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Md. M. N. Azim [1], Sujay Kumar Bhajan [2], Mithun Chandra Banik [3], Md Shihab Hussain [4], Md. Sohel Rana [4], Sanjit Biswas [5], Tasnim Elin Islam [6], SM Abu Sama Al Faruqee [6], Md Ataur Rahman [7], Maroua Jalouli [8], Jinwon Choi [9], Min Choi [9], Sohyun Park [9], Hyo Jeong Kim [9] and Amama Rani [9], Bonglee Kim [9,10,*]

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Abstract

Aging causes exhaustion of stem cells (SCs), loss of regenerative potential, and thereby makes them susceptible to age-related diseases (ARDs), known as cellular senescence. Senescent stem cells (SenSCs) secrete Senescence-Associated Secretory Phenotypes (SASPs) that synergistically exacerbate inflammation. Alongside this, they secrete Senescence-Derived extracellular vesicles (SenEVs) that carry a diverse array of molecules that transmit senescence-inducing signals to distant cells and tissues throughout the body, intensifying the detrimental effects of ageing and fostering a pro-tumorigenic microenvironment (PTME). In this review, we comprehensively assess these EVs, their distinct microRNA (miRNA) landscape, protein cargo, including extracellular matrix (ECM) remodeling enzymes and inflammatory cytokines, lipid profiles, and metabolomic signatures. Critically, we elucidate how SenEVs drive systemic ageing through paracrine transmission of senescence, impairing tissue regeneration by propagating oxidative stress, disrupting stem cell niches, and contributing to organ-specific ageing. Furthermore, we discussed their role as pro-cancer factors by remodeling the tumor microenvironment (TME), as they carry oncogenic miR-21 and miR-34a, which promote immune evasion and facilitate metastatic spread. Given their pervasive influence, SenEVs offer significant therapeutic opportunities, ranging from biomarkers of biological ageing to strategies to block harmful EVs and to engineer therapeutic EVs for targeted delivery. Future directions on SenEV research should focus on standardization, single-cell EV biology, organ-specific EV mapping, multi-omics integration, and AI-driven research. This integrated perspective underscores the profound clinical and global relevance of SenEVs as innovative targets for combating cancer and ARDs.

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1. Introduction

Stem Cells (SCs) are defined by their self-renewal capability to differentiate into various specialized cell types **[1]**. During ageing, they become exhausted, characterized by reduced self-renewal and differentiation potential, leading to decreased tissue regeneration and increased susceptibility to ARDs **[2].** The stem cell population also decreases, thereby losing its capacity to maintain tissue homeostasis and altering normal physiology **[3].** Cellular senescence involves a stable arrest of the cell cycle in response to multiple stresses, including DNA damage, oxidative stress, and oncogenic activation **[4].** This form of permanent cell cycle arrest is generally classified into two types: i) Replicative senescence, when it results from reaching the intrinsic division limit, for instance, as a consequence of telomere shortening and ii) Stress-induced senescence, when evoked by cellular assaults such as DNA damage, oxidative stress, or oncogene activity**[5,6]**. In addition to growth arrest, individual senescent cells (SenCs) can rapidly alter their immediate microenvironment by secreting SASP, which primarily comprises growth factors, cytokines/chemokines, and ECM remodeling proteins **[7].** While SASP can have beneficial effects, such as wound healing and immune cell recruitment, its chronic presence is associated with ARDs and cancer, due to excessive secretion of pro-inflammatory signals into the tissue microenvironment **[7,8]**. When SenSCs and their active SASP can disrupt tissue integrity and function, they can critically initiate a second wave of senescence that affects nearby non-SenSCs **[9]**. In addition, the accumulation of SenSCs can negatively impact SC function by altering a key niche through secreted mediators that are critical for tissue homeostasis and repair **[10].** EVs released by immune cells, tumor cells, and SCs carry signals over longer distances than soluble SASP factors and contribute to a variety of physiological and pathological processes, including immunomodulation, cell differentiation, metabolism, cancer, and autoimmunity **[7,11]**. SenEVs that can trigger senescence in neighboring cells, thereby amplifying the ageing process and leading to widespread regeneration failure **[12]**. Aged bone marrow macrophages also cause systemic dysfunction, helping to create a PTME that facilitates the development of cancer, such as when tumour EVs can produce distant metabolic disorders **[13].** This comprehensive review aims to bridge this knowledge gap by proposing a novel concept that precisely integrates the roles of SenEVs in orchestrating systemic ageing, debilitating regenerative capacity, and promoting cancer progression. By elucidating this "missing link," we anticipate gaining a more profound understanding of the ageing mechanism and identifying innovative therapeutic targets for ARDs and cancer.

2. Fundamentals of Extracellular Vesicle Biology

EVs are lipid bilayer-enclosed biomolecular packages released by cells into their surrounding environment **[14] Figure 1.** They transmit signals between cells, influencing a wide range of physiological and pathological processes throughout the body. EVs are categorized into three main subgroups: exosomes, microvesicles, and apoptotic bodies **[15]**. Exosomes are small EVs typically ranging in diameter from 30 to 150 nm. They originate from multivesicular bodies within the endosomal system, following a unique formation pathway **[16]**. In contrast, microvesicles are larger, measuring 100-1000 nm in diameter, and bud directly from the plasma membrane, while apoptotic bodies are released during cellular lysis **[17] Figure 1.** Besides these established types, researchers have identified newer entities like exomeres and supermeres, which are important in transporting proteins and nucleic acids. Once formed, EVs are released into the extracellular space and then taken up by recipient cells through various mechanisms, including clathrin-dependent endocytosis, where the cell membrane forms coated pits to internalize substances, caveolin-mediated uptake, characterized by small invaginations of the plasma membrane macropinocytosis, a non-specific

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pathway involving large vesicles phagocytosis, mainly used by immune cells to engulf larger particles and direct fusion with the plasma membrane, where the EV membrane merges directly with the cell membrane **[18,19]**. The secretion of EVs is affected by aging cells, which influences paracrine senescence and processes linked to inflammatory aging**[20]**. For example, recent research has identified new markers in small extracellular vesicles (sEVs) from senescent and progeria cells, indicating a unique profile of these vesicles associated with aging **[21]**. EVs carry tiny non-coding RNAs that are highly significant because they can alter gene expression, which impacts numerous cellular processes, ranging from development to disease progression **[22]**. The protein cargo of EVs can be distinct, showing what the parent cell is doing, and commonly contains SASP-like factors, metabolic enzymes, and stress-related proteins. Lipids maintain the structural integrity of EVs and facilitate signaling, including oxidized lipids and ceramides**[23]**. Moreover, EVs transport ageing-related metabolites, which facilitate the metabolic reprogramming of recipient cells, affecting their health and disease conditions **[24]**.

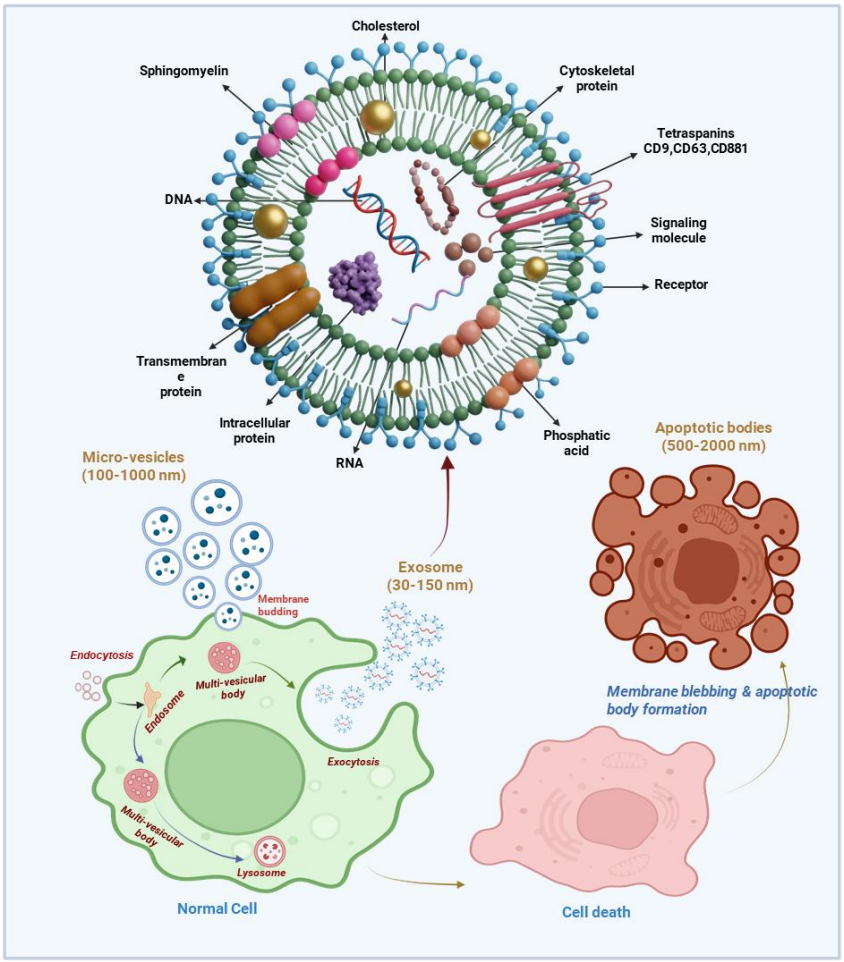

Figure 1. Biogenesis, molecular architecture, and heterogeneity of EVs. The upper panel illustrates a canonical EV membrane enriched in cholesterol, sphingomyelin, and phospholipids, decorated with tetraspanins (CD9, CD63, CD81), receptors, signaling molecules, and transmembrane and cytoskeletal proteins, and enclosing diverse bioactive cargo including DNA, RNA, and intracellular proteins. The lower panels depict EV biogenesis pathways: exosomes (30–150 nm) originate from the endosomal system and are released upon fusion of multivesicular bodies with the plasma membrane; microvesicles (100–1000 nm) are generated by direct outward budding of the plasma membrane; and apoptotic bodies (500–2000 nm) arise from membrane blebbing during programmed cell death.

3. Stem Cell Senescence: Mechanisms and Pathways

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Stem cell senescence causes permanent cell cycle arrest through stressors like DNA damage and oxidative stress, reducing regenerative capacity, and its key mechanisms include molecular drivers, core regulatory pathways, and telomere shortening, leading to SASP secretion.

