate communication among organs is a pivotal factor in initiating and exacerbating the detrimental cycle of insulin resistance (IR) and elevated blood glucose levels in T2D. Signaling molecules that enable inter-organ communication may be pivotal in the pathogenesis of both T1D and T2D. Diverse categories of signaling molecules, such as adipokines, hepatic factors, central nervous system peptides, and pancreatic and intestinal hormones, are integral to the initiation and advancement of both T1D and T2D.^{204,205} EVs are integral to the communication of information from progenitor cells to receptor cells. When EVs malfunction, they may lead to the onset of DM and its complications.²⁰⁶ EVs demonstrate advantageous effects in diabetes by improving pancreatic β -cell functionality, diminishing insulin resistance in peripheral tissues, and alleviating the severity of diabetic complications²⁰⁷ (Table 4) (Figure 2).

Diagnostic Potential

EVs derived from pancreatic β -cells and adipose tissue carry signatures reflecting insulin secretion, β -cell stress, and systemic metabolic state. These vesicles show potential as non-invasive biomarkers for early diabetes detection.²¹⁶ Beyond adipocytes, EVs contribute to immune–metabolic crosstalk. They transport pro-inflammatory mediators such as sphingosine-1-phosphate (S1P), TRAIL, integrin β 1, ceramides, miR-122, and miR-192-5p, which enhance monocyte recruitment, macrophage polarization, and hepatic inflammation.^{211,217–219} EVs derived from adipose tissue macrophages further propagate systemic inflammation, impairing insulin signaling in liver, muscle, and pancreatic islets.^{206,220} In T1D, inflamed β -cell–derived EVs carrying miRNAs (eg, miR-375-3p, miR-21-5p) promote β -cell apoptosis and autoimmune insulinitis.²¹² In T2D, high-fat diet (HFD) exposure alters the miRNA cargo of β -cell–derived EVs, notably elevating miR-29 while reducing miR-26a, thereby disrupting glucose homeostasis.^{221–223} Reduced miR-26a levels weaken hepatic insulin sensitivity, while increased miR-29/29a levels drive IR, metabolic dysfunction, and inflammation. Collectively,

Table 4 Role of EVs in DM

EV sources	Target Cells or Tissues	Concrete Path	Ref.
Adipocytes	Pancreatic β -cell, hepatocytes	Insulin reaction and glucose intake that damage receptor fatty cells	[208]
		As a fat factor carrier leading to peripheral IR and metabolic disorders	[209]
		Damage insulin signal conduction by affecting macrophages cells	[206]
		Abnormal fat accumulation and inflammation in the liver causing T2D	[210]
		Induces inflammatory cell immersion and inflammation by attracting circulating monocytes and polarizing macrophages	[211]
		Transmission of pathogenic miRNAs associated with adenoids and pancreatic damage to adjacent beta cells.	[212]
Mesenchymal stem cell, hucMSC	Pancreatic β -cell, hepatocytes	Promotes IAPP concentration and formation of starch-like proteins in pancreatic cells, leading to cell death	[213]
		Promotes the proliferation of β cells in damaged insulin and inhibits β cell death	[207]
		Protect β cells from oxygen-induced cell death	[214]
		Increase the storage of hepatic glucose to maintain a stable level	[207]
		Inhibits STZ-induced β -cell death and restores T2D's insulin secretion function	[207]
		Inhibits fat cell growth	[215]

