

Review

Extracellular Vesicles as Key SASP Carriers Driving Cellular Senescence, Inflammaging, and Therapeutic Opportunities in Aging and Age-Related Diseases

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ABSTRACT: The progressive decline in physiological processes with aging is a complex biological process that increases susceptibility to age-related diseases. Cellular senescence is a primary contributor to this process, a state of sustained cell cycle arrest accompanied by a distinctive secretory profile known as the Senescence-Associated Secretory Phenotype (SASP). In recent years, extracellular vesicles (EVs), including exosomes and microvesicles (MVs), have emerged as key mediators of intercellular communication by carrying bioactive molecules, such as proteins, lipids, and nucleic acids. In this review, we describe how EVs are important SASP vectors that transmit senescent signals to nearby cells, driving immunosenescence, persistent inflammation (inflammaging), and other aging characteristics, such as stem cell exhaustion and genomic instability. Furthermore, we highlight the dual function of EVs as both pathogenic drivers of aging-related dysfunctions and promising therapeutic agents. In addition, we emphasize their potential as diagnostic biomarkers for age-related diseases, including cardiovascular disease, osteoporosis, and Alzheimer's disease. Finally, we explore the emerging therapeutic uses of EVs, particularly those derived from mesenchymal stem cells (MSCs), to promote tissue repair, reduce aging phenotypes, and serve as engineered drug-delivery systems. This study highlights the critical role of EVs in aging mechanisms and establishes them as potent diagnostic and therapeutic tools for anti-aging.

Keywords: extracellular vesicle, aging, senescence, biomarkers, therapeutics

1. Introduction

Aging represents the progressive decline of physiological functions over time [1, 2], resulting from the gradual

accumulation of cellular and molecular damage that depletes the body's reserves and reduces its ability to respond to challenges. This deterioration contributes to various age-related conditions, such as

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neurodegenerative, cardiovascular, and metabolic disorders, arising from tissue dysfunction, physiological impairment, and cellular dysregulation [3]. These outcomes are linked to well-established hallmarks of aging. These include genomic instability, telomere shortening, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, chronic inflammation, altered nutrient-sensing, loss of proteostasis, impaired autophagy, dysbiosis, and disrupted intercellular communication [4]. Among these hallmarks, cellular senescence—a state marked by distinct phenotypic and genotypic alterations—is a pivotal process that deepens our understanding of aging. Often described as a “double-edged sword”, senescence exerts both beneficial and harmful effects. Senescent cells (SCs) exhibit a SASP [5]. This impacts the extracellular environment by increasing the secretion of Extracellular vesicles (EVs) [6]. SASP is also a means of intercellular communication characterized by pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF) and interleukins (IL-1, IL-6, IL-8), chemokines, growth factors, proteases, bioactive lipids, and EVs. EVs secreted by aged SCs (SnEVs) have characteristics of their parent cells. When these are transferred to neighbour cells, they alter the cell’s phenotype, causing persistent inflammation and

extracellular matrix degradation [7]. EVs are nanosized lipid bilayer-enclosed particles (40 nm to 1 μ m) lacking reproductive capacity [8]. Their molecular cargo comprises DNA, RNA, Proteins, lipids, metabolites, and amino acids [9], reflecting their cell of origin, making them valuable as pathophysiological biomarkers. These vesicles mediate intercellular communication by transferring their bioactive contents to recipient cells [10], thereby modulating cellular function and contributing to physiological and pathological processes. Intercellular communication plays an important role in maintaining homeostasis, coordinating development, differentiation, and enabling adaptive responses to external stimuli. It occurs either through direct cell contact or via the release of soluble factors that affect recipient-cell function [11]. It's crucial to remember that age-associated senescence has detrimental effects, yet it also confers advantages, including tissue remodeling, tumor suppression, wound healing, and embryonic development, and becomes pathological when SCs accumulate due to aging [12]. This review focuses on the multifaceted role of senescence in aging, emphasizing its interplay with EVs. It explores how EVs serve as biomarkers of aging, their role in age-related diseases, and, finally, their use as anti-senescence agents.

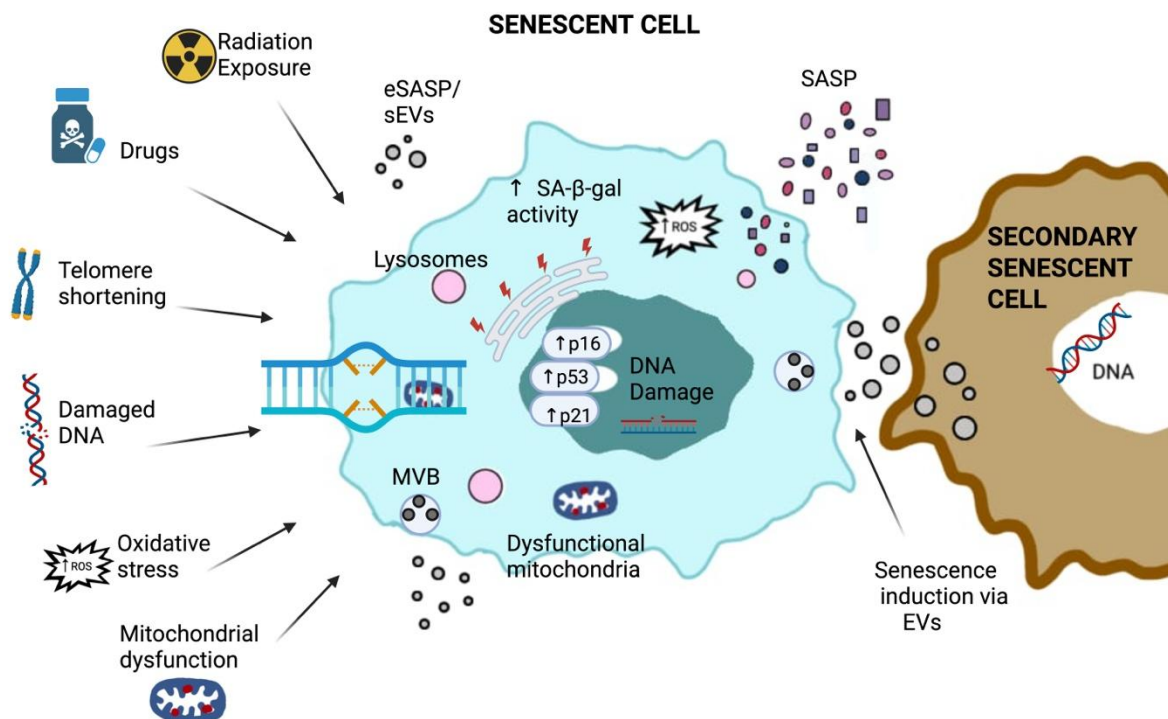


Figure 1. Characteristics of a Senescent Cell. This figure depicts the agents responsible for senescence and its characteristics, including irregular morphology, increased senescence-associated β -galactosidase (SA- β -gal) activity and SASP, as well as the induction of senescence in other cells via SASP (particularly via EVs) [22]. The figure was generated by <https://BioRender.com>.

2. EVs and cellular senescence

2.1 Senescence

The irreversible, stable cessation of the cell cycle (in the G1 or G2 phase) due to intrinsic or extrinsic factors is known as senescence. Oncogenic activation, chromatin disruption, inflammation, epigenetic dysregulation, oxidative stress, telomere shortening, and DNA damage are some of the causes of senescence [13]. In 1961, Hayflick and Moorhead were the first to describe senescence, demonstrating that telomere attrition limits the number of times human diploid cells can divide [14]. Senescence aims to limit the growth of damaged cells. Since SCs are apoptosis-resistant, the immune system typically removes them from the environment [15]. However, with aging, the immune system becomes dysregulated, leading to persistent inflammation and the accumulation of SCs, which cause age-associated chronic illnesses. For instance, brain SCs are more prevalent in Alzheimer's patients than in healthy individuals [16].