3.1. Stem Cell Types and Their Ageing Profiles

The aging of SCs is a widespread phenomenon. Each SC population displays unique aging characteristics that correspond to its specific functions and surrounding environments **[25].** Mesenchymal Stem Cells (MSCs) play a crucial role in tissue repair and regeneration **[26]**. Senescence in these cells results in a considerable decline in their beneficial functions, including immunomodulation and regenerative capabilities **[27]**. In contrast, they begin to exhibit pro-inflammatory and pro-ageing features, as observed in an *in vivo* model of systemic ageing and in prolonged culture *in vitro*, thereby limiting their therapeutic potential in regenerative medicine **[28]**. Similarly, Senescence in hematopoietic Stem Cells (HSCs) plays a significant role in the development of age-related immune dysfunction and elevates the risk of hematological malignancies **[29]**. Neural Stem Cells (NSCs) are crucial for brain repair and neurogenesis, Cardiac Progenitors are essential for maintaining heart tissue, and Satellite Cells are critical for muscle regeneration **[30]**. Senescence in these cells directly impacts their ability to contribute to tissue regeneration and repair [31] The molecular characteristics and specific vulnerabilities of aged SCs exhibit significant variability across tissues, underscoring the considerable differences among stem cell populations and the organ-specific aspects of ageing **[32].**

3.2. Molecular Drivers

SC ageing is influenced by a complex interaction of molecular mechanisms that compromise their integrity and functionality **Figure 2.** DNA damage accumulation and telomere shortening are two vital factors that influence cellular ageing and affect all cell types, including SCs **[33,34]**. During SC replication, telomeres gradually shorten, and once a critical length is reached, a DNA damage response is initiated, leading to cell cycle arrest and subsequent senescence **[5,35].** The accumulation of different kinds of DNA damage impairs the functionality of SCs and their ability to regenerate. Mitochondrial dysfunction is another important driver of cellular senescence, characterized by increased reactive oxygen species (ROS) production and accumulation of mitochondrial DNA mutations **[36]**. This condition significantly disrupts cellular metabolism and heightens oxidative stress, contributing to the decline and exhaustion of SCs **[37]**. Epigenetic modifications, which regulate gene expression while leaving the DNA sequence intact, exhibit notable alterations as organisms age **[38]**. Alterations in DNA methylation, histone modifications, and chromatin remodeling have the potential to modify gene expression patterns that are essential for maintaining SC identity and function **[39]**. Such changes may result in reduced stemness and diminished regenerative capacity**.** Finally, chronic inflammatory responses, commonly referred to as "inflammaging," create a sustained, low-grade inflammatory environment that adversely affects SCs. This condition leads to functional damage and accelerates the process of senescence **[40]**.

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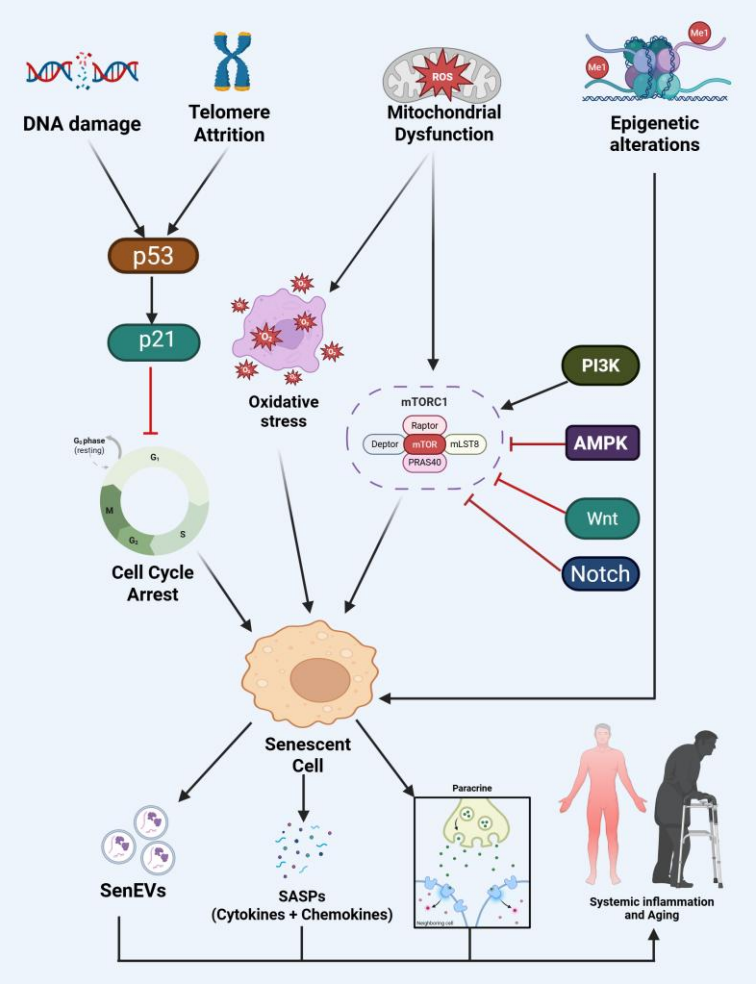

Figure 2. Molecular pathways driving cellular senescence and systemic ageing.
DNA damage, telomere attrition, mitochondrial dysfunction, and epigenetic alterations activate key regulatory pathways, such as the p53–p21 axis and metabolic signaling networks involving mTORC1, PI3K, AMPK, Wnt, and Notch, leading to irreversible cell-cycle arrest and the establishment of cellular senescence. Senescent cells subsequently develop SASP, releasing pro-inflammatory cytokines, chemokines, and SenEVs, which propagate paracrine senescence and contribute to inflammaging and progressive tissue dysfunction associated with ageing.

3.3. Core Regulatory Pathways

Numerous pathways (**Figure 2)** are intricately involved in controlling SC senescence and its progression. The cyclin-dependent kinase (CDK) inhibitors p21Cip1 and p16Ink4a have been identified as significant markers of cellular senescence **[41]**. Their increased expression leads to permanent cell cycle arrest. In particular, p16Ink4a inhibits CDK4/6, thereby blocking the transition from the G1 to the S phase of the cell cycle **[42]**. Conversely, p21Cip1 inhibits CDKs; the expression patterns of p21Cip1 and p16Ink4a transcripts vary across cell types and tissues, and co-expression is often absent **[43]**. Additionally, the tumor suppressor p53 protein is activated by stress signals, such as DNA damage, cell cycle arrest, or apoptosis, thereby contributing to senescence**[44]**. The mTOR-S6K pathway serves as an essential regulator of cell development, metabolic processes, and ageing, and its dysregulation speeds up senescence**[45]**. The AMPK-SIRT pathway plays a crucial role in nutrient sensing and metabolism regulation**[46]**. Dysregulation of this pathway may lead to SC senescence. Moreover, Wnt inhibition is required for SC self-renewal and differentiation, related to SC ageing and loss of regenerative ability**[47]**. Moreover, Notch dysregulation affects SC niches, controls SC fate, and triggers SCs to act strangely during ageing **[48]**. The interplay of these pathways creates a multifaceted network that regulates the senescent phenotype in stem cells.

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3.4. Distinctive Senescence-Associated Secretory Phenotype (SASP) in Stem Cells

The SASP in stem cells differs from that in fibroblasts, with cytokines, chemokines, growth factors, and proteases that vary significantly depending on the cell type and tissue of origin **[49]**.This tissue-specific variation raises the possibility that the SASP of SenSCs contains special elements designed to modulate their regeneration capabilities**[7]**. For example, the SASP of senescent MSCs loses its beneficial features and acquires pro-inflammatory and pro-ageing activities, promoting detrimental effects rather than repair **[50]**.Additionally, there are tissue-specific differences in SASP and specific senescence markers, such as p21Cip1 or p16Ink4a, suggesting a close regulatory link between the activation of senescence pathways and subsequent secretion. Additionally, SenEVs and the SASP interact through paracrine senescence, thereby effectively spreading tissue signals to nearby cells and distant tissues, amplifying the systemic effects of ageing and disease **(Figure 2)[51]**.

4. Composition of Senescent Stem Cell–Derived EVs

SenEVs carry a complex cargo of biomolecules, which reflects the senescent state and metabolic reprogramming of the parent SC, acting as potent messengers that can propagate pro-ageing and pro-tumorigenic signals throughout the organism **(Figure 3)**.

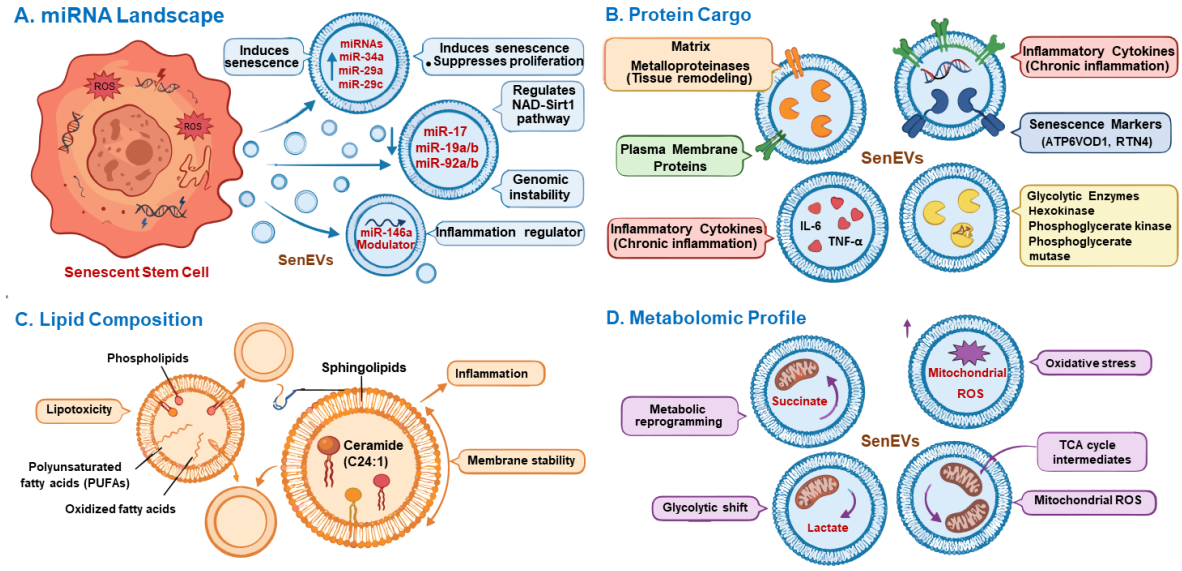

Figure 3. Molecular composition of senescent stem cell–derived extracellular vesicles. (A) The miRNA profile shows enrichment of senescence-associated and proliferation-suppressing miRNAs, along with reduced levels of miRNAs regulating metabolic and inflammatory pathways. **(B)** Protein cargo comprises ECM–remodeling enzymes, inflammatory cytokines, senescence markers, glycolytic enzymes, and DNA fragments associated with genomic instability. **(C)** Lipid composition includes ceramides and oxidized fatty acids linked to lipotoxicity and membrane dynamics. **(D)** Metabolomic features include elevated succinate and lactate levels, accompanied by increased ROS, collectively promoting paracrine senescence and age-related tissue dysfunction.