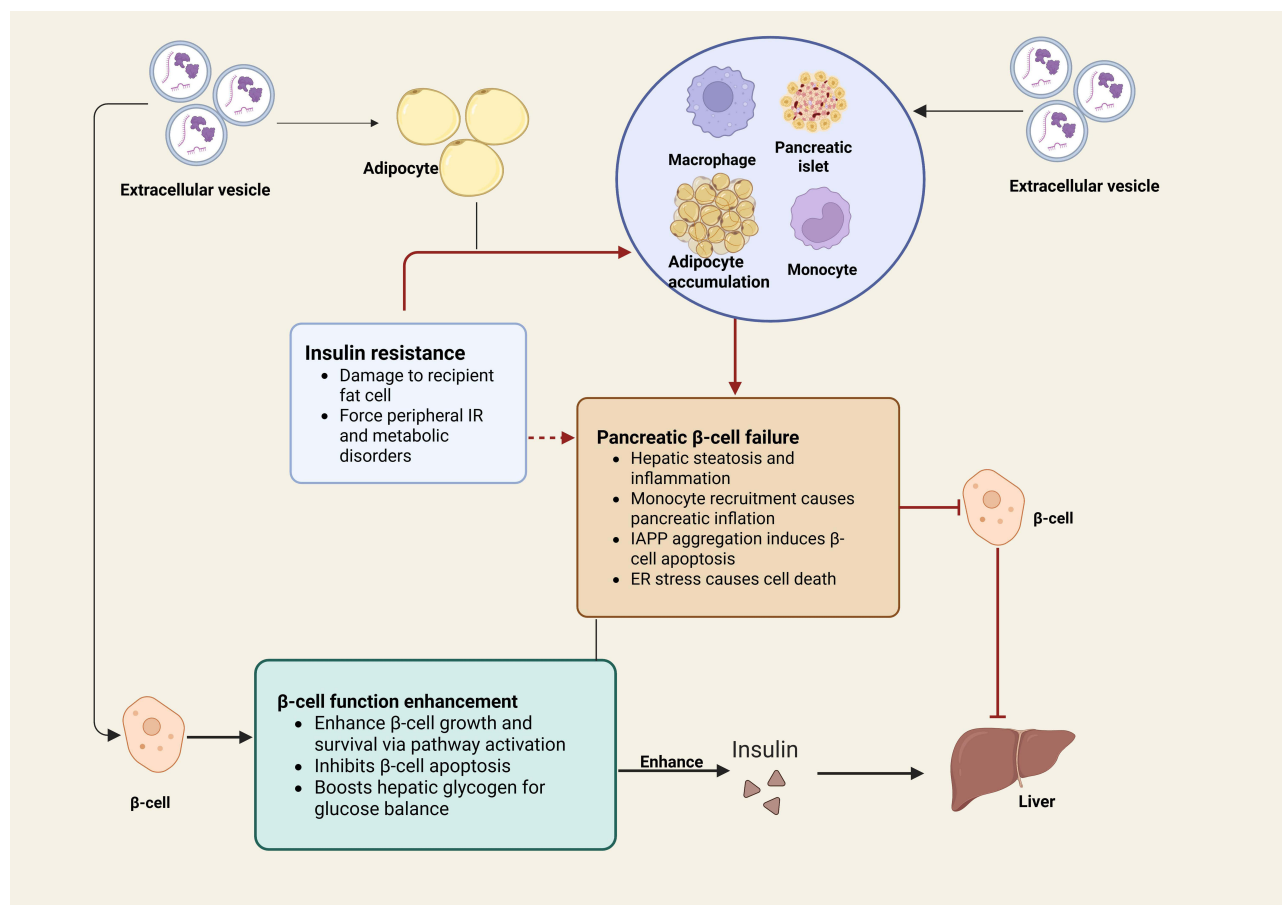


Figure 2 EVs play a dual role in diabetes mellitus, promoting disease by inducing insulin resistance and β -cell loss, while also offering therapeutic potential by supporting β -cell function. Black arrows indicate positive promotion effects, brown arrows indicate pathogenic exacerbation effects, brown stop lines indicate inhibitory effects, and dashed arrows indicate potential pathways.

these findings highlight EVs as active mediators in adipose–liver–pancreas communication that exacerbate systemic insulin resistance and β -cell failure.

Pathogenic Mechanisms

Pathological EVs transfer deleterious miRNAs and proteins that exacerbate insulin resistance and β -cell apoptosis, such as miR-375, which targets insulin transcription pathways. They also propagate inflammatory signals in adipose tissue macrophages.²²⁴ DM is primarily driven by insulin resistance (IR) and pancreatic β -cell dysfunction, with adipose tissue (AT) acting as a central regulator of systemic insulin sensitivity through the release of free fatty acids (FFA), adipokines, and inflammatory mediators.^{204,205} In obesity, enlarged and metabolically active adipocytes generate elevated levels of EVs, which contribute to IR and β -cell dysfunction via paracrine and systemic signaling.^{208,225,226} Adipocyte-derived EVs (ADEVs) disrupt insulin response and glucose uptake in recipient adipocytes and deliver adipokines that exacerbate metabolic dysfunction in peripheral tissues.^{208,209} sEVs enriched in resistin promote endoplasmic reticulum stress in hepatocytes, driving hepatic steatosis.²²⁷ ADEVs also transport regulatory cargos, including lncRNAs (eg, MALAT1), miRNAs (eg, miR-27a, miR-141-3p), and proteins (eg, CD36, Akrlb7), which alter metabolic processes in remote organs and worsen insulin resistance.^{228,229}

Protective/Therapeutic Roles

MSC-EVs and engineered EVs carrying anti-apoptotic or pro-regenerative cargos have demonstrated robust therapeutic effects in preclinical models of diabetes.²³⁰ Rather than merely delivering protective molecules, MSC-sEVs orchestrate

specific downstream signaling pathways to restore β -cell function, enhance insulin sensitivity, and ameliorate hyperglycemia.