Additionally, SCs can induce senescence in other non-SCs, which has been linked to aging disorders. SCs secrete SASP in skeletal diseases, thereby accelerating the establishment of an inflammatory milieu and bone loss. Changes in bone cell function induced by senescence eventually contribute to the development of osteoporosis, osteoarthritis, and other bone diseases [17]. Cellular senescence can also serve as a marker of disease, as a recent study associates cystic fibrosis (C'F) with elevated cellular senescence markers [18].

2.2 Senescence-associated secretory phenotype

Cellular or organ senescence plays a key role in the decline of bodily functions. The SASP is one of the characteristics of SCs, along with notable morphological alterations, including cell flattening and enlargement, altered chromatin structure, unregulated metabolism, and increased lysosomal activity, as shown by increased SA- β -gal staining [19], as shown in Figure 1. First formally described by Coppé and associates, SASP encompasses several factors, including growth factors (e.g., heregulin, HGF, SCF), matrix metalloproteinases, chemokines, TNF, and inflammatory cytokines. These impact both healthy physiological functions and the course of illness [7]. Its composition is not fixed; it varies with cell type and the mechanism triggering senescence, thus it depends on the cell environment [20]. Understanding and targeting the diverse and dynamic phenomenon of SASP and its delivery system, i.e., the EVs, particularly exosomes, can help develop anti-aging therapies [21].

2.3 Extracellular vesicles in senescence

EVs are broadly categorized into exosomes, MVs, and apoptotic bodies based on their size and biogenesis pathways [23], as detailed in Table 1. Figure 2 shows the components of SASP, including EV-mediated SASP. Compared with non-SCs, SCs release more EVs (20%-30%). For example, EV production and secretion in senescent Human Dermal Fibroblasts (HDFs) is higher than in young HDFs due to impaired lysosomal activity. This may result in clinical symptoms observed in aging skin, such as dryness, slowed wound healing, and heightened vulnerability to inflammatory skin conditions [24].

Many SASP-associated proteins and senescence-related microRNAs are present within these EVs [25], several of which are listed in Table 2. Among them is MicroRNA-34a (miR-34a). In Chronic Obstructive Pulmonary Disease (COPD), EVs derived from diseased airway cells are produced at ~ 10 -fold higher concentrations than those from healthy cells (1.35×10^{11} vs 1.13×10^{10} particles/ml). They contain elevated levels of miR-34a. When these EVs transfer miR-34a to recipient cells, it leads to reduced expression of the anti-aging protein Sirtuin 1 (SIRT1) after 12 hours. After 48 hours, increased expression of senescence markers, such as p21 (cyclin-dependent kinase inhibitor 1), was observed. Inhibition of miR-34a prevents these effects. This indicates that EV-mediated transfer of specific microRNA (miRNAs), particularly miR-34a, facilitates the dissemination of senescence and contributes to COPD progression [26]. Therefore, like SASP factors, SnEVs exhibit distinct functional characteristics that influence recipient cell behavior, including the promotion of premature senescence. This, in turn, drives inflammation, stem cell failure, and cancer progression [27], as shown in Figure 3. However, the downstream signaling cascade linking miR-34a delivery to the SASP remains incompletely characterized. Most of the information is limited to in vitro tests or animal studies. Thus, for the therapeutic strategy of targeting EV-mediated miR-34a transfer to be considered a promising pathway for COPD, in vivo validation of EV-targeted medicines is required. Aside from the miRNAs, the diverse composition of EVs also gives much insight into the complex process of senescence, the details of which are given below.

2.4 A Conceptual Framework: Mechanistic and Functional Distinctions Between Soluble and EV-Mediated SASP

EVs are increasingly recognized as components of the senescence-associated secretory phenotype (SASP),

although they differ fundamentally from soluble SASP (sSASP) factors in their mechanistic and functional characteristics. Interleukins (IL-6, IL-8), TNF- α , chemokines, and matrix metalloproteinases are examples of soluble SASP components. These substances mainly function via receptor-mediated signaling pathways. They stimulate downstream cascades, including the NF- κ B, JAK/STAT, and MAPK pathways, upon binding to cell surface receptors [28]. This reinforces paracrine senescence and increases the inflammatory gene expression. These signals are usually transitory, diffusion-limited, and susceptible to extracellular clearance or degradation, though. Conversely, EV-mediated SASP (eSASP) is a mechanistically unique and structurally

protected form of intercellular communication. The EV cargo, including mitochondrial DNA, telomeric DNA, microRNAs, and other bioactive substances, is protected from enzymatic destruction by encapsulation within a lipid bilayer. Crucially, EV uptake by recipient cells enables direct delivery of bioactive compounds into cells, bypassing traditional receptor–ligand limitations [29]. This enables the horizontal transmission of damage-associated molecular patterns and regulatory nucleic acids, thereby causing long-lasting transcriptional, epigenetic, and metabolic reprogramming in recipient cells. There are three non-exclusive levels at which EV-mediated SASP can function:

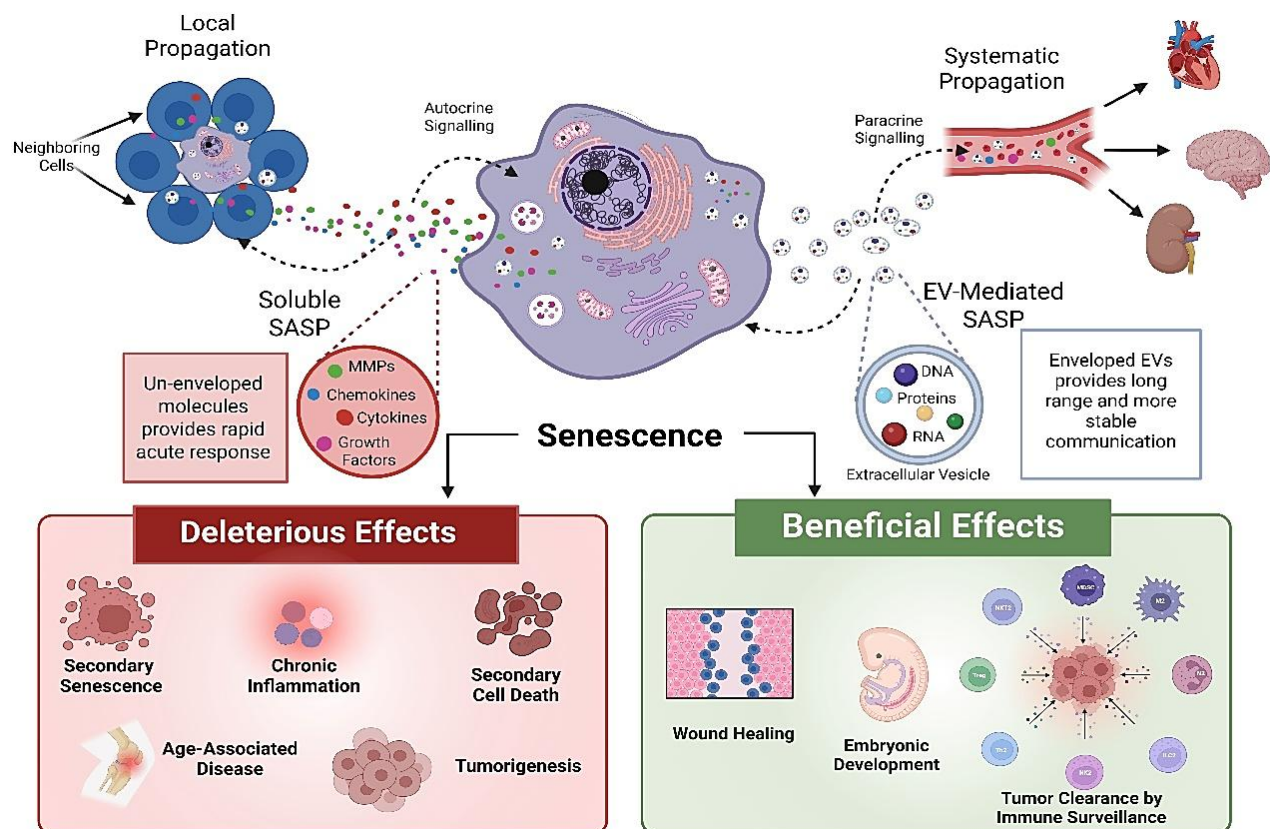


Figure 2. Soluble and Extracellular Vesicle-Mediated SASP Signaling in Senescence. This schematic figure illustrates the molecular and functional distinctions between soluble SASP (sSASP) and EV-mediated SASP (eSASP). By acting through receptor-mediated signaling pathways soluble SASP components such as cytokines, chemokines, and proteases cause temporary inflammatory reactions and strengthen local paracrine senescence. On the other hand, lipid bilayer-encapsulated vesicles released during EV-mediated SASP allow direct transcriptional, epigenetic, and metabolic reprogramming upon uptake by recipient cells.

2.4.1 Propagators of Senescence:

Senescent cell-derived EVs (SnEVs) carry pro-senescent microRNAs (such as miR-34a and miR-21) and DNA fragments that cause cell-cycle arrest, mitochondrial malfunction, and DNA damage responses in nearby or distant cells [26]. This turns localized cellular damage into

a tissue-level and possibly systemic aging phenotype by promoting the spread of secondary senescence beyond the original site of stress.

2.4.2 Amplifiers of Inflammatory Signaling:

EVs maintain and amplify inflammatory circuits that are first initiated by soluble cytokines by transporting cargo

that supports NF- κ B activation, inflammasome signaling, or cGAS–STING pathway involvement [30]. Thus, EVs transform short-lived inflammatory reactions into self-sustaining feedforward loops that maintain the senescent state.

2.4.3 Context-Dependent Modulators:

Not all EVs contribute to aging. By reducing oxidative stress, inhibiting SASP synthesis, and restoring mitochondrial dynamics, EVs derived from mesenchymal stem cells (MSCs), youthful plasma, or induced pluripotent stem cells (iPSCs) may reverse senescence. Small extracellular vesicles (sEVs) derived from human amniotic MSCs can also be used to control elevated ROS

levels [31], a significant factor in aging in the mouse model. Therefore, depending on the cellular origin and cargo content, EVs might either worsen or lessen senescence. When combined, soluble SASP mainly promotes receptor-dependent inflammatory signaling, while EV-mediated SASP facilitates intracellular molecular reprogramming [32]. We suggest that EVs might serve as vectors for stability, converting transient stress signals into transmissible, long-lasting senescence programs. As a unique, higher-order regulatory layer within the SASP network, EVs provide a mechanistic link between organismal aging and local cellular senescence by safely transporting cargo and spreading throughout the body.

Table 1. Types of Extracellular vesicles based on size and biogenesis, along with possible biomarkers.

Type (size)	Origin	Morphology	Biogenesis	Pathway	Possible Markers	Ref.
Exosomes or sEVs (30–150nm)	Early Endosomal membrane	Cup-shaped (more homogenous than other EVs)	Inward budding from the Plasma Membrane (PM), followed by exocytosis after multivesicular body (MVB) fusion with the PM.	ESCRT-dependent	Tetraspanin proteins (CD9, CD81, CD63, CD82), ALIX TSG101, Flotillin-1, Clathrin	[37, 38]
Microvesicles (100–1000nm)	Plasma membrane	Cup-shaped	Direct outward blebbing following pinching of the PM.	Ca ²⁺ -dependent	Integrins, Selectins, and CD40	[39, 40]
Apoptotic bodies (05–5000nm)	Plasma membrane, Endoplasmic Reticulum	heterogenous	Outward budding of PM of dying cells	Apoptotic pathway	Caspase 3, Annexin V, Thrombospondin-1, histones	[41, 42]

2.5 Extracellular Vesicle Molecular Cargo

EVs carry diverse molecular cargo, including microRNAs, mitochondrial DNA (mtDNA), telomeric DNA fragments, proteins, and lipids, which reflect the physiological state of their cells of origin. SnEVs disseminate cargo fragments that are linked to damage to other organs. These can strengthen a feedforward cycle of aging and inflammation in tissues that are otherwise unharmed. In vitro study with in vivo validation of tumor progression in Colorectal cancer shows that therapy-induced senescent cells secrete EVs that are highly enriched in SERPINE1 (plasminogen activator inhibitor-1). These paradoxically activate the NF- κ B pathway in neighboring tumor cells, thereby driving proliferation and undermining the intended therapeutic effect of chemotherapy or radiation [33]. SnEVs also contain a variety of DNA. In models of neurodegeneration, microglia-derived EVs deliver cytosolic double-stranded DNA (dsDNA) to neurons. This triggers apoptosis via activation of the innate immune system. Remarkably, in *Ercc1Δ*, a mouse model of accelerated aging, engineered

removal of cytosolic dsDNA using EV-based strategies was sufficient to suppress neuroinflammation. This reduced neuronal death and delayed symptom onset [34]. This suggests their roles in inflammation and in removing specific harmful particles. SnEVs also contain mtDNA, which is released into the cytoplasm and promotes local immunosuppression. This is also an important factor in SASP activation. This exacerbates inflammatory conditions associated with tissue damage or disease progression, and contributes to age-related illnesses and cancer [35]. EVs have also been found to contain telomeric DNA, and the quantity of telomeric DNA in EVs is inversely correlated with cell proliferative ability due to telomere erosion. This may lead to inflammatory responses and neurotoxicity, which significantly contribute to age-associated disorders [36]. In summary, senescent cell-derived EVs spread pro-inflammatory and damage-associated cargo that drives tumor progression, neuroinflammation, and age-related tissue dysfunction.

3. Extracellular vesicles as hallmarks of aging

EVs have revealed their diverse origins, characteristics, and nature, leading to the use of various terms to describe them. These terms cover different aspects, such as scale (using prefixes like micro or nano, as in microparticles, microvesicles (MVs), nanovesicles, nanoparticles), their origin within cells or tissues (such as prostasomes, oncosomes), suggested roles (like calcifying matrix vesicles, autosomes, tolerosomes), or their existence outside cells (with prefixes exo or ecto, including ectosomes, exosomes, exovesicles, and exosome-like vesicles). Exosomes, with a diameter smaller than 150 nm, mainly appear in three distinct forms determined by their size and method of release: microvesicles, shedding particles, and apoptotic bodies exceeding 100 nm in size

[49]. Small extracellular vesicles (sEVs) are membrane-bound vesicles smaller than 200 nm, released by cells. Because of their relatively low molecular weight and ability to participate in intercellular communication, sEVs can serve not only as carriers of disease biomarkers but also as effective drug delivery agents. These vesicles regulate the onset and progression of various diseases, reflecting the physiological and functional states of cells [50]. EVs have emerged as key players linking several hallmarks of aging. Their composition and secretion patterns change significantly with age, reflecting and influencing cellular and tissue aging processes. SCs release increased numbers of EVs enriched with pro-inflammatory and stress-related molecules, reinforcing age-associated phenotypes in neighboring cells.