4.1. miRNA Landscape

The miRNA landscape within SenEVs undergoes significant alterations compared to EVs from young, healthy SCs **(Figure 3A)**. For instance, senescence-associated miR-34a has been observed to increase with age in circulating EVs derived from muscle, inducing senescence in bone marrow stem cells (BMSCs) and thereby impairing their regenerative potential**[52]**. Additionally, miR-34a is deeply implicated in the MSC senescence process by targeting NAMPT and regulating the NAD+-Sirt1 pathway, which is essential for cellular metabolism and longevity **[53]**. Moreover, miR-29a and miR-29c have been identified in plasma EVs from aged mice and humans, contributing to the propagation of the senescent phenotype**[54]**. Conversely, miR-146a has been reported to alleviate UVA-induced

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inhibition of proliferation and to suppress ageing-related genes, indicating its role in ageing **[55]** . In stark contrast to these pro-senescence miR-17, miR-19a/b, and miR-92a/b were observed to be downregulated in EVs from aged mice compared to those from young mice. This downregulation is directly linked to increased p21/CDKN1A expression, a key cell cycle inhibitor regulating senescence and proliferation**[56]**. These shifts in miRNA cargo within SenEVs underscore their profound impact on cellular function, influencing a wide array of age-related conditions by modulating gene expression in recipient cells**[57].**

4.2. Protein Cargo

The protein cargo of SenEVs transports ECM remodeling proteins, including Matrix Metalloproteinase, which degrade the ECM and, consequently, damage tissue architecture and repair **(Figure 3B) [58,59].** Proteomic investigation of the SASP of fibroblasts has demonstrated a significant presence of plasma membrane proteins within EVs, suggesting the active packaging and release of specific cellular components **[60]**. Inflammatory cytokines are also packed into these EVs in large amounts, which triggers "inflammaging". Moreover, additional senescent markers, including ATP6V0D1 and RTN4, are specific indicators for detecting and monitoring senescence within EV cargo **[21]**. Furthermore, SenSCs display markedly modified metabolic states, characterized by elevated amounts of enzymes associated with the glycolytic pathway, including hexokinase, phosphoglycerate kinase, and phosphoglycerate mutase **[61]**.These metabolic enzymes alter the metabolic programs to recipient cells. SenEVs also contain various DNA fragments that are not direct protein markers of DNA damage but rather parts related to genomic instability that can trigger inflammatory pathways in nearby cells, causing stress and dysfunction **[62,63].**

4.3. Lipid Composition

Lipids from structural integrity of the EV membrane influence its biological characteristics and signaling roles, thereby affecting EV stability, targeting, and fusion with recipient cells **(Figure 3C)[64]**. The lipid composition of SenEVs changes notably, leading to metabolic imbalance and stress in ageing cells **[65].** Significant lipidomic signatures associated with ageing have been observed in quiescent NSCs from older individuals, revealing notable alterations in complex membrane lipids, including phospholipids and sphingolipids, as well as a remarkable rise in polyunsaturated fatty acids**[66]**. These compositional alterations enhance the levels of oxidized fatty acids and lipid profiles associated with inflammation. However, ceramide production is essential for the release of these lipotoxic EVs. In particular, ceramide C24:1 has been directly linked to cellular senescence, underscoring its role in the production of various lipid species during the ageing process **[67].**

4.4. Metabolomic Profile

Metabolic changes are a key component of cellular senescence, which influences the ageing process **(Figure 3D)[68]**. SenSCs frequently show increased mitochondrial ROS production and elevated succinate levels **[69].** Succinate is an essential intermediate in the TCA cycle that accumulates in cells **[70]** . It is released into the extracellular environment by various cell types, including cancer cells, strongly suggesting its presence in SenEVs **[71].** Similarly, the increased activity of glycolytic enzymes in SenSCs suggests a greater production and possible encapsulation of metabolites, such as lactate, within their EVs, indicating a transition towards glycolysis for energy generation**[71]**. Although existing research does not provide direct data on fumarate in SenEVs, the overall metabolic changes observed in SCs suggest that various ageing-related intermediates may also play a crucial role in EV cargo composition. The principal mechanisms and signaling pathways through which SenEV cargo influences recipient cell function are summarized in **Table 1**.

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Table 1. SenEV-mediated signaling mechanisms, target pathways, and biological consequences in recipient cells.

SenEV-mediated mechanism	Major signaling pathways involved	Primary recipient cell types	Cellular effects	Physiological/ pathological outcomes	References
Propagation of cellular senescence	p53–p21/CDKN1A pathway; cell-cycle regulatory networks	Stem cells, progenitor cells, stromal cells	Induction of cell-cycle arrest and secondary senescence	Decline in tissue regenerative capacity and stem cell exhaustion	**[72]**
Metabolic reprogramming	NAD^+–SIRT1 signaling; glycolytic metabolic pathways	Muscle stem cells, mesenchymal stem cells, stromal cells	Mitochondrial dysfunction, increased glycolysis, metabolic imbalance	Age-related metabolic dysregulation	**[73]**
Oxidative stress signaling	Mitochondrial ROS pathways; redox signaling cascades	Endothelial cells, stem cells, tissue progenitor cells	Increased oxidative damage and mitochondrial stress	Tissue ageing and functional decline	**[74]**
Extracellular matrix remodeling	MMP-mediated ECM degradation pathways	Fibroblasts, stromal cells, connective tissue cells	ECM breakdown and impaired tissue repair	Tissue degeneration and fibrosis	**[75]**
Chronic inflammatory activation	NF-κB signaling; inflammatory cytokine pathways	Immune cells, macrophages, stromal cells	Persistent inflammatory signaling and cytokine production	Inflammaging and chronic low-grade inflammation	**[76]**
Intercellular communication and paracrine signaling	EV-mediated signaling networks; receptor-mediated uptake pathways	Neighboring stem cells and tissue cells	Spread of senescence-associated signaling	Amplification of tissue dysfunction	**[77]**
Tumor microenvironment modulation	PI3K–AKT and MAPK signaling pathways	Cancer cells, tumor-associated stromal cells, immune cells	Enhanced proliferation, immune modulation, survival signaling	Tumor progression and metastasis	**[78]**
Immune system regulation	Immune checkpoint and inflammatory signaling pathways	T cells, macrophages, dendritic cells	Altered immune surveillance and inflammatory responses	Immune dysregulation in ageing and cancer	[79]
Tissue niche disruption	Stem cell niche regulatory pathways (Wnt/Notch signaling)	Stem cell niches in muscle, bone marrow, and other tissues	Impaired stem cell maintenance and differentiation	Organ-specific ageing and reduced regenerative potential	**[80]**

5. EVs as Drivers of Stem Cell Aging and Systemic Aging

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SenEVs drive both localized SC ageing and the systemic propagation of ageing, owing to their unique cargo and potent intercellular communication capabilities, thereby extending the detrimental effects of senescence far beyond the originating cell. The paracrine and systemic propagation of senescence mediated by SenEVs is illustrated in Figure 4.

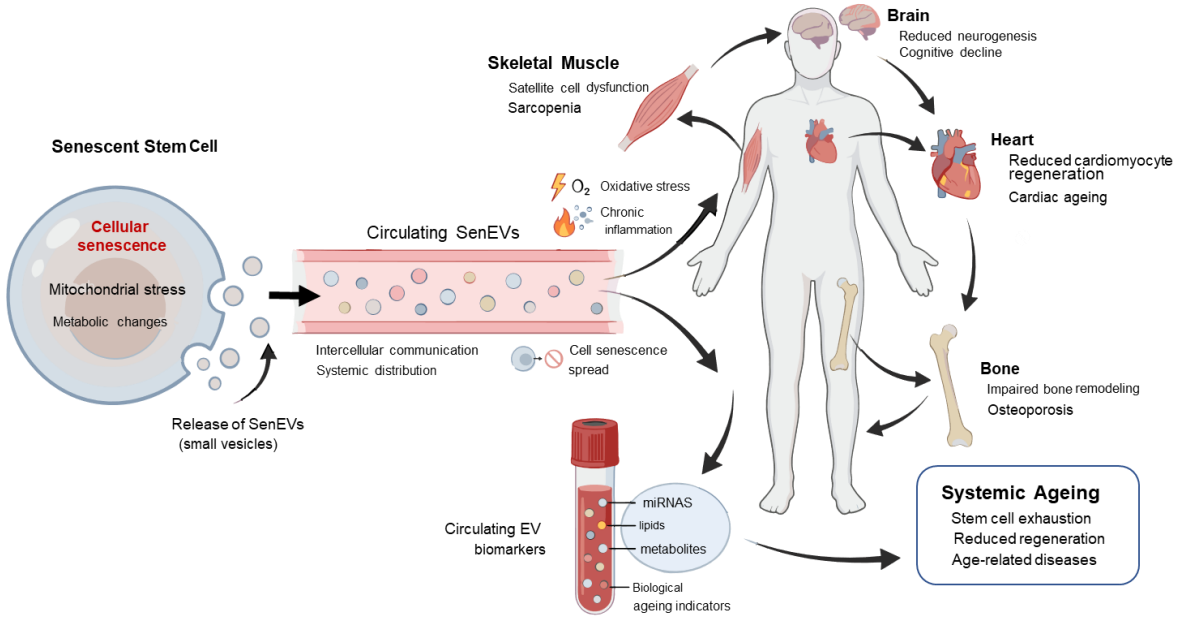

Figure 4. Senescent stem cell–derived extracellular vesicles promote systemic ageing. SenEVs containing senescence-associated molecular cargo that enter the circulation and are taken up by distant tissues. These vesicles propagate senescence signals, impair regenerative capacity, and contribute to organ-specific ageing in skeletal muscle, heart, brain, and bone. Circulating SenEV cargo, including miRNAs, lipids, and metabolites, may also serve as biomarkers of biological ageing. Collectively, SenEV signaling promotes stem cell exhaustion, reduced tissue regeneration, and the development of age-related diseases.

5.1. Paracrine Transmission of Senescence

SenEVs influence ageing through paracrine transmission of senescence, as aged bone marrow macrophages release EVs that trigger a secondary senescence response in adjacent non-SCs, via a bystander effect **[81,82].** The molecular mechanisms behind this effect are complex, involving the transfer of particular EV cargo, including miRNAs, proteins, and even DNA fragments, which can induce a senescent state in recipient cells. Evidence for this widespread phenomenon comes from both *in vitro & in vivo* studies, in which healthy cells exposed to SenEVs acquire senescent traits. For example, *in vivo* engraftment-based senescence models have demonstrated that SenEVs modulate inflammatory responses and may influence cancer recurrence**[83]**.This evidence suggests that circulating SenEVs can play a crucial role in extrinsically induced senescence across various cell types and tissues, thereby hastening the overall ageing process throughout the organism **[84].**

5.2. Impaired Regeneration Mechanisms

SenEVs significantly to hamper tissue regeneration by spreading oxidative stress. However, EVs originating from healthy cells can reverse oxidative damage by delivering antioxidant enzymes and molecules. Additionally, oxidative stress can unexpectedly alter the redox status of target cells, possibly transporting pro-oxidant species that worsen cellular injury and ultimately impair their ability to regenerate **[85].** The function of SCs depends on their niche, which declines with age, leading to a significant decrease in regenerative capacity throughout the body **[86]**. Although direct, comprehensive evidence for the suppression of all Wnt, Hedgehog, and JAK/STAT pathways by SenEVs within the SC niche is still emerging, research clearly shows that Wnt signalling activation

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plays a crucial role in MSC ageing **[80].** This pathway, when activated, causes a significant reduction in senescence. Conversely, noncanonical Wnt5a signalling has been shown to regulate tendon stem/progenitor cell senescence**[87]**. Therefore, the contents of SenEVs may disrupt these essential pathways, further undermining the integrity and functionality of the SC niche and hindering effective regenerative processes.

5.3. Organ-Specific Ageing

The impact of SenEVs on ageing manifests differently across organs, depending to their effects on tissue regeneration and ageing, as summarized in Figure 5.