In pancreatic β -cells, MSC-sEVs activate the PDX1 pathway, a key transcriptional regulator of β -cell development and insulin gene expression.^{207,214,231} Concurrently, EV-delivered miRNAs, such as miR-21, reduce endoplasmic reticulum (ER) stress by inhibiting pro-apoptotic pathways (eg, CHOP-mediated apoptosis) and promote β -cell survival. This combination of transcriptional activation and miRNA-mediated ER stress mitigation enhances β -cell proliferation, restores insulin synthesis, and improves glucose-stimulated insulin secretion.²¹⁴

Beyond β -cells, MSC-sEVs modulate peripheral metabolism through coordinated signaling in liver, muscle, and adipose tissue. EVs enhance glycolysis and glycogen synthesis by activating AKT and AMPK pathways, promote GLUT4 translocation in skeletal muscle to facilitate glucose uptake, and suppress hepatic gluconeogenesis via down-regulation of PEPCK and G6Pase expression.^{232,233} Autophagy induction further contributes to improved cellular metabolism and insulin sensitivity, creating a network of synergistic metabolic effects.

Immune modulation is another critical mechanism. Adipose-derived EVs (ADEVs) can transfer STAT3, biasing macrophages toward an anti-inflammatory M2 phenotype, thereby reducing chronic inflammation in white adipose tissue. This immunomodulatory action indirectly enhances systemic insulin sensitivity and complements the direct metabolic effects of MSC-sEVs.^{215,234,235} MSC-sEVs can also be engineered to deliver targeted therapeutic cargos, such as siFas or anti-miR-375, which protect transplanted islets from cytokine-induced apoptosis and enhance insulin secretion under inflammatory stress.²³⁶ Silencing Fas inhibits extrinsic apoptotic signaling via the Fas/FADD/caspase-8 pathway, while anti-miR-375 restores β -cell function by derepressing transcription factors essential for insulin gene expression. The combined delivery of these molecules synergistically reduces islet apoptosis and improves glucose homeostasis.²⁰⁷ Collectively, MSC-derived EVs employ a multi-layered signaling strategy, integrating transcriptional regulation, miRNA-mediated ER stress mitigation, metabolic pathway modulation, and immunomodulation to restore β -cell function, improve systemic insulin sensitivity, and counteract the pathological processes of DM.

Extracellular Vesicles in Cardiovascular Diseases

Cardiovascular disease represents the leading cause of morbidity and mortality, accounting for one-third of global deaths in 2019. Cardiovascular diseases encompass atherosclerosis, ischemic heart disease, and heart failure (HF), which represent the leading causes of mortality.²³⁷ Inflammation plays a significant role in the development of cardiovascular disease. EVs serve as important mediators in the intricate pathways of inflammation associated with cardiovascular disease, as evidenced by growing data²³⁸ (Table 5)(Figure 3).

Diagnostic Potential

Circulating EVs from endothelial cells, cardiomyocytes, and platelets provide diagnostic information for conditions such as atherosclerosis, myocardial infarction, and heart failure. Cargo components, including adhesion molecules, coagulation factors, and cardiac-specific miRNAs, show promise as biomarkers.²⁵⁴ Given their presence in circulation and involvement in vascular pathology, EVs represent emerging biomarkers for atherosclerosis. Elevated levels of platelet- and leukocyte-derived EVs have been correlated with endothelial dysfunction and cardiovascular risk,^{255,256} while EV-associated pro-inflammatory mediators (eg, ICAM-1, VCAM-1, CCL2) and calcification-promoting cargos have been detected in patients with advanced plaques.^{257,258} EV counts in plasma are significantly higher in individuals with unstable angina or acute coronary syndrome, correlating with plaque vulnerability and severity.²⁵⁹ Furthermore, specific miRNAs carried by endothelial or macrophage-derived EVs, such as miR-92a, miR-155, and miR-223, have been linked to endothelial activation, inflammation, and plaque instability.^{260,261}

The abundance and composition of EVs in circulation are closely associated with the extent of myocardial damage, underscoring their potential as diagnostic and prognostic biomarkers. Elevated EV levels have been detected shortly after myocardial infarction (MI) onset, and their cellular origin reflects key pathological processes. Specific EV cargo, including cardiomyocyte-derived miR-1, miR-208, and miR-499, has been proposed as minimally invasive biomarkers for early MI detection.^{262,263} Moreover, macrophage-derived EVs enriched in pro-inflammatory miRNAs such as miR-