Table 2. List of miRNAs upregulated in EVs used as possible biomarkers for senescence, with their effects.

miRNA	EVs source	Model System	Senescence Type/Induction Method	Pathways Affected	Effect / Role in Senescence	Ref.
miR-217-5p	Epithelial cells	Mouse	Paraquat intoxication	Downregulation of SIRT1 expression, subsequently promoting acetylation of β -catenin and Wnt signaling activation	Promote fibrogenesis, inflammation and senescence across various tissues	[43]
miR-21-5p	Vascular endothelial cells,	Mouse	Natural aged	MSH2-MSH3 pathway	Cellular senescence due to reduced DNA replication and cell cycle arrest, increased SA β -gal activity.	[44]
miR-21 and miR-217	Senescent Human umbilical vein endothelial cells	Human	Doxorubicin treatment	DNMT1 and SIRT1 modulation	increased SA β -gal activity, growth arrest, telomere shortening	[45]
miR-34a	C2C12 myoblasts, human myotubes, Muscle-derived EVs	Human	Oxidative damage by treatment with Hydrogen peroxide (H ₂ O ₂)	Reduced Sirt1 expression in Bone Marrow Stem Cells (BMSCs), p53 activation	Promote DNA damage and inhibit DNA repair, reduced BMSC viability and increased senescence	[46]
miRNA-146a-5p	Hepatocellular Carcinoma Cells	Human	H ₂ O ₂ and oxaliplatin used to induce senescence	Reduced expression IRF7, Upregulation of p21 protein, glycolysis/gluconeogenesis pathways	Inhibition of Aerobic Glycolysis, accelerated aging, reduced cell proliferation	[47]
miR-23b-3p	Liver tissue	Mice	Naturally aged	Tnfaip3, p21WAF1/Cip1 pathway	Irregular lipid metabolism, promotes cellular senescence,	[48]

3.1 Inflammaging and immunosenescence

Like cellular senescence, chronic inflammation also exerts numerous effects, including increased levels of damage-associated molecular patterns (DAMPs). These factors account for a significant proportion of global mortality [51]. Chronic inflammation due to aging, a

consequence of immunosenescence, is termed “inflammaging” [52]. Inflammaging is characterized by an abundance of proinflammatory molecules, which links it to SASP, given its ability to produce cytokines [53]. Immunosenescence, or aging-related decline in immune function, characterized by reduced capacity to respond to infections, increases the risk of age-related illnesses and

alters immune cells, thereby contributing to several age-related diseases [54]. Shaun Hanley and colleagues provide a summary of the impact of sEVs on inflammaging and immunosenescence, particularly by inhibiting macrophage responses and immunoregulatory effects, preventing excessive production of pro-inflammatory cytokines, and reducing macrophage activation, thereby promoting the maturation of pro-inflammatory cytokines [55]. According to a recent study on EVs from Hutchinson-Gilford Progeria Syndrome fibroblasts grown in vitro, EVs may influence immune responses to senescent cells, potentially explaining why

such cells accumulate in age-related diseases due to reduced clearance [56]. In a human study on HIV-associated immunological aging, plasma EVs were found to carry upregulated miR-21-5p, which, in vitro, led to increased IL-6 production, suggesting a mechanism for accelerated immunosenescence [57]. While the therapeutic potential of targeting EV-mediated communication in inflammaging is promising, in vivo validation remains limited, hindering conclusions about whether modifying EV cargo in living systems will yield similar results.

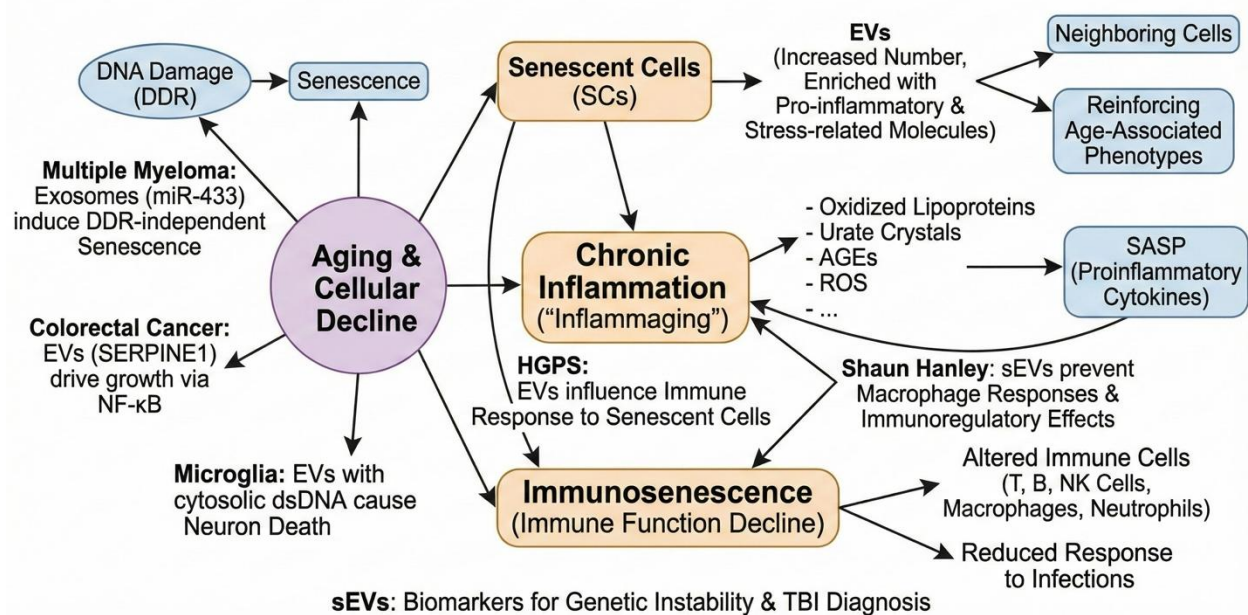


Figure 3. The role of Extracellular vesicles in aging, inflammation, and senescence. Aging and cellular decline lead to the buildup of senescent cells (SCs), chronic inflammation ("inflammaging"), and immunosenescence. EVs serve as key mediators in this process by transporting pro-inflammatory molecules and stress signals that reinforce age-related phenotypes in nearby cells. The diagram shows how EV signaling contributes to various pathological conditions, including oncogenesis (Multiple Myeloma, Colorectal Cancer), neurodegeneration (Microglia), and systemic immune dysfunction, while also acting as potential biomarkers for genetic instability.

3.2 Genomic instability

Cellular senescence, induced by oxidative, oncogenic, or telomere stress, is mediated by DNA damage. Age-related declines in DNA repair capacity and increased production of reactive oxygen species (ROS) could contribute to the accumulation of DNA damage [58]. Senescence is driven by the DNA damage response (DDR), a signaling cascade triggered by DNA damage. This is supported by the claim that inhibition of DDR signaling kinases enables SCs to re-enter the cell cycle in human cytomegalovirus [59]. However, senescence induction can occur even in the absence of DDR signaling. In vitro, SCs in multiple myeloma release exosomes that contain miR-433. These can induce doxorubicin-assisted senescence without

involving the DDR pathway. This could affect the tumor microenvironment and lead to cell-cycle arrest associated with senescence [60]. A study using a mouse model, which diagnosed various stages of traumatic brain injury (TBI) by examining changes in the DNA and protein content of circulating EVs in plasma, revealed that EVs are emerging biomarkers for diagnosing the acute phase of TBI [61]. This suggests sEVs as an excellent marker for genetic instability due to their direct effect on sEV's cargo. Similarly, EVs play a prominent role in other hallmarks of aging, as summarized in Table 3.