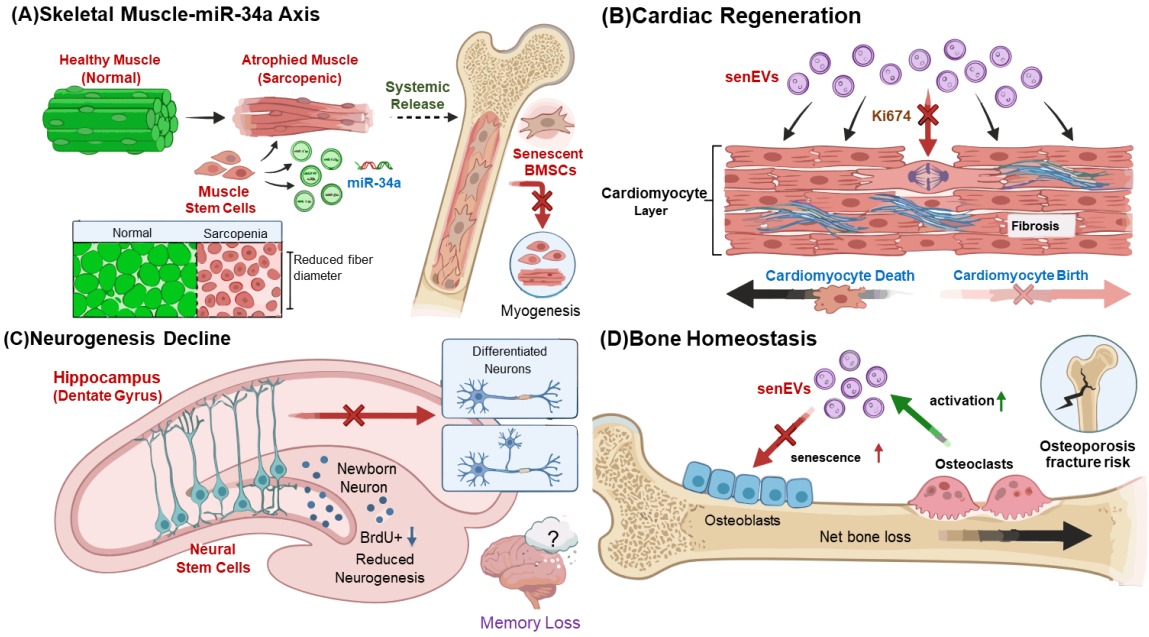

Figure 5. Senescent extracellular vesicles drive age-related tissue degeneration across organs. This schematic illustrates the organ-specific effects of senEVs. **(A) Skeletal muscle:** senEV-associated miR-34a signaling impairs muscle stem cell function, reducing myogenesis and muscle fiber size, leading to sarcopenia. **(B) Heart:** senEVs suppress cardiomyocyte proliferation and promote fibrosis, limiting cardiac regeneration. **(C)** Brain: senescence signaling reduces hippocampal neurogenesis by inhibiting neural stem cell differentiation, contributing to cognitive decline. **(D) Bone:** senEVs disrupt bone homeostasis by decreasing osteoblast activity and increasing osteoclast activation, resulting in net bone loss and increased fracture risk.

5.3.1. Skeletal Muscle Ageing

The ageing of skeletal muscle is marked by a notable reduction in both muscle mass and functionality, known as sarcopenia **[88]**, and it is linked to the impairment of muscle SCs, particularly satellite cells **[89].** EVs are essential for the complex interactions between satellite cells and other skeletal muscle cells throughout muscle regeneration **[90]**. However, alterations in the secretome and EVs from older skeletal muscle cells can significantly contribute to the decline associated with ageing **[91]**. Therefore, the quality of Satellite cell EVs is vital for proper ECM deposition and hypertrophy, both of which are crucial for muscle repair and growth **(Figure 5A)**.

5.3.2. Cardiac Ageing

Cardiovascular ageing impairs the regenerative capacity of the heart muscle by altering cardiomyocyte turnover and increasing the risk of cardiovascular diseases (CVDs) **[92]**. SC-derived EVs have shown significant promise in cardiac repair and regeneration, offering protection to the heart from various pathological conditions by reducing cellular senescence **[93,94].** However, cardiomyocytes are vulnerable to stress due to their limited regenerative capacity. EVs can serve as

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essential biomarkers for CVDs by reflecting the condition of cardiac tissue with high precision **[95].** The specific role of SenEVs in reducing cardiomyocyte turnover and the resulting cardiac dysfunction remains a vigorous area of current research. Several studies have confirmed that the pro-senescent factors released by SenEVs are associated with declines in cardiac function and regenerative capacity with ageing **(Figure 5B)**.

5.3.3. Neuroregeneration

The ageing human brain accumulates SCs, which play a direct role in neurodegenerative diseases because NSC-derived EVs typically facilitate neurogenesis, immunomodulation, and neuroprotection **[96,97]**. Additionally, MSC-derived EVs have demonstrated potential to enhance cognitive function by stimulating neurogenesis in the ageing brain **[98]**. Furthermore, studies have shown that SenEVs diminish the brain's regenerative capacity by accelerating vascular senescence and releasing SASPs during aging **[99].** As a result, SenEVs directly contribute to decreased neurogenesis and cognitive decline by spreading senescent signals or negatively affecting the brain microenvironment, hence exacerbating age-related neurological problems **(Figure 5C)**.

5.3.4. Bone Ageing

EVs are significant mediators in the intricate interaction between bone and muscle, as miRNAs from skeletal muscle and bone tissue cell EVs move between these tissues to control this critical interaction **[100].** As a result, senescent bone cells' EV cargo directly contributes to age-related deterioration in bone density and function, potentially yielding specific osteoporosis-related EV profiles that could serve as diagnostic markers **(Figure 5D)**.

5.4. EVs as Biomarkers of Biological Ageing

SenEVs harbor certain miRNAs that serve as significant indicators of biological age and ARDs. For instance, circulating miRNAs 486 and 146a serve as potential biomarkers for sarcopenia [101]. Moreover, miRNAs encapsulated in EVs have the capability to initiate and advance muscle wasting, underscoring their potential as epigenetic regulators and diagnostic indicators for these disorders **[102]**. These EV miRNA panels offer a non-invasive and informative method to assess cellular senescence and the ageing process in an individual. The lipidome of EVs is used to diagnose various pathological disorders, as EV lipidomics is used to identify non-alcoholic steatohepatitis **[103].** These distinctive lipid profiles of EVs are indicative of oxidative stress and metabolic dysregulation associated with ageing cells. Thus, a thorough examination of EV lipid profiles may yield innovative and essential insights into physiological functions, thereby greatly facilitating the development of predictive instruments to identify individuals predisposed to frailty **[104].**

6. Senescent Stem Cell EVs in Tissue Regeneration

SenEVs inhibit progenitor differentiation, a crucial step in SC differentiation into other cell types essential for tissue repair and maintenance **[105].** For example, muscle-derived EVs (MEVs) with elevated miR-34a levels have been shown to trigger senescence in BMSCs, thereby directly affecting their ability to facilitate bone regeneration and resulting in a significant decline in the number of essential SC types required for bone repair **[106].** In addition, SC-derived EVs contribute to a hostile tissue milieu that promotes fibrosis, in which the pro-inflammatory components of SenEVs exacerbate inflammatory ageing and compromise tissue function by releasing factors that promote scarring and rigidity. These EVs further inhibit adipogenesis and stimulate SASP factor production in recipient cells **[107]**. These factors influence fibrotic processes that damage tissue structure and function. This long-term, inflammatory, and dysfunctional environment may prevent angiogenesis, the formation of new blood vessels, which is crucial for supplying oxygen and nutrients to the healing tissues. Disruption in angiogenesis hinders efficient regeneration, keeping affected tissues unhealed **(Figure 6)** [108]. SenEVs adversely impact the proliferation and differentiation of both somatic cells

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and several SC populations through bystander mechanisms **[109]**. For instance, Muscle-derived EVs that express miR-34a directly affect BMSCs, accelerating their ageing and making it harder to support bone recovery. Endothelial cells may not always be immediately identified as targets of SenEVs in every scenario. However, when SenEVs induce chronic inflammation, endothelial cells are affected, potentially inhibiting angiogenesis. Studies on heterochronic parabiosis, a method that connects the circulatory systems of young and old organisms, have shown that EVs from the plasma of young mice can make elderly tissues look and feel younger**[54]**. These youthful EVs effectively improved age-associated functional losses and have even been shown to increase lifespan by fundamentally enhancing mitochondrial energy metabolism**.** In addition, MSC-derived EVs have been shown to actively alter the omic profiles of different organs in older rodents, making them appear younger and healthier **[110].** These rejuvenating EVs have different cargo than their senescent counterparts. For example, they miR-17–92 cluster (downregulated in aged EVs), as well as numerous growth factors and proteins that activate essential pathways, including IGF-1 and SIRT**[111].** These factors enhance cellular repair, boost antioxidant defense mechanisms, restore metabolic equilibrium, and create an environment for tissue regeneration and cellular rejuvenation **(Figure 6)**.

Studies also demonstrated that exercise-induced circulating EVs have been shown to have regenerative capabilities. They enhance the function of ageing skeletal muscle following injury, underscoring a potential therapeutic approach in which beneficial EVs may mitigate the adverse effects of senescent EVs to restore muscle regenerative capacity and facilitate functional recovery. Additionally, studies have also demonstrated that EVs can help fight skin ageing by assisting cells to communicating with each other and speeding up the process of rejuvenation **[112]**. On the other hand, senescent adipose tissue SC-derived EVs disrupt tissue function and healing ability when adipogenesis is stopped. This increases the expression of SASP factors and ECM remodeling proteins, creating a microenvironment that remains constantly inflamed and severely affects tissue integrity and function **[7]**. As a result, skin wounds heal more slowly and exhibit the signs of ageing **(Figure 6)**.

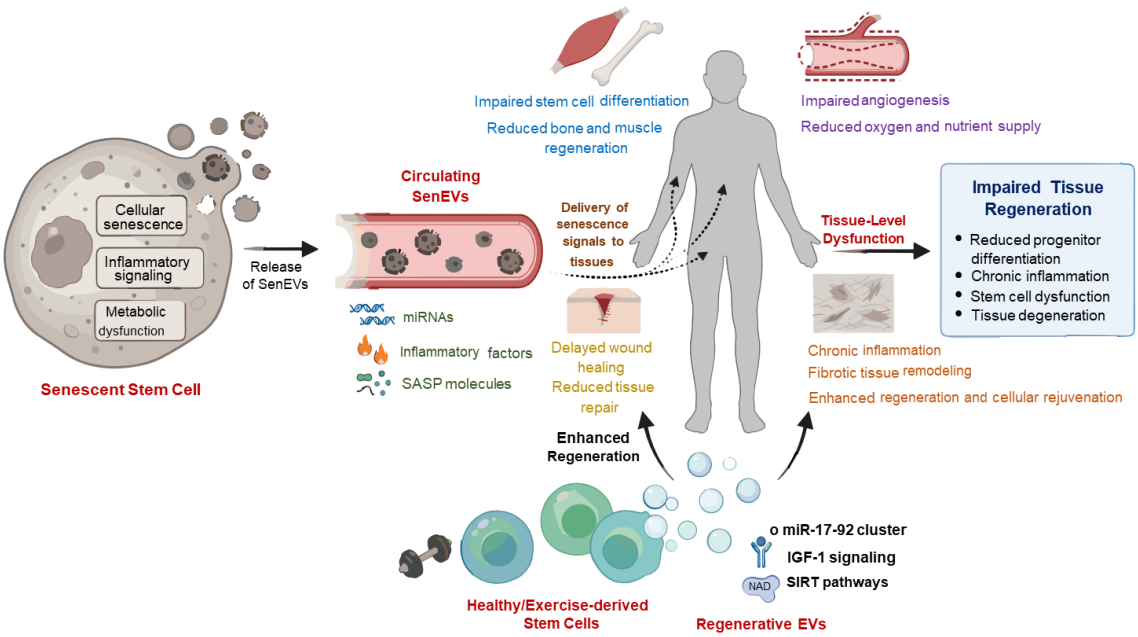

Figure 6. Senescent stem cell–derived extracellular vesicles impair tissue regeneration, while regenerative EVs promote repair. SenEVs enriched with pro-senescent cargo, including miRNAs, inflammatory mediators, and SASP-associated molecules. They enter the circulation and deliver senescence signals to distant tissues, disrupting SC differentiation and reducing bone and muscle regeneration. SenEV-mediated signaling also impairs angiogenesis, delays wound healing, causes chronic inflammation, and leads to fibrotic tissue remodeling, leading to tissue dysfunction and reduced regenerative capacity. In contrast, healthy or exercise-

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activated SC-derived EVs contain regenerative factors that enhance cellular repair, restore metabolic balance, and promote tissue regeneration and rejuvenation.