Table 5 Role of EVs in Cardiovascular Diseases

EV Sources	Target cells or tissues	Pathway	Ref.
Endothelial cells, monocytes, neutrophils, platelets, macrophages, cardiomyocytes, fibroblasts	Monocytes, endothelial cells, neutrophils, cardiac vasculature	Plaque EVs transfer ICAM-1 to endocrine cells	[239]
		Enhanced trans-endocrine migration of mononucleosis cells	[240]
		Transfer of platelet adhesive molecule GPIIb/IIIa directly to mononuclear cells	[241]
		Promoting adhesion of neutrophilic cells to endocrine cells through P-selectin	[242]
		Improve VCAM-1 expression on endocrine cells and enhance white cell attachment	[243]
		Promoting endometrial microcalcification	[243]
Macrophages, neutrophils,	Low-density lipoprotein, arterial wall	HSPG inhibits atherosclerosis by combining with APRIL	[244]
		Improves LDL clearance rate and prevents the formation of atherosclerosis plaque	[245]
		Activates platelet reaction protein I to regulate vascular production of receptor cells	[246]
Inflammatory cells, cardiomyocytes, endothelial cells	Monocytes, bone marrow monocytes, cardiac fibroblasts, cardiac vasculature	Promote immersive mononuclear release of convergence factors and inflammatory cell factors	[247]
		Inhibits the proliferation of fibrous cells in the heart and promotes inflammation	[248]
		Anti-vascular formation, exacerbating anemic damage	[249]
Cardiovascular stem cells	Endothelial cells, smooth muscle cells, and cardiomyocytes	Strengthen T cells by increasing the proliferation of regulatory T-cells and the production of IL-10	[250]
MI macrophages, fibroblasts	Cardiac muscle cells, sorbin protein, SORBS2, MI-macrophages	Cardiomyopathy as an adenoid signaling mediator	[251]
		Activate MI macrophage cells to promote inflammation	[252]
Cardiomyocytes	Vascular cells	Increased expression of VEGF-2 in endocrine cells to promote vascular production	[253]

155 correlate with heightened inflammatory activity and poor prognosis.²⁴⁷ These observations suggest that EV-based signatures may facilitate risk stratification, early diagnosis, and monitoring of therapeutic responses in MI.

EVs have also emerged as promising biomarkers for HF due to their stability in circulation and disease-specific cargos. EV-associated miRNAs, including miR-21-3p and miR-192-5p, reflect pathological processes such as hypertrophy, inflammation, and macrophage activation, making them potential indicators of disease progression.^{251,252,264,265}

Elevated levels of circulating EVs enriched with inflammatory mediators have been linked to worse prognosis, while changes in EV subtypes and cargo composition correlate with functional impairment in HF patients. These features highlight the potential of EV-derived molecular signatures to provide minimally invasive tools for early diagnosis, risk stratification, and therapeutic monitoring in HF.

Pathogenic Mechanisms

EVs promote vascular inflammation and atherogenesis by transferring adhesion molecules and pro-inflammatory miRNAs. In ischemic heart disease, EVs exacerbate endothelial dysfunction and thrombosis.²⁶⁶ Atherosclerosis is characterized by the accumulation of fibrofatty deposits within arterial walls, ultimately restricting blood flow and predisposing to severe cardiovascular events such as myocardial infarction, stroke, and peripheral arterial disease.²⁶⁷ The disease begins with endothelial dysfunction and LDL deposition, which promote leukocyte adhesion and infiltration. EVs act as key mediators of these processes. Endothelial EVs promote intercellular adhesion molecule-1 (ICAM-1) expression, enhancing monocyte adhesion,^{239,268} while monocyte-derived EVs activate the NF-κB pathway to upregulate ICAM-1 and chemokine ligand 2(CCL2).²⁶⁹ Neutrophil-derived EVs facilitate transendothelial migration by elevating CCL2, ICAM-1, and vascular cell adhesion molecule-1 (VCAM-1).²⁴⁰ Platelet-derived EVs release RANTES and