The two main tumor-suppressor pathways that induce irreversible cell cycle arrest in SCs are p53/p21CIP1 and p16INK4a/RB. Significant mitochondrial dysfunction actively reinforces this arrest, making it more than just a

passive endpoint. The accumulation of mitochondrial DNA (mtDNA) mutations reduces pyruvate dehydrogenase complex (PDHC) activity, leading to

cytoplasmic pyruvate accumulation and mitochondrial dysfunction. These metabolic changes increase glycolysis and also hinder oxidative phosphorylation [69].

Table 3. Changes in EVs in aging and their effect.

	Hallmark	Changes in EVs	Effect	Reference
1	Telomere shortening	Presence of telomeric DNA in plasma EVs.	Causes Proinflammatory Inflammation response in recipient cells, T-cell activation/division.	[62]
2	Genomic instability	Polymorphonuclear neutrophils-derived EVs contain miR-23a and miR-155 (PI miRNAs).	Cause double-strand breaks in DNA, which accelerates the development of colorectal cancer by increasing genetic instability and impairing mucosal repair.	[63]
3	DNA damage	Increased sEVs biogenesis.	Establishing cellular homeostasis by preventing DNA damage accumulation, preventing apoptosis leading to accumulation of SCs.	[64]
3	Stem cell exhaustion	cell raised miR-34a levels.	Reduced BMSC viability and elevated BMSC senescence.	[65]
4	Loss of proteostasis	of increased sEVs release, containing proteins that are ubiquitinated and oligomerized.	Accumulation of protein aggregates.	[66]
5	Oxidative stress	Decreased Glutathione S-transferase Mu 2 activity.	Decreased glutathione and elevated lipid peroxidation and Oxidative stress.	[67, 68]

3.3 Mitochondrial dysfunction

Mitochondrial dysfunction increases Reactive Oxygen Species (ROS) levels, which in turn further impair mitochondrial function. Chronic oxidative stress can cause DNA damage, which, if unrepaired, may lead to genomic instability and accelerate telomere shortening. However, EVs can also be used effectively to combat senescence by targeting mitochondrial disruption. In cell culture, young sEVs from human deciduous teeth stem cells restore pluripotency and immunoregulatory functions in senescent bone marrow-derived mesenchymal stem cells (MSCs). This occurs by facilitating the translocation of Dynamin-related protein 1, an up-regulator of replicative senescence, from the cytoplasm to the mitochondria, remodeling mitochondrial disruption [70]. By promoting mitophagy, which is hindered due to senescence, a rat study showed that Erxian Decoction-induced serum exosomes can prevent bone marrow stromal cells (BMSC) senescence [71]. The importance of exosomes in enhancing mitochondrial activity is increasingly recognized as pivotal in modulating aging and age-related diseases.

3.4 Epigenetic alterations

Aging is influenced by a range of epigenetic changes, including defects in non-coding RNAs (ncRNAs), abnormal post-translational modifications of histones, disrupted chromatin remodeling, and altered DNA methylation patterns. In addition, aging is closely

associated with the loss of intracellular protein homeostasis. This disruption is often driven by the increased production of incorrectly translated, misfolded, or incomplete proteins, which accumulate over time and impair normal cellular processes [72]. These can lead to genomic instability, loss of stem cell function and regenerative capacity, and mitochondrial dysfunction, thereby contributing to aging and age-associated disease. Exosomes can modulate some of these epigenetic changes by regulating the gene SIRT1 (Sirtuin-1), which is linked to early aging and longevity. It encodes a deacetylase that regulates multiple epigenetic changes affecting chromatin structure and gene expression. This also downregulates the SASP. In a senescent mouse model, MSC-exosomes can markedly increase SIRT1 gene expression. This may delay brain aging [73], MSC-derived EVs (MSC-EVs) have been shown to mitigate renal interstitial fibrosis in aged mice by delivering miR-133b, which suppresses epithelial-mesenchymal transition (EMT) in renal tubular cells [74]. Similarly, exosomes derived from human umbilical cord mesenchymal stem cells (hUCMSCs) can attenuate kidney aging in naturally aged rats. This effect occurs through modulation of the phosphorylation status of Lamin A/C at Ser390 and Ser392, a key nuclear envelope protein whose dysregulation is associated with progeroid syndromes and normal physiological aging [75]. Through complex epigenetic pathways, exosomes can promote or hinder disease progression by upregulating or silencing relevant genes. These reversible epigenetic alterations offer therapeutic targets for reducing age-related decline. Via methyltransferase and

demethyltransferase targeting, EVs can reprogram the epigenomic profile by altering DNA, RNA, and histone modifications in recipient cells [76].

3.5 Telomere attrition

Repetitive DNA sequences present at the end of linear chromosomes are called telomeres. With each cell division, the telomere length gradually decreases. When it reaches a certain point, the cell will either cease proliferating and enter senescence or undergo apoptosis. Premature telomere shortening can result from cellular injury. This accelerates biological aging [77]. It is unknown, however, whether telomere loss reaches a critical threshold with age. Studies show that exosomes also contribute to telomere shortening in certain age-associated illnesses. A multi-model study demonstrated that macrophage-derived exosomes that encapsulate miR-155 negatively regulate TRF1. This induces telomere shortening and telomere dysfunction in chronic kidney disease, leading to cellular senescence and renal fibrosis [78]. X-ray irradiation can also alter telomere metabolism not only in directly exposed breast epithelial cancer cells but also in nearby, non-irradiated “bystander” cells through exosome-mediated communication. According to an in vitro study, when exosomes were both RNase-treated and boiled, all telomeric changes disappeared in irradiated and bystander cells alike. This indicates that exosomal RNA and proteins transmit radiation-induced signals that disrupt telomere maintenance, potentially promoting genomic instability even in cells not directly irradiated [79]. Exosomes can also be used as a therapeutic approach to restore the telomere length. Telomerase reverse transcriptase (TERT) plays a vital role in maintaining genome stability by protecting telomeres and delaying cellular senescence. Exosomes derived from TERT-overexpressing human fibroblast cells mimic the effects of Human Telomerase Reverse Transcriptase (hTERT) gene therapy, thereby restoring telomere length and reducing the markers of cellular senescence [80]. Thus, EVs can both promote telomere dysfunction in age-related diseases and potentially restore telomere maintenance through telomerase-related cargo.

4. EVs in age-associated disease

EVs play a prominent role in age-associated diseases. Understanding disease-specific EV signatures can help improve the detection, prevention, and treatment of these conditions. The potential therapeutic role of EVs in certain diseases, as outlined below and via miRNA therapy, including increased angiogenesis, improved insulin binding, anti-inflammatory effects, and more, as well as inhibition of A β deposition, neurofibrillary

tangles, osteoclast proliferation, and other processes, is depicted in Figure 4.