7. Senescent Stem Cell EVs as Pro-Cancer Factors

SenEVs play a critical role in the progression and promotion of cancer[113]. While cellular senescence can initially act as a potent tumor suppressor, SCs and their associated EVs can paradoxically shift their role to foster a pro-tumorigenic environment, thereby contributing to malignancy through intricate pathways. This duality makes understanding their precise role crucial for the effective implementation of cancer interventions **(Figure 7)**.

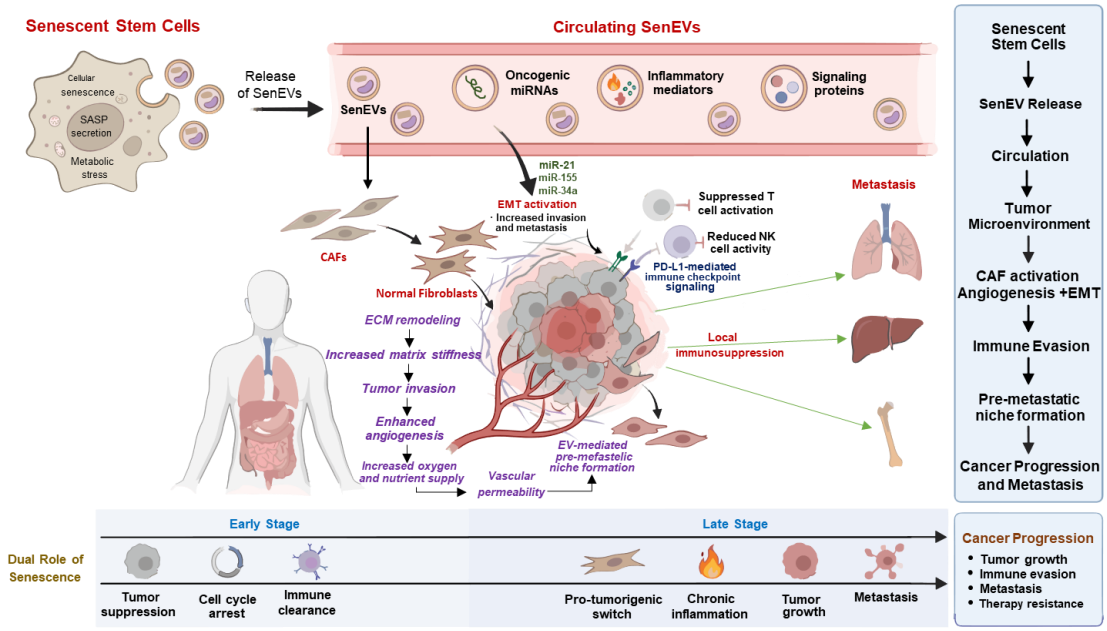

Figure 7. Senescent stem cell–derived extracellular vesicles drive tumor progression. SenEVs contain oncogenic miRNAs, inflammatory mediators, and signaling proteins. Circulating SenEVs remodel the TME by inducing CAF activation, EMT, ECM remodeling, angiogenesis, and immune suppression. These signals promote tumor growth, metabolic reprogramming, and the formation of pre-metastatic niches in distant organs, such as the lung, liver, and bone, thereby facilitating metastasis. While cellular senescence initially acts as a tumor-suppressive mechanism, persistent SenEV signaling contributes to chronic inflammation, tumor progression, immune evasion, and metastasis.

7.1. Remodeling of Tumor Microenvironment

SenEVs activate cancer-associated fibroblasts (CAFs), thereby converting inactive, normal fibroblasts into highly active, protumorigenic CAFs that play a vital role in cancer progression by significantly altering the stromal ECM, which facilitates tumour cell migration and invasion **[114].** Due to ageing, increased ECM stiffness promotes cancer cell invasion, which is further intensified by SenEVs **[115]**. The SASP comprises inflammatory agents and matrix metalloproteases that modify the ECM, leading to a rigid, desmoplastic microenvironment that fosters tumor development and progression **[116,117]**. Additionally, SenEVs promote angiogenesis, ensuring a steady supply of oxygen and essential nutrients to rapidly growing tumors **[114]**. Tumour-derived EVs containing inflammatory, cachectic, and angiogenic factors, which, combined with SenEVs in the TME, facilitate communication between tumour cells and endothelial cells, thereby contributing to angiogenesis, promoting substantial tumour growth and expansion **[118].**

7.2. Oncogenic miRNAs

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miRNAs from SenEVs can have a significant impact on cancer progression, particularly in Epithelial-Mesenchymal Transition (EMT) and metastasis **[119].** Specifically, oncogenic miRNAs, including miR-21, miR-155, and miR-34a, are associated with various stages of cancer development and progression **[120]**. The deregulation of significant miRNAs such as miR-21, miR-155, and miR-34 has been widely documented in individuals with colorectal cancer**[120]**. This evidence suggests that these miRNAs play a significant role in sustaining the CSC phenotype and affecting their eventual outcomes within the tumor **[121].** The oncogenic miRNAs carried by SenEVs have a notable capacity to reprogram recipient cells, leading to significant alterations that promote EMT through which cancer cells shed their epithelial traits, acquire mesenchymal features, and enhance their migratory and invasive capabilities. This transformation is a fundamental step for the successful invasion and metastasis of cancer cells.

7.3. Immune Evasion

SenEVs enable cancer cells to bypass the body's innate immune surveillance and evade immune cell elimination. Additionally, SenCs that accumulate around tumors play a significant role in creating a unique immune-privileged milieu that enables this immunological escape **[122]** . The SASP and exosomes released by SenCs can directly and indirectly impair the function of T cells and NK cells, which are crucial components of the immune response that fight tumours **[123].** Studies have shown that EVs from SenCs can inhibit T cell activation and significantly reduce dendritic cell activity, which is crucial for initiating and coordinating efficient anti-tumour response **[124].** Additionally, persistent SenCs diminish MMPs-dependent release of NKG2D ligands and the paracrine inhibition of NKG2D receptor-mediated immunosurveillance, thereby impairing the immune system's capacity to identify and eradicate cancerous cells **[125].** In anticancer therapy, therapy-induced SenCs promote tumor progression by enhancing programmed death-ligand 1 (PD-L1) expression, a primary ligand that binds to the PD-1 receptor on T cells, thereby inhibiting their function. This is a crucial mechanism that blocks the immune checkpoint, causing therapeutic resistance **[126]**.

7.4. Metastatic Spread

EVs released from primary tumors can effectively affect distant organs by establishing a preconditioned environment that facilitates the successful colonization of disseminated tumor cells before they arrive **[127].** This pre-metastatic niche precisely heightens vascular permeability, ECM remodeling, increased angiogenesis, and localized immunosuppression, all of which promote the survival and proliferation of metastatic cells **[127]**. The unique integrin expression patterns on the EV surface substantially dictate this organ-specific homing. For example, lung-tropic EVs have integrin ITGa6, while liver-tropic EVs have completely different integrin profiles, which determine where they like to metastasise **[128]**. The effect of the EV-conditioned pre-metastatic niche is so strong that EVs from lung-tropic cancer cells can even change the course of bone-tropic cancer cells' metastasis to the lungs. This complex EV-mediated communication welcomes them to a new environment in organs distant from the cancer cells, making it much easier for the cancer cells to travel throughout the body [129].

7.5. Duality: Early Anti-Proliferative Signals vs. Late Pro-Tumorigenic Switch

Cellular senescence can prevent cells from growing too rapidly by stopping stressed or pre-cancerous cells from replicating uncontrollably **[130].** During this initial protective phase, SenCs can actively trigger a strong immune response that successfully eliminates nascent tumour cells, therefore contributing positively to cancer prevention and early tumour suppression **[131]**. However, in a late pro-tumorigenic phase, SenCs, along with their continuous release of SASP factors, establish a chronic inflammatory and remodelling TME that facilitates tumor progression rather than inhibiting it **[123].** This dual role means that senescence initially acts as an important tumor suppressor, but

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continuous release of senescent EVs contributes to tumor growth, invasion, and spread, and even renders treatments less effective, leading to relapses **[132]**. This intricate interaction underscores that SenEVs can also inhibit cancer progression and may be helpful for cancer therapies.

8. Therapeutic Opportunities, Challenges, and Future Directions

SenEVs possess significant promise for diagnostic and therapeutic applications. Their distinct molecular profiles, including cytokines and microRNAs, make them potential biomarkers for ageing and disease progression **[133].** Circulating levels of SenEVs, such as miR-146a, miR-21, and let-7a, have been shown to reflect cellular senescence and correlate with age-related systemic characteristics, including adiposity, dysregulated lipid metabolism, and chronic inflammation **[134,135]**. Similarly, urinary exosomes that express markers such as p16INK4a may be useful for studying kidney ageing **[136]**. However, numerous SASP components are also produced by non-SenCs, which constitutes a substantial barrier to their translational application**[137]**. Preventing the harmful effects of senescent EVs is a new area of research. One way to prevent EV secretion is to use EV secretion inhibitors, which block vesicle release without harming cells **[138]**. Senolytic and senomorphic therapies help to diminish both the quantity and impact of senescent EVs. For example, Dasatinib and quercetin have been shown to reduce age-related miRNAs in plasma EVs to restore some youthful EV profiles **[139].** Another technique is immunotherapeutic clearance, which targets senescent EVs through surface antigens **[140]**. However, this approach is limited by the absence of distinctive markers that differentiate senescent EVs from normal ones. Therapeutic EV engineering has emerged as an interesting area of research, as these EVs can be loaded with therapeutic molecules, such as miRNAs, siRNAs, and regulatory proteins, to inhibit oncogenic or inflammatory pathways **[141,142]**. This can be done through genetic or chemical alteration or Surface engineering, which involves adding targeting ligands or homing peptides, thereby making EVs much more selective and bio-distributed, with an improved therapeutic index for the delivered payload **[143].** Simultaneously, rejuvenation techniques that replace harmful senescent EVs from youthful or pluripotent SCs are also demonstrating promise. Young MSC-derived EVs diminish senescence markers, enhance mitochondrial metabolism, and restore tissue regenerative potential, demonstrated in both in vitro and in vivo studies **[144]**. Induced pluripotent SC-derived EVs replicate the functions of embryonic SCs by mitigating oxidative damage, enhancing angiogenesis, and facilitating fibroblast renewal to prolong lifespan**[145] .** However, the practical application of EV-based therapeutics faces regulatory and technical challenges, despite thousands of clinical studies for EV treatments already being registered. There are still problems with standardization, quality control, and regulatory classification **[146].** The inherent variability of EV payloads affects dosage uniformity and reproducibility, posing challenges for both efficacy assessment and manufacturing compliance. Additionally, Safety hazards, including tumorigenicity and immunological activation, are concerning, especially when utilizing EVs produced from immortalized or oncogenic cells **[146]**. Therefore, thorough preclinical studies examining bio distribution, prolonged exposure, and route-dependent dynamics are crucial to ensure safety and therapeutic efficacy **[147].** There is also a lack of standardization in EV research, hindering the isolation, quantification, and classification of EVs, slowing progress in translation and regulatory approval **[148].**