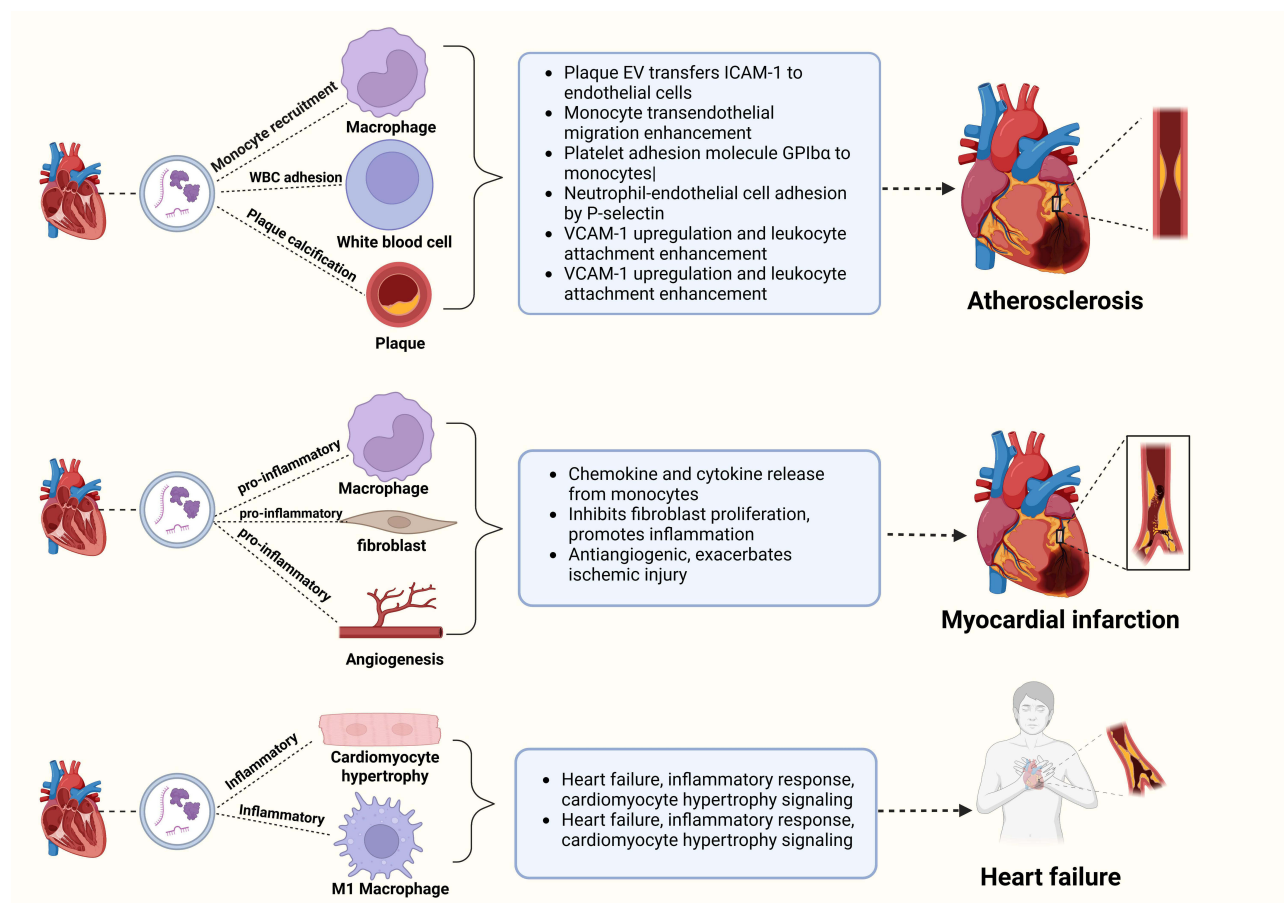


Figure 3 Pathogenic mechanisms of EVs in cardiovascular disease.

GPIIb α , fostering endothelial–monocyte interactions and neutrophil adhesion through P-selectin.^{241,242,270} ADEVs further amplify endothelial VCAM-1 expression, promoting leukocyte infiltration.²⁴³ Beyond inflammation, macrophage-derived EVs drive vascular calcification by depositing calcium in the arterial intima, aggravating plaque stability and disease severity.^{271,272} Collectively, these findings demonstrate the dual role of EVs in fueling vascular inflammation and contributing to plaque progression.

MI, a major manifestation of ischemic heart disease, arises from coronary artery obstruction that critically disrupts myocardial blood flow and energy metabolism, leading to tissue necrosis.²⁷³ In response to ischemic injury, inflammation is rapidly activated, playing a dual role in initiating repair while simultaneously driving fibrotic scar formation. Within 15–24 hours after MI, there is a marked increase in EV release from inflammatory cells in cardiac tissue.²⁴⁷ EVs derived from cardiomyocytes and endothelial cells interact with infiltrating monocytes, stimulating the secretion of chemokines and pro-inflammatory cytokines that amplify the inflammatory cascade.²⁴⁷ Cardiomyocyte-derived EVs also carry specific miRNAs, such as miR-1, miR-208, and miR-499, which modulate systemic responses by inhibiting CXCR4 in bone marrow monocytes, thereby promoting their mobilization into circulation.²⁶² In addition, macrophage-derived EVs transport miR-155 to cardiac fibroblasts, where they suppress proliferation, aggravate inflammation, and increase susceptibility to myocardial rupture.²⁴⁸ EV-mediated delivery of miR-155 to endothelial cells further impairs angiogenesis, exacerbating ischemic injury.²⁴⁹ Collectively, these findings highlight the multifaceted role of EVs in orchestrating post-MI inflammation, fibrosis, and adverse remodeling. HF may arise from both ischemic and non-ischemic etiologies, involving dysfunction of either the left or right ventricles.²⁷⁴ EVs are closely associated with chronic inflammation, a key contributor to HF progression. Reduced levels of M1 macrophage-derived EVs in animal models of myocardial infarction improved cardiac function, as reflected by decreased IL-1 α , IL-1 β , and RANTES expression, underscoring