4.1 Alzheimer’s Disease

Alzheimer’s disease (AD) is the most common form of dementia and is characterized by the accumulation of amyloid- β (A β) plaques and neurofibrillary tangles (NFTs) in the brain. These hallmark features are accompanied by several pathological changes, including neuroinflammation, synaptic dysfunction, mitochondrial and energy-metabolism disturbances, and vascular irregularities. Amnesic cognitive impairment is a main feature of AD. The exact mechanisms underlying the onset of AD remain unclear. However, its development is influenced by a combination of environmental factors, genetic predisposition, and aging. Several biological processes have also been implicated in AD progression, including neuroinflammation, oxidative stress, glutamate imbalance, insulin resistance, abnormalities of the gut microbiome, and disruption of cholesterol homeostasis [81]. Increasing evidence suggests that EVs may participate in the intercellular communication processes associated with AD pathology. Some studies suggest that EVs may facilitate the dissemination of misfolded proteins, such as in Huntington’s disease [82]. Other evidence indicates that EV-mediated export of toxic protein aggregates might represent a protective cellular response aimed at maintaining neuronal homeostasis and preventing endosomal and lysosomal abnormalities associated with aging and neurodegenerative diseases (NDs) [83]. This potential dual function underscores the need for further investigation to fully understand the role of EV-mediated signaling in neurodegenerative processes. EVs have attracted significant interest as biomarkers for NDs in addition to AD, such as Parkinson’s and Huntington’s disease [84]. In particular, in people with AD and mild cognitive impairment, neuron derived EVs in plasma have elevated levels of tau and amyloid beta (A β). Compared with healthy controls, these elevated A β levels are detectable up to 10 years prior to clinical diagnosis. This suggests their potential as early indicators of disease progression and facilitators of early diagnosis [85]. Numerous studies also suggest that neuronal-enriched EVs could serve as blood biomarkers for NDs [86]. Overall, neuronal EVs may represent promising candidates for minimally invasive biomarkers and provide insight into the mechanisms underlying neurodegeneration.

4.2 Bone Disease

EVs have been increasingly implicated in age-associated bone dysfunction through their ability to transfer

senescence-related signals between cells and tissues. A recent mouse study suggested that aged bone marrow macrophages may contribute to age-associated dysfunction by transmitting senescence signals to other tissues via EVs [87]. Furthermore, EVs isolated from bone marrow interstitial fluid of young and old mice showed substantially higher miR-183 expression in EVs from aged animals. In vitro observations indicate that primary BMSCs release EVs that inhibit osteogenic differentiation in young BMSCs, which may contribute to stem cell senescence [88]. These findings suggest that altered EV cargo in aging may contribute to diminished bone formation, although direct causal evidence in humans remains limited. Dysregulation mediated by EVs seems more prominent in disease contexts. Reduced osteogenesis in bone marrow-derived mesenchymal stem cells (BM-MSCs) is a characteristic feature of multiple myeloma (MM) bone disease (MBD). Studies have reported that MM-derived EVs can impair BM-MSC osteogenic differentiation both in vitro and in vivo, potentially through increased miR-103a-3p expression in BM-MSCs and enhanced MM cell viability and interleukin-6 release. These findings suggest that MM-EVs may represent potential therapeutic targets [89]. In osteoporosis, EVs derived from aged bone matrix (AB-EVs) during bone resorption have been reported to favor BMSC adipogenesis over osteogenesis. This shift may be linked to marrow adiposity associated with aging and menopause and has also been associated with vascular smooth muscle cell calcification, a process related to osteoporosis [90]. Overall, current evidence suggests that extracellular vesicles may play a role in age-related bone disease by promoting stem cell senescence, limiting osteogenic differentiation, and influencing bone marrow stromal cell fate toward adipogenesis. These processes may collectively contribute to the progression of osteoporosis and increased fracture susceptibility.

4.3. Cardiovascular Disease

The risk of cardiovascular disease (CVD), including hypertension, atherosclerosis, myocardial infarction, and stroke, increases with age due to multiple physiological and environmental changes within the body [91]. Heart failure typically develops when the myocardium undergoes maladaptive remodeling to compensate for the loss of contractile tissue following ischemic injury. Emerging evidence indicates that EVs and their miRNA cargo may participate in the progression of heart failure. Several EV-associated miRNAs have been implicated in key pathological processes. For instance, miRNAs such as miR-1, miR-19, and miR-21 have been reported to regulate cardiac cell growth and stress adaptation, which may influence cardiomyocyte hypertrophy. Similarly,

miR-7, miR-16, and miR-29 have been associated with fibrotic remodeling processes that increase myocardial stiffness and contribute to reduced cardiac function. In contrast, other miRNAs, including miR-16 and miR-31, have been suggested to promote angiogenesis by facilitating new blood vessel formation and tissue repair following myocardial infarction [91–92]. Platelet-derived EVs also exhibit functional heterogeneity depending on their origin and activation status. Some subsets have been reported to promote endothelial apoptosis and neutrophil-mediated inflammatory responses, whereas others appear to inhibit platelet activation, aggregation, and endothelial inflammatory injury through targeted delivery of miRNAs and proteins. These observations highlight the source-dependent variability of platelet-derived EVs and their potentially divergent effects on thrombosis and inflammation [94]. These results highlight how crucial the EV source, cargo composition, and isolation technique are in understanding functional results. EVs have also attracted interest as potential biomarkers for cardiovascular disease. Several studies suggest that proteins such as hERG1 and Hsp47 present in plasma EVs may serve as diagnostic indicators of cardiac conditions, including heart failure and cardiac ischemia. For example, EV-associated hERG1 levels were reported to be approximately 10-fold lower in patients with decompensated heart failure than in compensated heart failure or healthy individuals ($p < 0.005$), accompanied by reduced EV-Hsp47 concentrations, which may help distinguish disease severity [95].

Additionally, myocardial infarction has been associated with increased release of platelet-derived EVs into plasma, while fibrinogen levels in plasma EVs have been reported to decrease [96–97]. By transporting bioactive cargo molecules, EVs may influence vascular and cardiac remodeling processes and are increasingly considered to play roles in both cardioprotective mechanisms and cardiovascular disease development. Circulating Extracellular Vesicles As Biomarkers and Drug Delivery Vehicles in Cardiovascular Diseases Plasma-derived Extracellular Vesicles Contain Predictive Biomarkers and Potential Therapeutic Targets for Myocardial Ischemic (MI) Injury,

4.4. Metabolic Disorder

EVs are essential messengers in inflammation, coagulation, and angiogenesis. Their release is a primary cellular response to endothelial damage [98]. Under physiological conditions, endothelial cells secrete a small percentage of EVs, whereas in pathological states such as diabetes or other conditions characterized by endothelial dysfunction, their release is dramatically increased. Elevated endothelium EV levels are thought to be a

significant indicator of vascular damage. In a mouse model, PD-L1 overexpression prevents diabetes. This is because PD-L1 signaling is essential for beta cell survival in type 1 diabetes. EVs derived from islet beta cells exhibit PD-L1 upregulation due to inflammation. This might help beta cell survival in type 1 diabetes, similar to cellular PD-L1 [99–100]. The pathophysiology of cognitive deterioration in type 2 diabetes appears to involve sEVs. Alterations in sEV-associated proteins in patients with diabetes can increase vascular permeability, potentially leading to hyperpermeability and cerebrovascular dysfunction [101]. EVs are also being

explored as a potential treatment for diabetes. An innovative treatment for the effective healing of chronic diabetic wounds may be the MSC-EV-7A hydrogel, which combines EVs and 7A in an alginate hydrogel [102]. Increased osteoblast development and proliferation by targeting miR-3064 with BMSC-derived EVs may also provide a potentially effective therapy for diabetic osteoporosis [103]. EVs appear to play an important role in metabolic disorders and show potential as therapeutic tools for beta-cell protection, wound healing, and diabetic osteoporosis.