In the future, the emerging field of single-cell EV biology may mitigate many issues, as it shows that cells differ significantly to their EV secretion, which can determine variations in EV composition among senescent subpopulations[149]. Creating organ-specific senescent EV maps is another important area of research. Senescent EVs have different effects depending on the organ they come from. For example, MEVs accelerate BMSC aging, while NSC-derived EVs help neurons survive. Therefore, mapping organ-specific vesicular cargoes could lead to new ways to treat tissues **[97].** It will be important to combine this mapping with multi-omics methods to determine how miRNAs, proteins, lipids, and metabolites are linked in senescent EVs **[150]**. This multi-layered analysis will help to understand the regulatory axes that control EV function, making it easier to precisely modulate age-related signaling. Artificial intelligence (AI) may also help to play a transformative role

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in managing the complexities of EV datasets. Machine learning algorithms can use information from multiple omics to classify EV subtypes, infer their origins and composition, and identify new patterns for diagnosis or treatment **[151,152]**. AI-assisted models might also develop "EV aging clocks" that can estimate biological age, predict the likelihood to illness, and tailor rejuvenation treatments **[153].** These approaches together will help to establish individualized regenerative medicine, new ways to diagnose diseases, and systemic rejuvenation therapy in the future.

9. Conclusions

SenEVs contribute to systemic ageing, loss of regenerative potential, and cancer progression by mediating intercellular communication, propagating paracrine senescence that impairs tissue integrity and promotes degeneration across multiple organs, including muscle, bone, heart, and brain. Though SenEVs are initially tumour-suppressive, their prolonged persistence fosters a PTME by activating CAFs, thereby stimulating angiogenesis and enabling immune evasion. The oncogenic miRNA cargo within SenEVs, particularly miR-21 and miR-34a, can further induce EMT and metastasis**.** Despite these detrimental effects, SenEVs present promising diagnostic and therapeutic opportunities by providing non-invasive biomarkers to assess biological ageing and disease progression. Therapeutically, EV secretion inhibitors or senolytic agents may offer a potential strategy for managing ARDs and cancer. Furthermore, Engineering EVs to deliver therapeutic cargo, such as modified miRNAs or targeted surface ligands, enables precise interference with pathogenic signaling. Replacing SenEVs with rejuvenating EVs derived from young MSCs or iPSCs can reverse ageing phenotypes and restore tissue homeostasis. Although clinical translation remains challenged by issues of standardization, regulation, and safety, advances in single-cell EV biology and AI-driven analytics hold great promise for overcoming these obstacles. Finally, these developments may shift the field closer to optimizing the full therapeutic and diagnostic potential of SenEVs in ageing and cancer intervention.

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References

 doi:10.20944/preprints202605.1104.v1

1. Cumplido-Laso, G., et al., *Transcriptional regulation of airway epithelial cell differentiation: insights into the notch pathway and beyond.* International Journal of Molecular Sciences, 2023. **24**(19): p. 14789.
2. Kumar, N. and H.K. Walia, *Cellular Senescence and Stem Cell Exhaustion: Implications for Aging and Regeneration*, in *Cellular Senescence, Age-Related Disorders, and Emerging Treatments*. 2025, Springer. p. 103-133.
3. Mannino, G., et al., *Adult stem cell niches for tissue homeostasis.* Journal of Cellular Physiology, 2022. **237**(1): p. 239-257.
4. Li, C., et al., *Cellular senescence: From homeostasis to pathological implications and therapeutic strategies.* Frontiers in immunology, 2025. **16**: p. 1534263.
5. Eppard, M., J.F. Passos, and S. Victorelli, *Telomeres, cellular senescence, and aging: past and future.* Biogerontology, 2024. **25**(2): p. 329-339.
6. Stojanovic, B., et al., *Oxidative stress-driven cellular senescence: mechanistic crosstalk and therapeutic horizons.* Antioxidants, 2025. **14**(8): p. 987.
7. Alqahtani, S., et al., *SASP modulation for cellular rejuvenation and tissue homeostasis: therapeutic strategies and molecular insights.* Cells, 2025. **14**(8): p. 608.
8. Zhao, S., et al., *Modulation of fracture healing by senescence-associated secretory phenotype (SASP): a narrative review of the current literature.* European journal of medical research, 2024. **29**(1): p. 38.
9. Roger, L., F. Tomas, and V. Gire, *Mechanisms and regulation of cellular senescence.* International journal of molecular sciences, 2021. **22**(23): p. 13173.
10. Yue, Z., et al., *Senescence-associated secretory phenotype and its impact on oral immune homeostasis.* Frontiers in immunology, 2022. **13**: p. 1019313.
11. Romero-García, N., et al., *Extracellular vesicles and cellular ageing*, in *Biochemistry and Cell Biology of Ageing: Part III Biomedical Science*. 2023, Springer. p. 271-311.
12. Shvedova, M., et al., *Cellular senescence in aging, tissue repair, and regeneration.* Plastic and reconstructive surgery, 2022. **150**: p. 4S-11S.
13. Lin, Y., et al., *Roles of extracellular vesicles on macrophages in inflammatory bone diseases.* Molecular and Cellular Biochemistry, 2024. **479**(6): p. 1401-1414.
14. Ripoll, L., et al., *Biology and therapeutic potential of extracellular vesicle targeting and uptake.* Nature Reviews Molecular Cell Biology, 2026: p. 1-19.
15. Gregory, C.D. and M.P. Rimmer, *Extracellular vesicles arising from apoptosis: forms, functions, and applications.* The Journal of Pathology, 2023. **260**(5): p. 592-608.
16. Waqas, M.Y., et al., *Extracellular vesicles and exosome: insight from physiological regulatory perspectives.* Journal of physiology and biochemistry, 2022. **78**(3): p. 573-580.
17. Wang, Y., et al., *Apoptotic cell-derived micro/nanosized extracellular vesicles in tissue regeneration.* Nanotechnology Reviews, 2022. **11**(1): p. 957-972.
18. Jackson Cullison, S.R., et al., *Mechanisms of extracellular vesicle uptake and implications for the design of cancer therapeutics.* Journal of extracellular biology, 2024. **3**(11): p. e70017.
19. Ragni, E., *Extracellular vesicles: recent advances and perspectives.* Frontiers in Bioscience-Landmark, 2025. **30**(6): p. 36405.
20. Manni, G., et al., *Extracellular vesicles in aging: an emerging hallmark?* Cells, 2023. **12**(4): p. 527.
21. Misawa, T., et al., *Identification of novel senescent markers in small extracellular vesicles.* International journal of molecular sciences, 2023. **24**(3): p. 2421.
22. D'Amico, G., et al., *Air pollution: role of extracellular vesicles-derived non-coding RNAs in environmental stress response.* Cells, 2023. **12**(11): p. 1498.
23. Horbay, R., et al., *Role of ceramides and lysosomes in extracellular vesicle biogenesis, cargo sorting and release.* International journal of molecular sciences, 2022. **23**(23): p. 15317.
24. Chen, R. and T. Skutella, *Synergistic anti-ageing through senescent cells specific reprogramming.* Cells, 2022. **11**(5): p. 830.
25. Luo, O.J., et al., *Multidimensional single-cell analysis of human peripheral blood reveals characteristic features of the immune system landscape in aging and frailty.* Nature Aging, 2022. **2**(4): p. 348-364.

 doi:10.20944/preprints202605.1104.v1

26. Long, R. and S. Wang, *Exosomes from preconditioned mesenchymal stem cells: tissue repair and regeneration.* Regenerative Therapy, 2024. **25**: p. 355-366.
27. Wang, X., et al., *Clinical application of mesenchymal stem cells in immunosenescence: a qualitative review of their potential and challenges.* Stem cell research & therapy, 2025. **16**(1): p. 265.
28. Kyryk, V. and O. Parkhomenko, *Potential prognostic markers of cellular senescence in age-associated cardiovascular pathology.* Physiological Journal/Fiziologichnyi Zhurnal, 2025. **71**(2).
29. Shevyrev, D., et al., *Hematopoietic stem cells and the immune system in development and aging.* International Journal of Molecular Sciences, 2023. **24**(6): p. 5862.
30. Sekhar, A. and M. Kandasamy, *Heart-brain axis, gliotransmitters and peripheral neurogenesis: Emerging regenerative roles of cardiac nexus glia in health and disease.* World Journal of Cardiology, 2025. **17**(10): p. 109174.
31. Zheng, Q., et al., *Dose-dependent biphasic effect of environmental UVA on stem cell function through PRPF40A, TGF-β1, NFATc1 signaling.* Journal of Photochemistry and Photobiology B: Biology, 2026: p. 113435.
32. Shi, W., et al., *Nasal Mucosa-Derived Extracellular Vesicles as a Systemic Antiaging Intervention.* Advanced Science, 2026: p. e11372.
33. Zhong, Y., et al., *The role of DNA damage in neural stem cells ageing.* Journal of Cellular Physiology, 2024. **239**(4): p. e31187.
34. Arellano, M.Y.G., et al., *Role of mesenchymal stem/stromal cells (MSCs) and MSC-derived extracellular vesicles (EVs) in prevention of telomere length shortening, cellular senescence, and accelerated biological aging.* Bioengineering, 2024. **11**(6): p. 524.
35. Lupatov, A.Y. and K.N. Yarygin, *Telomeres and telomerase in the control of stem cells.* Biomedicines, 2022. **10**(10): p. 2335.
36. Martini, H. and J.F. Passos, *Cellular senescence: all roads lead to mitochondria.* The FEBS journal, 2023. **290**(5): p. 1186-1202.
37. Selvaraj, N.R., et al., *Oxidative stress and redox imbalance: common mechanisms in cancer stem cells and neurodegenerative diseases.* Cells, 2025. **14**(7): p. 511.
38. López-Gil, L., A. Pascual-Ahuir, and M. Proft, *Genomic instability and epigenetic changes during aging.* International journal of molecular sciences, 2023. **24**(18): p. 14279.
39. Peng, J., et al., *The dynamics of chromatin states mediated by epigenetic modifications during somatic cell reprogramming.* Frontiers in Cell and Developmental Biology, 2023. **11**: p. 1097780.
40. Ganesh, B.H., et al., *The role of extracellular vesicles in aging and age-related disorders.* Antioxidants, 2025. **14**(2): p. 177.
41. Wagner, K.-D. and N. Wagner, *The senescence markers p16INK4A, p14ARF/p19ARF, and p21 in organ development and homeostasis.* Cells, 2022. **11**(12): p. 1966.
42. Hu, Q. and T. Huang, *Regulation of the cell cycle by ncRNAs affects the efficiency of CDK4/6 inhibition.* International Journal of Molecular Sciences, 2023. **24**(10): p. 8939.
43. Pessoa, B., et al., *Senescent Astrocytes: A New Player in Brain Aging and Cognitive Decline.* Brain Sciences, 2026. **16**(1): p. 76.
44. Zarneshan, S.N., et al., *Exploiting pivotal mechanisms behind the senescence-like cell cycle arrest in cancer.* Advances in Protein Chemistry and Structural Biology, 2023. **135**: p. 1-19.
45. Jinesh, S., B. Özüpek, and P. Aditi, *Premature aging and metabolic diseases: the impact of telomere attrition.* Frontiers in aging, 2025. **6**: p. 1541127.
46. Guan, G., Y. Chen, and Y. Dong, *Unraveling the AMPK-SIRT1-FOXO pathway: the in-depth analysis and breakthrough prospects of oxidative stress-induced diseases.* Antioxidants, 2025. **14**(1): p. 70.
47. Mazzella, M., et al., *Regulation of self-renewal and senescence in primitive mesenchymal stem cells by Wnt and TGFβ signaling.* Stem cell research & therapy, 2023. **14**(1): p. 305.
48. Zamfirescu, A.-M., A.S. Yatsenko, and H.R. Shcherbata, *Notch signaling sculpts the stem cell niche.* Frontiers in Cell and Developmental Biology, 2022. **10**: p. 1027222.
49. Pan, Y., et al., *Link between senescence and cell fate: senescence-Associated secretory phenotype and its effects on stem cell fate transition.* Rejuvenation Research, 2022. **25**(4): p. 160-172.
50. Hejazian, S.M., et al., *Targeting cellular senescence in kidney diseases and aging: a focus on mesenchymal stem cells and their paracrine factors.* Cell Communication and Signaling, 2024. **22**(1): p. 609.