their role in inflammatory signaling.²⁷⁵ EV-derived miRNAs and proteins modulate inflammatory and remodeling processes central to HF pathophysiology.²⁶⁴ For example, fibroblast-derived EVs enriched in miR-21-3p promote cardiomyocyte hypertrophy by targeting sorbin and SH3 domain-containing protein (SORBS2), thereby contributing to pathological remodeling.²⁵¹ Similarly, EV-associated miR-192-5p activates p53 and stimulates M1 macrophage polarization, exacerbating inflammation and accelerating HF progression.^{252,265} Together, these findings emphasize that EVs actively participate in myocardial inflammation, hypertrophy, and maladaptive remodeling that drive HF pathogenesis.

Protective/Therapeutic Roles

Cardiosphere-derived EVs and MSC-EVs deliver angiogenic miRNAs (eg, miR-126, miR-210) and growth factors that support endothelial repair, reduce fibrosis, and improve cardiac function in animal models.²⁷⁶ While EVs may induce inflammation in the heart and blood vessels, they also provide potential for the prevention and treatment of cardiovascular diseases. EVs are pivotal in modulating inflammation linked to atherosclerosis. Heparan sulfate proteoglycan (HSPG) is a crucial component in EVs that aids in preserving vascular homeostasis during atherosclerosis. HSPG is persistently expressed by immune cells, including macrophages and neutrophils, and it aids in preventing the accumulation of LDL in the artery wall.²⁷⁷ Another protective component associated with EVs is APRIL (A Proliferation-Inducing Ligand). While elevated circulating levels of APRIL correlate with heightened cardiovascular mortality in atherosclerotic individuals,²⁴⁴ it also promotes the endocytosis and clearance of LDL-containing EVs. This activity reduces both LDL levels and plaque accumulation in the arteries.²⁴⁵

Numerous miRNAs included in EVs have demonstrated anti-atherogenic properties. For instance, miR-92a-3p, found in endothelial-derived EVs, modulates angiogenesis in target cells by activating platelet-responsive protein 1, a crucial element for TGF- β synthesis and immunological regulation.^{246,278} In hypoxic situations, cardiomyocytes secrete sEVs high in HIF-1 α , which enhances the expression of VEGFR-2 and Hsp20 in vascular cells, thus facilitating angiogenesis.²⁵³ Furthermore, cardiosphere-derived cells (CDCs) generate EVs clusters that encompass miRNAs, including miR-146a, miR-181b, and miR-126. In acute myocardial infarction (AMI) models, miR-181b is conveyed through sEVs to macrophages, leading to the downregulation of PKC ϵ in endothelial cells. This diminishes the expression of adhesion molecules such as E-selectin, VCAM-1, and ICAM-1, offering cardioprotection akin to that of CDCs.²⁷⁹ sEVs modulate macrophage activity by augmenting interleukin-10 (IL-10) production and gene expression, thereby safeguarding damaged cardiomyocytes.²⁸⁰ Moreover, cardiac sEVs facilitate the transfer of miRNAs to attract progenitor cells, hence enhancing heart repair and regeneration. These data substantiate the notion that sEVs promote communication between the ischemic heart and bone marrow, hence augmenting coordinated repair.²⁶²

Furthermore, EVs derived from cardiovascular stem cells improve immune regulation by facilitating the proliferation of regulatory T cells and the release of IL-10. The immunomodulatory action plays a role in cardioprotection under inflammatory conditions.²⁵⁰ sEVs directly impact essential elements of cardiovascular tissue, such as the endothelium, smooth muscle cells, and cardiomyocytes. They facilitate communication among immune cells, including monocytes, dendritic cells, and fibroblasts.^{281,282} sEVs are consistently exchanged between endothelial cells and cardiomyocytes, promoting intercellular signaling.