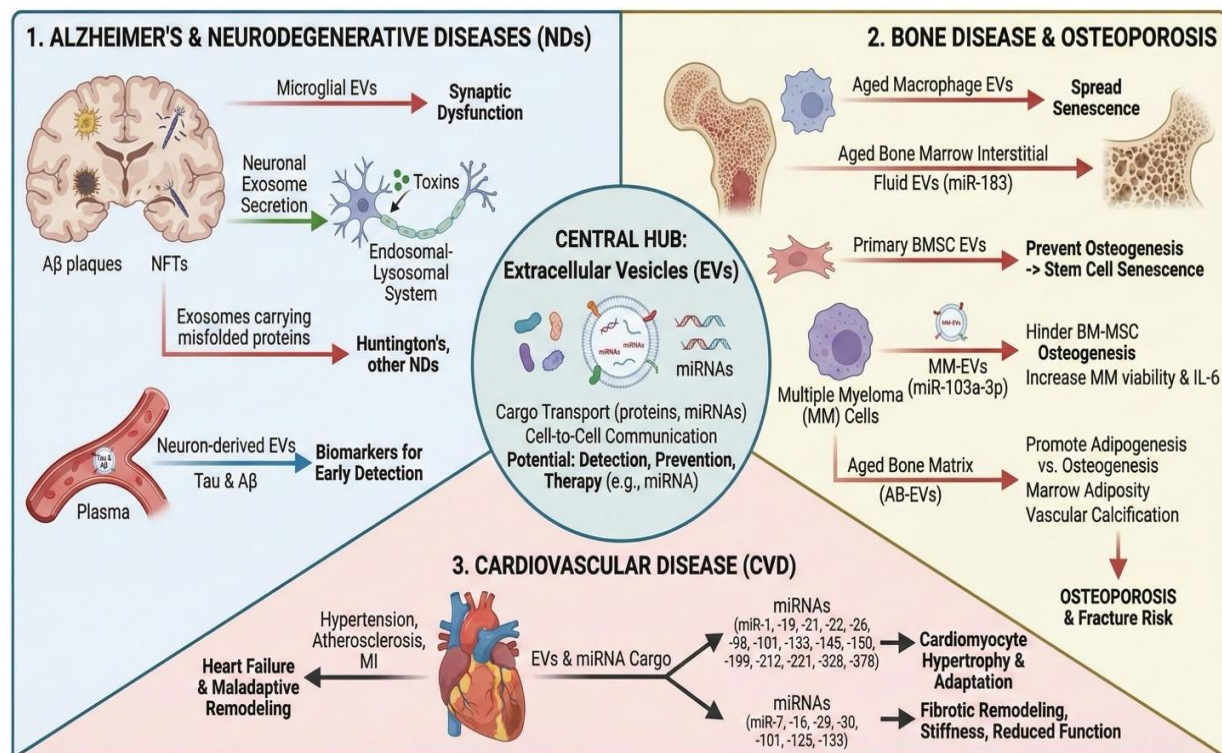


Figure 4. Potential therapeutic role of exosomes in the regulation of different age-associated diseases. This figure shows the disease state and the therapeutic effects of exosomes, including increased angiogenesis, anti-inflammatory effects, and more. These insights could lead to new possibilities and more effective treatments for these diseases [104–105].

5. Therapeutic Potential of EVs:

Although MSC therapies have been shown to enhance tissue regeneration, EVs have emerged as a particularly intriguing option due to the low survival rate of MSCs in hosts (less than 1% remain after some time) [106] and the nanoscale size of sEVs, which leads to more efficient drug delivery [107]. Table 4 summarises some of the beneficial uses of MSC-derived EVs in aging [108]. Engineered exosomes delivered via the nose are also being explored as a beneficial therapy for AD [109]. SC-Exosomes contribute to anti-inflammatory and immunomodulatory effects by regulating pattern-recognition receptors (PRRs)

[110], inhibiting oxidative stress, and exerting regenerative effects [111]. These, in turn, enable treatments and might aid the reversal of age-associated conditions. EVs from human induced pluripotent stem cells (iPSCs) and neonatal umbilical cord MSCs [112] also show similar effects, such as rejuvenation, with iPSCs-EVs having the advantage of being chemically cultured indefinitely [113]. However, they raise concerns about tumorigenicity and epigenetic memory, which require careful evaluation. EVs from young individual specimen sources can also reverse the aging phenotype. In aged mice (20–21 months), weekly intravenous administration of young plasma sEVs (200 μ l at 1.80

µg/µl) significantly increased PGC-1α expression in vivo, accompanied by a 12.42% extension in median lifespan (34.4 vs. 30.6 months), indicating improved mitochondrial biogenesis associated with EV-mediated rejuvenation [114]. This work elevates sEVs beyond mere biomarkers to active therapeutic agents. However, it currently lacks the standardization, defined active principle, and human clinical validation required for regulatory approval as a conventional drug. However, it points to the potential use of sEVs as a drug for an efficient anti-aging effect. In the mouse model, engineered EVs, such as those containing metformin, can also be employed to promote wound healing that is otherwise disrupted by aging and SnC regeneration. However, this falls squarely within the nutraceutical or cosmeceutical category, rather than that of a conventional pharmacological agent [115]. Even plant-derived EVs, such as those from *Ecklonia cava*, containing heat shock protein 70 (HSP70), exhibit anti-aging activity. This is done by inhibiting TNF-α, MAPKs, and NF-κB signaling, leading to downregulation of matrix metalloproteinases (MMPs) and improved skin health in a mouse model. This body of work has also not yet addressed the critical requirements for pharmacological status and falls within the nutraceutical category [116]. Thus, these findings require further clinical validation in human trials to confirm their efficacy and safety for human use. The detailed functional representation is presented in Figure 5.

Despite significant advances, several translational issues in EV research remain to be addressed, including the complexity of human aging and ethical considerations. Another major limitation of EV research is the heterogeneity of vesicles arising from differences in source, individual donor, metabolic state, and environment [117]. sEV preparations often contain mixed populations of vesicles and non-vesicular particles, making mechanistic interpretation and reproducibility more difficult. Therefore, standardized isolation and characterization methods are essential, as recommended by MISEV2018. Clinical translation of EV-based therapies is further complicated by concerns related to long-term safety, regulatory approval, dosage optimization, pharmacokinetics, and administration methods. EV cargo may trigger immune activation, fibrosis, or oncogenesis if not carefully controlled [118]. Furthermore, acknowledging sex-dependent differences in aging trajectories and drug responses is crucial, as biological sex significantly influences disease susceptibility and therapeutic efficacy. This highlights the need for sex-disaggregated data and analyses in geroprotective research. Since EVs are classified as biological products by the FDA and EMA in the United States, they must also be rigorously characterized in terms of their identification, purity, potency, and stability.