 doi:10.20944/preprints202605.1104.v1

51. Sahu, P. and T. Satapathy, *Immunopharmacology of senescence: targeting the senescence-associated secretory phenotype (SASP)—a mechanism-based review.* Inflammopharmacology, 2025. **33**(8): p. 4291-4310.
52. Alfonzo, M.C., et al., *Extracellular vesicles as communicators of senescence in musculoskeletal aging.* Journal of Bone and Mineral Research Plus, 2022. **6**(11): p. e10686.
53. Pi, C., et al., *MiR-34a suppression targets Nampt to ameliorate bone marrow mesenchymal stem cell senescence by regulating NAD+-Sirt1 pathway.* Stem cell research & therapy, 2021. **12**(1): p. 271.
54. Chen, X., et al., *Small extracellular vesicles from young plasma reverse age-related functional declines by improving mitochondrial energy metabolism.* Nature Aging, 2024. **4**(6): p. 814-838.
55. Gerasymchuk, M., et al., *The role of microRNAs in organismal and skin aging.* International journal of molecular sciences, 2020. **21**(15): p. 5281.
56. Aijaz, A., et al., *Young extracellular vesicles restore burn-induced adipose tissue immunometabolic and mitochondrial function in older mice.* Scientific Reports, 2025. **15**(1): p. 35328.
57. Huang, M., et al., *Advancements in research on mesenchymal stem-cell-derived exosomal miRnas: a pivotal insight into aging and age-related diseases.* Biomolecules, 2024. **14**(11): p. 1354.
58. Vun, J., et al., *Anti-aging potential of platelet rich plasma (PRP): evidence from osteoarthritis (OA) and applications in senescence and inflammaging.* Bioengineering, 2023. **10**(8): p. 987.
59. Fullard, N., et al., *Cell senescence-independent changes of human skin fibroblasts with age.* Cells, 2024. **13**(8): p. 659.
60. Herrmann, M., et al., *Extracellular vesicles in musculoskeletal pathologies and regeneration.* Frontiers in bioengineering and biotechnology, 2021. **8**: p. 624096.
61. Le, N.-T., *Metabolic regulation of endothelial senescence.* Frontiers in Cardiovascular Medicine, 2023. **10**: p. 1232681.
62. Lananna, B.V. and S.i. Imai, *Friends and foes: Extracellular vesicles in aging and rejuvenation.* FASEB bioadvances, 2021. **3**(10): p. 787.
63. Boulestreau, J., et al., *Mesenchymal stem cell derived extracellular vesicles in aging.* Frontiers in cell and developmental biology, 2020. **8**: p. 107.
64. Buratta, S., et al., *Lipotoxic stress alters the membrane lipid profile of extracellular vesicles released by Huh-7 hepatocarcinoma cells.* Scientific Reports, 2021. **11**(1): p. 4613.
65. Liu, B., et al., *Lipid and glucose metabolism in senescence.* Frontiers in Nutrition, 2023. **10**: p. 1157352.
66. Zhao, X., et al., *Lipidomic profiling reveals age-dependent changes in complex plasma membrane lipids that regulate neural stem cell aging.* Biorxiv, 2022: p. 2022-08.
67. Nakao, Y., et al., *A comparative proteomic analysis of extracellular vesicles associated with lipotoxicity.* Frontiers in cell and developmental biology, 2021. **9**: p. 735001.
68. Mycielska, M.E., E.N. James, and E.K. Parkinson, *Metabolic alterations in cellular senescence: the role of citrate in ageing and age-related disease.* International Journal of Molecular Sciences, 2022. **23**(7): p. 3652.
69. Huang, H., et al., *Cellular succinate metabolism and signaling in inflammation: implications for therapeutic intervention.* Frontiers in Immunology, 2024. **15**: p. 1404441.
70. Singh, M.K., et al., *Hypoxia, ROS, and HIF Signaling in I/R Injury: Implications and Future Prospects.* Antioxidants, 2026. **15**(2): p. 153.
71. Kuo, C.-C., J.-Y. Wu, and K.K. Wu, *Cancer-derived extracellular succinate: a driver of cancer metastasis.* Journal of biomedical science, 2022. **29**(1): p. 93.
72. Liu, Y., J. Schwam, and Q. Chen, *Senescence-associated cell transition and interaction (sactai): A proposed mechanism for tissue aging, repair, and degeneration.* Cells, 2022. **11**(7): p. 1089.
73. Wei, Y., et al., *Metabolic regulation in the senescence process of stem cells.* Stem Cells Translational Medicine, 2025. **14**(9): p. szaf041.
74. Leyane, T.S., S.W. Jere, and N.N. Houreld, *Oxidative stress in ageing and chronic degenerative pathologies: molecular mechanisms involved in counteracting oxidative stress and chronic inflammation.* International journal of molecular sciences, 2022. **23**(13): p. 7273.
75. Zhao, P., et al., *Cell mediated ECM-degradation as an emerging tool for anti-fibrotic strategy.* Cell Regeneration, 2023. **12**(1): p. 29.
76. Cifuentes, M., et al., *Low-grade chronic inflammation: a shared mechanism for chronic diseases.* Physiology, 2024.

 doi:10.20944/preprints202605.1104.v1

77. Yan, M., et al., *Unveiling the lncRNA cargo of extracellular vesicles: A new language of aging communication.* 2026.
78. Goenka, A., et al., *Tumor microenvironment signaling and therapeutics in cancer progression.* Cancer Communications, 2023. **43**(5): p. 525-561.
79. Al-Danakh, A., et al., *Aging-related biomarker discovery in the era of immune checkpoint inhibitors for cancer patients.* Frontiers in immunology, 2024. **15**: p. 1348189.
80. Farahzadi, R., et al., *Targeting the stem cell niche micro-environment as therapeutic strategies in aging.* Frontiers in cell and developmental biology, 2023. **11**: p. 1162136.
81. Hou, J., et al., *Aged bone marrow macrophages drive systemic aging and age-related dysfunction via extracellular vesicle-mediated induction of paracrine senescence.* Nature Aging, 2024. **4**(11): p. 1562-1581.
82. Mato-Basalo, R., et al., *Action mechanisms of small extracellular vesicles in inflammaging.* Life, 2022. **12**(4): p. 546.
83. Ziglari, T., et al., *Senescent cell–derived extracellular vesicles inhibit cancer recurrence by coordinating immune surveillance.* Cancer research, 2025. **85**(5): p. 859-874.
84. Zhang, Y., et al., *Cellular Senescence and Interorgan Communication in Health and Disease.* Physiology, 2026. **41**(3): p. 000-000.
85. Allegra, A., et al., *Targeting redox regulation as a therapeutic opportunity against acute leukemia: pro-oxidant strategy or antioxidant approach?* Antioxidants, 2022. **11**(9): p. 1696.
86. Brunet, A., M.A. Goodell, and T.A. Rando, *Ageing and rejuvenation of tissue stem cells and their niches.* Nature reviews Molecular cell biology, 2023. **24**(1): p. 45-62.
87. Tang, J., et al., *Stem cell-derived exosomes: a potential therapeutic strategy for enhancing tendon stem/progenitor cells function in tendon-bone healing.* Journal of Orthopaedic Surgery and Research, 2025. **20**(1): p. 658.
88. Won, C.W., M. Kim, and H.E. Shin, *From a solitary blood-derived biomarker to combined biomarkers of sarcopenia: experiences from the Korean Frailty and Aging Cohort Study.* The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2025. **80**(6): p. glae237.
89. Huo, F., Q. Liu, and H. Liu, *Contribution of muscle satellite cells to sarcopenia.* Frontiers in physiology, 2022. **13**: p. 892749.
90. Murach, K.A., et al., *Early satellite cell communication creates a permissive environment for long-term muscle growth.* IScience, 2021. **24**(4).
91. He, C., et al., *Bone and muscle crosstalk in aging.* Frontiers in cell and developmental biology, 2020. **8**: p. 585644.
92. Yun, H.R., et al., *Integrating Senescence and Oxidative Stress in Cardiac Disease.* International Journal of Molecular Sciences, 2025. **26**(24): p. 11917.
93. Femminò, S., et al., *Extracellular vesicles and cardiovascular system: Biomarkers and Cardioprotective Effectors.* Vascular pharmacology, 2020. **135**: p. 106790.
94. Karim Rony, R.M.I. and J.D. Tompkins, *Cardiac repair and regeneration: cell therapy, in vivo reprogramming, and the promise of extracellular vesicles.* Experimental & Molecular Medicine, 2025. **57**(10): p. 2182-2200.
95. Bernáth-Nagy, D., et al., *Circulating extracellular vesicles as biomarkers in the diagnosis, prognosis and therapy of cardiovascular diseases.* Frontiers in Cardiovascular Medicine, 2024. **11**: p. 1425159.
96. Bonetto, V. and M. Grilli, *Neural stem cell-derived extracellular vesicles: mini players with key roles in neurogenesis, immunomodulation, neuroprotection and aging.* Frontiers in Molecular Biosciences, 2023. **10**: p. 1187263.
97. Moretti, E.H., et al., *Neural Stem Cell-Derived Extracellular Vesicles for Advanced Neural Repair.* Journal of Neurochemistry, 2025. **169**(8): p. e70170.
98. Zhang, X., et al., *Mesenchymal stem cells and exosomes improve cognitive function in the aging brain by promoting neurogenesis.* Frontiers in Aging Neuroscience, 2022. **14**: p. 1010562.
99. Rojas-Vázquez, S., et al., *Vascular senescence: a potential bridge between physiological aging and neurogenic decline.* Frontiers in Neuroscience, 2021. **15**: p. 666881.
100. Jia, J., et al., *Muscle-derived extracellular vesicles mediate crosstalk between skeletal muscle and other organs.* Frontiers in physiology, 2025. **15**: p. 1501957.
101. Liu, H.-C., et al., *Circulating MicroRNA-486 and MicroRNA-146a serve as potential biomarkers of sarcopenia in the older adults.* BMC geriatrics, 2021. **21**(1): p. 86.