Extracellular Vesicles in Stroke

Stroke is a critical neurological condition linked to a considerable risk of mortality and disability.²⁸³ Two primary categories of stroke exist: ischemic stroke, which results from obstructed blood vessels, and hemorrhagic stroke, which occurs due to ruptured blood vessels.²⁸⁴ An ischemic stroke is characterized as the primary type of stroke where blood flow to the brain is obstructed, leading to damage in brain tissue.²⁸⁵ Thrombosis is a condition that impedes blood flow in the brain, resulting in a disruption of energy supply, which can damage blood vessels and lead to neuronal loss. The blood–brain barrier (BBB) is influenced by ischemic stroke, leading to heightened permeability. Consequently, secondary neuronal inflammation is initiated, which expedites the advancement of tissue damage resulting from diminished blood flow.²⁸⁶ EVs significantly contribute to the improvement of communication among cells and tissues through the effective transport of proteins and miRNAs.²⁸⁷ EVs have demonstrated effective applications in diagnostics, neuroprotection, vasculogenesis, anti-inflammation, and the function of the blood-brain barrier.²⁸⁸

Diagnostic Potential

Blood-derived EVs containing brain-enriched miRNAs (eg, miR-124, miR-9) and neuroinflammatory markers correlate with stroke onset and prognosis. They may serve as rapid diagnostic biomarkers for ischemic injury.²⁸⁹ EVs also carry significant diagnostic value in ischemic stroke due to their stable cargo, particularly miRNAs, which reflect disease stage and severity. For instance, plasma sEVs containing miR-134 are elevated in acute ischemic stroke patients, with higher levels correlating with larger infarct sizes and poorer outcomes.²⁹⁰ Distinct EV-associated miRNA expression patterns have been observed across the hyperacute (within 6 h), acute (1–7 d), subacute (8–14 d), and recovery (>14 d) phases, including changes in miR-30a-5p, miR-422a, miR-21-5p, and miR-125b-2-3p.²⁹¹ Serum sEVs from stroke patients also show elevated miR-223 levels, which are associated with unfavorable prognosis.²⁹² Furthermore, serum EV-derived miR-126 decreases within 3 h of irreversible ischemia but normalizes within 24 h, distinguishing transient ischemic attacks (TIAs) from persistent ischemia.²⁹² Another marker, miR-152-3p, is lowest in large-artery atherosclerosis compared to other stroke subtypes and is reduced in the acute phase relative to the chronic phase, underscoring its potential in stroke classification and progression monitoring.²⁹³ Collectively, these findings highlight EV-derived miRNAs as dynamic, minimally invasive biomarkers for diagnosis, subtyping, and prognosis in ischemic stroke.

Pathogenic Mechanisms

Pathological EVs derived from activated endothelial cells and platelets enhance thrombosis, disrupt the blood–brain barrier, and intensify neuroinflammation, exacerbating ischemic injury.²⁹⁴ Reperfusion of the central nervous system following ischemic events induces a strong inflammatory response primarily mediated by innate immunity.²⁹⁵ Microglia, the resident immune cells of the brain, serve as first responders to ischemic injury. Upon activation, microglia predominantly polarize toward the proinflammatory M1 phenotype and release EVs enriched with inflammatory mediators. These proinflammatory vesicles exacerbate neuronal injury, amplify secondary damage, and promote disease progression by stimulating neuroinflammation and disrupting tissue repair mechanisms. Thus, EVs represent important mediators of post-ischemic inflammation and neuronal degeneration.

Protective/Therapeutic Roles

Astrocyte and MSC-derived EVs deliver neuroprotective miRNAs, growth factors, and antioxidants that attenuate ischemic damage, promote angiogenesis, and support neuronal survival. Intravenous administration of EVs has been shown to reduce infarct volume and improve neurological outcomes in experimental stroke models.²⁹⁶ Beyond their pathogenic roles, EVs exert robust protective effects in ischemic stroke by coordinating angiogenesis, neurogenesis, and stabilization of the blood–brain barrier (BBB). Stem cell–derived EVs transport therapeutic proteins and regulatory RNAs that modulate angiogenic signaling pathways, thereby enhancing neovascularization within ischemic regions.^{297,298} sEVs further facilitate vascular remodeling by upregulating pro-angiogenic factors while suppressing anti-angiogenic signals.²⁹⁹ In vivo, induced pluripotent stem cell (iPSC)-derived MSC-EVs significantly increase microvessel density in murine ischemia models,³⁰⁰ while adipose tissue–derived MSC-EVs enhance vascular branching and vessel length, underscoring their potent pro-angiogenic capacity.