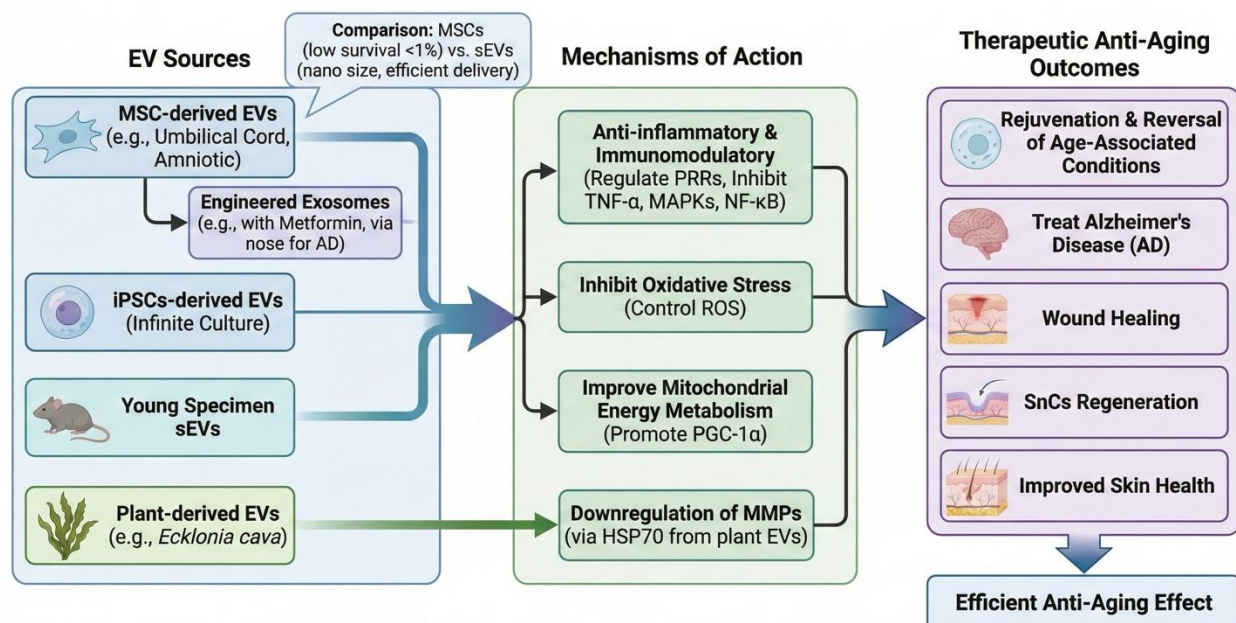


Figure 5. Schematic representation of EV-based Anti-aging therapies. This figure highlights various origins, including Mesenchymal Stem Cells (MSCs), induced Pluripotent Stem Cells (iPSCs), young specimens, and plant-derived sources (e.g., *Ecklonia cava*), as well as engineered exosomes for targeted delivery. Therapeutic EVs work through anti-inflammatory signaling (inhibiting TNF-α and NF-κB), reducing oxidative stress, enhancing mitochondrial metabolism (PGC-1α), and downregulating Matrix Metalloproteinases (MMPs). These pathways combine to produce effective anti-aging results, such as neuroprotection in Alzheimer's disease, faster wound healing, skin rejuvenation, and systemic tissue regeneration.

Table 4. Therapeutic effect of MSC-Derived sEVs in Aging.

S. No.	Source	Species	Disease	Mechanism of action	Reference
1	olfactory mucosa MSCs exosomes	Human	AD	Lower neuronal apoptosis, less neuroinflammation, less Endoplasmic reticulum stress, and enhanced cognitive function	[119]
2	BM-MSCs-EVs	Mice	Aging	Extended lifespan and health, restored the function of senescent fibroblasts and aged stem cells	[120]
3	MSC-EVs	Rhesus monkeys	Cortical injury	Improved myelination, decreased oligodendrocyte DNA damage, and higher mature oligodendrocyte densities after CI	[121]
4	MSC-Exosomes	Mice	Brain aging	Reduced oxidative stress, anti-apoptotic effect, and elevated SIRT1 gene expression	[122]
5	hUCMSC-Exosomes	Mice	Cardiovascular diseases	Reduced amounts of NLRP3, cleaved Caspase-1, and other proteins, as well as increased cell viability and decreased cell death	[123]
6	MSC-derived exosome	Mice	Diabetic keratopathy	Preventing endoplasmic reticulum stress brought on by elevated glucose levels.	[124]
7	hUCMSC-exosomes	Mice	Kidney aging	Modulate the amounts of Lamin A/C phosphorylation to control renal cellular senescence.	[125]
8	MSC exosomes	Mice	Dry age-related macular degeneration	Promoting MGC dedifferentiation and controlling oxidative stress and the Müller Glial Cells-to-Epithelial transition by blocking the TGFβ1 signalling cascade.	[126]
9	MSC derived Hi- exosomes	Human	Intervertebral disc degeneration	Controlled the DDIT4/NF-κB signalling pathway via delivering miR-221-3p to SCs, thereby reducing senescence.	[127]

6. Future Perspective:

In the context of aging, EVs, including exosomes and microvesicles, have significant potential as therapeutic agents and diagnostic tools. They are potent modulators of age-related cellular processes. It may be possible to prevent early aging and age-related diseases by understanding the functions and mechanisms of EVs originating from multiple sources, including senescent cells, in the context of aging and its hallmarks. Additionally, we emphasize that EVs can serve as biomarkers for the early detection of age-related diseases, thereby enabling precision medicine and early intervention. By delivering bioactive compounds that reduce inflammation and promote tissue regeneration via targeted delivery systems, EVs can facilitate healthy aging. By reversing proliferative arrest, human embryonic stem cell-derived exosomes can reverse cellular senescence via delivery of miR-302b in aging mice [128]. The therapeutic potential of EVs in modulating processes that drive aging has also been investigated in numerous studies. sEVs from the plasma of young specimens increase PGC-1α expression in vitro and in vivo via their miRNA cargo, thereby improving mitochondrial function and reducing mitochondrial deficits in aging tissues. Thus, they demonstrate the potential to reverse degenerative changes and age-related dysfunction [129].

Exosomes offer advantages over conventional stem cell therapies as a cell-free alternative, including stability, biocompatibility, and a lower risk of immune rejection and tumor formation. However, to determine whether EV-based interventions can significantly affect aging trajectories in human subjects, further research is required. Translating geroprotective therapies from bench to bedside will require standardized EV characterization techniques, longitudinal human studies, and long-term clinical trials to demonstrate safety and efficacy in diverse populations. It may also be possible to better understand the role of EVs in both age-related disease and healthy aging by broadening research beyond well-established aging pathways to include newly discovered regulatory mechanisms of EV signaling.

7. Conclusion:

The data presented in this review indicate that EVs play an important role in the biology of aging. They seem to function not only as passive byproducts but also as active mediators that may promote senescence and contribute to the pathophysiology of age-related decline by their involvement in SASP. EVs are linked to a variety of diseases, including osteoporosis and dementia, by perhaps dispersing molecular cargo that promotes a pro-

inflammatory environment. However, this insight also highlights a prospective therapeutic opportunity. Targeting the processes via which EVs spread aging signals is an area of increasing attention. EVs are being investigated as potential platforms for enhanced diagnostics and treatment because of their intrinsic targetability and biocompatibility. Preliminary evidence on MSC-derived and young plasma-derived EVs suggests a potential paradigm shift in addressing basic aging mechanisms, as these EVs have demonstrated the capacity to lower oxidative stress and enhance regeneration in some animals. It will be necessary to overcome significant obstacles in accurate engineering, standardization, and scalable production to realize the potential of EV-based medicines in clinical practice. Clarifying the different molecular signatures of "pro-aging" and "rejuvenating" EVs should be a major goal of future study. To completely characterize the role of EVs in human aging and age-related illnesses, thorough biomarker validation and robust clinical trials are necessary, as many of these discoveries are still in the preclinical stage.

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