 doi:10.20944/preprints202605.1104.v1

102. Yedigaryan, L., et al., *Shared and divergent epigenetic mechanisms in cachexia and sarcopenia.* Cells, 2022. **11**(15): p. 2293.
103. Zhu, Q., et al., *Lipidomic identification of urinary extracellular vesicles for non-alcoholic steatohepatitis diagnosis.* Journal of Nanobiotechnology, 2022. **20**(1): p. 349.
104. Hornburg, D., et al., *Dynamic lipidome alterations associated with human health, disease and ageing.* Nature metabolism, 2023. **5**(9): p. 1578-1594.
105. Yushkov, B., et al., *Stem-cell niches in health and disease: microenvironmental determinants of regeneration and pathology.* Cells, 2025. **14**(13): p. 981.
106. He, L., et al., *Senescence of mesenchymal stem cells: implications in extracellular vesicles, miRNAs and their functional and therapeutic potentials.* Aging Pathobiology and Therapeutics, 2023. **5**(1): p. 03-17.
107. Chen, X., et al., *Senescence of donor cells impairs fat graft regeneration by suppressing adipogenesis and increasing expression of senescence-associated secretory phenotype factors.* Stem Cell Research & Therapy, 2021. **12**(1): p. 311.
108. Shi, Z., et al., *Research progress on the mechanism of angiogenesis in wound repair and regeneration.* Frontiers in physiology, 2023. **14**: p. 1284981.
109. Shemetun, O.V., et al., *Development of radiation-induced bystander effect in the somatic cells of persons from different age groups.* Problems of radiation medicine and radiobiology, 2018. **23**: p. 499-509.
110. Rudnitsky, E., et al., *Mesenchymal stem cells and their derivatives as potential longevity-promoting tools.* Biogerontology, 2025. **26**(3): p. 96.
111. Zia, A., et al., *Key miRNAs in modulating aging and longevity: a focus on signaling pathways and cellular targets.* Current Molecular Pharmacology, 2022. **15**(5): p. 736-762.
112. Liang, C., et al., *Unveiling exosomes in combating skin aging: insights into resources, mechanisms and challenges.* Stem Cell Research & Therapy, 2025. **16**(1): p. 474.
113. Almeida, S. and S.A. Melo, *Unlocking the Role of Senescent Cell–Derived Extracellular Vesicles in Immune-Mediated Tumor Suppression.* Cancer Research, 2025. **85**(5): p. 833-835.
114. Bao, Q., et al., *Tumor-derived extracellular vesicles regulate cancer progression in the tumor microenvironment.* Frontiers in molecular biosciences, 2022. **8**: p. 796385.
115. Jiang, X., et al., *Recent advances in the aging microenvironment of breast cancer.* Cancers, 2022. **14**(20): p. 4990.
116. Mojsilović, S., et al., *Tumorigenic aspects of MSC senescence—implication in cancer development and therapy.* Journal of Personalized Medicine, 2021. **11**(11): p. 1133.
117. Morales-Valencia, J. and G. David, *The contribution of physiological and accelerated aging to cancer progression through senescence-induced inflammation.* Frontiers in Oncology, 2021. **11**: p. 747822.
118. Zhang, C., et al., *Tumor-derived small extracellular vesicles in cancer invasion and metastasis: molecular mechanisms, and clinical significance.* Molecular cancer, 2024. **23**(1): p. 18.
119. Semina, E.V., et al., *MicroRNAs in cancer: from gene expression regulation to the metastatic niche reprogramming.* Biochemistry (Moscow), 2021. **86**(7): p. 785-799.
120. Qian, H., et al., *Decoding the promise and challenges of miRNA-based cancer therapies: an essential update on miR-21, miR-34, and miR-155.* International journal of medical sciences, 2024. **21**(14): p. 2781.
121. Farace, C., et al., *Deregulation of cancer-stem-cell-associated miRNAs in tissues and sera of colorectal cancer patients.* Oncotarget, 2020. **11**(2): p. 116.
122. Fu, T.E. and Z. Zhou, *Senescent cells as a target for anti-aging interventions: From senolytics to immune therapies.* Journal of Translational Internal Medicine, 2025. **13**(1): p. 33-47.
123. Cao, L., et al., *The controversial role of senescence-associated secretory phenotype (SASP) in cancer therapy.* Molecular Cancer, 2025. **24**(1): p. 283.
124. Qian, K., et al., *The roles of small extracellular vesicles in cancer and immune regulation and translational potential in cancer therapy.* Journal of Experimental & Clinical Cancer Research, 2022. **41**(1): p. 286.
125. Muñoz, D.P., et al., *Targetable mechanisms driving immunoevasion of persistent senescent cells link chemotherapy-resistant cancer to aging.* JCI insight, 2019. **4**(14): p. e124716.
126. Hwang, H.J., et al., *Therapy-induced senescent cancer cells contribute to cancer progression by promoting ribophorin 1-dependent PD-L1 upregulation.* Nature communications, 2025. **16**(1): p. 353.

 doi:10.20944/preprints202605.1104.v1

127. Dong, Q., et al., *Pre-metastatic niche formation in different organs induced by tumor extracellular vesicles.* Frontiers in Cell and Developmental Biology, 2021. **9**: p. 733627.
128. Sohal, I.S. and A.L. Kasinski, *Emerging diversity in extracellular vesicles and their roles in cancer.* Frontiers in oncology, 2023. **13**: p. 1167717.
129. Wang, S.E., *Extracellular vesicles and metastasis.* Cold Spring Harbor perspectives in medicine, 2020. **10**(7): p. a037275.
130. Liu, B., et al., *Regulation of cellular senescence in tumor progression and therapeutic targeting: mechanisms and pathways.* Molecular cancer, 2025. **24**(1): p. 106.
131. Piskorz, W.M. and M. Cechowska-Pasko, *Senescence of tumor cells in anticancer therapy—Beneficial and detrimental effects.* International Journal of Molecular Sciences, 2022. **23**(19): p. 11082.
132. Veenstra, J.P., L.F.F. Bittencourt, and K.M. Aird, *The senescence-associated secretory phenotype in ovarian cancer dissemination.* American Journal of Physiology-Cell Physiology, 2022. **323**(1): p. C125-C132.
133. He, R.-R., et al., *Sepsis biomarkers: advancements and clinical applications—a narrative review.* International journal of molecular sciences, 2024. **25**(16): p. 9010.
134. Basisty, N., et al., *A plasma proteomic signature links secretome of senescent monocytes to aging-and obesity-related clinical outcomes in humans.* 2024.
135. Alibhai, F.J. and R.-K. Li, *Understanding systemic factors in aging and rejuvenation.* Aging (Albany NY), 2020. **12**(21): p. 20936.
136. Santelli, A., et al., *Senescent kidney cells in hypertensive patients release urinary extracellular vesicles.* Journal of the American Heart Association, 2019. **8**(11): p. e012584.
137. Brinkley, T.E., et al., *Research priorities for measuring biologic age: summary and future directions from the Research Centers Collaborative Network Workshop.* Geroscience, 2022. **44**(6): p. 2573-2583.
138. Ma, Y., et al., *Identification of small compounds regulating the secretion of extracellular vesicles via a TIM4-affinity ELISA.* Scientific Reports, 2021. **11**(1): p. 13471.
139. Sun, Y., et al., *The multifaceted role of the SASP in atherosclerosis: from mechanisms to therapeutic opportunities.* Cell & Bioscience, 2022. **12**(1): p. 74.
140. Ji, P., et al., *Targeted clearance of senescent cells via engineered extracellular vesicles reprograms tumor immunosuppressive microenvironment.* Advanced Healthcare Materials, 2024. **13**(23): p. 2400945.
141. Menjivar, N.G., et al., *MicroRNA nano-shuttles: Engineering extracellular vesicles as a cutting-edge biotechnology platform for clinical use in therapeutics.* Biological Procedures Online, 2024. **26**(1): p. 14.
142. Liu, Q., et al., *Targeted therapy using engineered extracellular vesicles: principles and strategies for membrane modification.* Journal of Nanobiotechnology, 2023. **21**(1): p. 334.
143. Frolova, L. and I.T.S. Li, *Targeting capabilities of native and bioengineered extracellular vesicles for drug delivery.* Bioengineering, 2022. **9**(10): p. 496.
144. Grigorian Shamagian, L., et al., *Rejuvenating effects of young extracellular vesicles in aged rats and in cellular models of human senescence.* Scientific reports, 2023. **13**(1): p. 12240.
145. Jia, Z., S. Zhang, and W. Li, *Harnessing stem cell-derived extracellular vesicles for the regeneration of degenerative bone conditions.* International Journal of Nanomedicine, 2023: p. 5561-5578.
146. Johnson, J., et al., *From mesenchymal stromal cells to engineered extracellular vesicles: a new therapeutic paradigm.* Frontiers in Cell and Developmental Biology, 2021. **9**: p. 705676.
147. Takakura, Y., et al., *Quality and safety considerations for therapeutic products based on extracellular vesicles.* Pharmaceutical Research, 2024. **41**(8): p. 1573-1594.
148. Stine, S.J., et al., *Exosome and biomimetic nanoparticle therapies for cardiac regenerative medicine.* Current stem cell research & therapy, 2020. **15**(8): p. 674-684.
149. Nikoloff, J.M., et al., *Identifying extracellular vesicle populations from single cells.* Proceedings of the National Academy of Sciences, 2021. **118**(38): p. e2106630118.
150. Santos, F.M., et al., *Multi-omics integrative approach of senescent endothelial cells and derived extracellular vesicles in a replicative senescence model.* bioRxiv, 2025: p. 2025-11.
151. Thakur, A., et al., *The mini player with diverse functions: extracellular vesicles in cell biology, disease, and therapeutics.* Protein & cell, 2022. **13**(9): p. 631-654.

 doi:10.20944/preprints202605.1104.v1

152. Amoako, K., et al., *Enhancing nucleic acid delivery by the integration of artificial intelligence into lipid nanoparticle formulation.* Frontiers in Medical Technology, 2025. **7**: p. 1591119.
153. Uthamacumaran, A., et al., *Machine intelligence-driven classification of cancer patients-derived extracellular vesicles using fluorescence correlation spectroscopy: results from a pilot study.* Neural Computing and Applications, 2023. **35**(11): p. 8407-8422.