In parallel, EVs actively support post-ischemic neurogenesis. sEV-based therapies promote neural stem cell differentiation and neuronal regeneration following ischemic injury.³⁰¹ miR-124, a brain-enriched miRNA critical for neuronal differentiation, is upregulated in ischemic regions after middle cerebral artery occlusion. Moreover, adipose-derived EVs carrying miR-3c and miR-17-5p target TLR7 and BINP2, thereby reducing neuronal apoptosis and oxidative stress while improving functional recovery.³⁰² EVs also play a pivotal role in preserving BBB integrity. Endothelial colony-forming cell (ECFC)-derived sEVs, particularly after hypoxic preconditioning, enhance tight junction protein expression via modulation of the PTEN/AKT pathway, limiting secondary brain injury.^{303,304} Similarly, EVs derived from MSCs and neural stem cells (NSCs) reduce cerebral damage and maintain BBB structure and function.³⁰⁴

Importantly, beyond these well-established paracrine and regulatory effects, emerging evidence reveals a previously underappreciated bioenergetic mechanism by which EVs directly restore mitochondrial function in ischemic neurons. Extracellular vesicles can transport intact mitochondria or mitochondrial components to injured cells, thereby rescuing cellular energy metabolism after stroke. A seminal study by Hayakawa et al demonstrated that astrocytes release

mitochondria-containing EVs that are internalized by neurons in the peri-infarct region, resulting in increased ATP production, reduced oxidative stress, and improved neuronal survival following cerebral ischemia.²⁰⁰ This astrocyte-to-neuron mitochondrial transfer represents an endogenous repair mechanism that complements classical EV-mediated signaling pathways. Subsequent studies further corroborated the therapeutic relevance of EV-mediated mitochondrial delivery. MSC-derived EVs have been shown to carry functional mitochondria or mitochondrial DNA that integrate into recipient neural cells, enhance mitochondrial respiration, and attenuate ischemia-induced apoptosis.^{305,306} Collectively, these findings indicate that EVs promote stroke recovery through a multi-layered mechanism encompassing angiogenesis, neurogenesis, BBB stabilization, and direct restoration of cellular bioenergetics, positioning EV-mediated mitochondrial transfer as a promising, non-cell-based therapeutic strategy for ischemic stroke.

Conclusion and Future Perspectives

EVs are increasingly recognized as systemic regulators of intercellular communication during aging, orchestrating information exchange across tissues and organ systems. Rather than acting solely as passive byproducts of cellular stress or degeneration, EVs actively shape age-associated phenotypes by modulating inflammation, metabolic homeostasis, proteostasis, and tissue repair. Importantly, accumulating evidence highlights the inherently “double-edged sword” nature of EVs: while physiological EV signaling contributes to adaptive stress responses and regenerative capacity, age-associated alterations in EV composition and signaling fidelity may propagate chronic inflammation, cellular dysfunction, and disease progression. This duality underscores the need to understand EVs not only as disease biomarkers or therapeutic tools, but as integral components of the aging regulatory network.

Encouragingly, the translational momentum of EV-based therapeutics is beginning to materialize. Early-phase clinical trials have been initiated across several age-related conditions, including neurodegenerative diseases, ischemic stroke, myocardial infarction, and immune-mediated disorders. Studies employing MSC-EVs are currently evaluating safety, biomarker modulation, and preliminary efficacy in AD, PD, and cardiovascular injury.^{307–310} Although these trials remain exploratory, they collectively provide critical proof-of-concept that EV-based interventions can be manufactured, administered, and monitored in humans. Among the various disease areas, neurological and cardiovascular disorders appear particularly promising, reflecting both strong preclinical efficacy and clear unmet clinical need. Together, these developments indicate that the clinical feasibility of EV therapeutics is no longer hypothetical but is actively being established.

From a regulatory and translational perspective, the successful advancement of EV-based products will depend on adherence to overarching principles rather than narrowly defined technical solutions. Regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency emphasize rigorous product characterization, reproducible manufacturing, and comprehensive safety assessment as foundational requirements for clinical development.^{311,312} Given the biological complexity and heterogeneity inherent to EVs, early and continuous engagement between developers, academic investigators, and regulatory authorities is increasingly viewed as essential. Such dialogue will be critical for aligning expectations regarding quality attributes, potency assessment, and acceptable clinical endpoints, thereby reducing uncertainty and de-risking development pathways.

Looking forward, EVs are poised to become central components of precision aging medicine. Beyond their therapeutic potential, EVs offer minimally invasive biomarkers that reflect systemic aging trajectories and disease states. As delivery vehicles, EVs provide a flexible platform for cell- and tissue-specific modulation of pathological signaling. In this context, emerging EV sources such as iPSCs-EVs illustrate the future direction of the field, combining regenerative and neuroprotective capacity with the potential for patient-specific customization in heterogeneous disorders such as AD and ALS.^{313–317} More broadly, EVs represent powerful system-level regulators capable of reshaping maladaptive intercellular communication networks that arise with age. With continued interdisciplinary collaboration and regulatory alignment, EV-based strategies hold promise to transform how aging and age-related diseases are diagnosed, monitored, and treated.

Ethical Approval and Consent to Participate

This article does not include any studies with human participants performed by any of the authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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