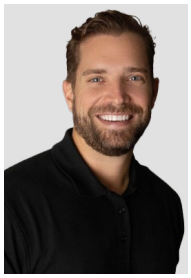

Mesenchymal Stem Cell Derived Extracellular Vesicles

The New Age of Regenerative Medicine

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Aging is the most significant risk factor for a wide array of chronic diseases, including respiratory diseases, neurological disorders (ND), cardiovascular disease (CVD), osteoarthritis (OA), and other metabolic disorders.[1,6] Although these diseases have different physiological manifestations, they share a common origin — inflammation and cellular dysfunction.

Over time, intrinsic and extrinsic stressors drive genomic instability, mitochondrial inefficiency, and oxidative stress.6 Additionally, cells have a finite replicative lifespan. With each division, telomeres, the protective caps at the end of chromosomes, shorten. These changes push cells into senescence, a nondividing but metabolically active state characterized by the secretion of pro-inflammatory cytokines, chemokines, and proteases collectively termed the senescence-associated secretory phenotype (SASP).[4]

SASP factors activate immune cells and induce neighboring cells to also enter senescence, creating a self-perpetuating cycle of tissue dysfunction. This leads to chronic inflammation, or "inflammaging,"[7] which disrupts tissue microenvironments, stem cell niches, and intercellular communication, ultimately impairing tissue repair and increasing disease susceptibility.

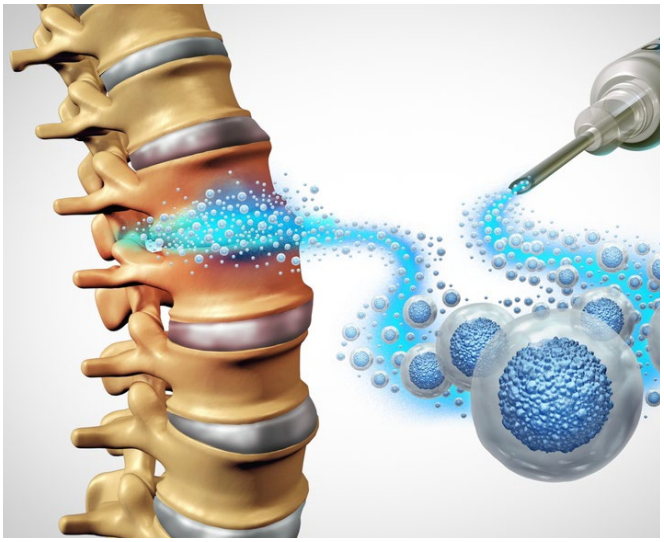
Reversing these changes requires regenerative therapies that reduce inflammation, restore homeostasis, and reactivate intrinsic repair mechanisms. Such therapies offer promising potential for treating age-related diseases.[2]

"SASP factors activate immune cells and induce neighboring cells to also enter senescence, creating a self-perpetuating cycle of tissue dysfunction."

Mesenchymal Stem Cell Extracellular Vesicles: Cell-Free Regenerative Medicine

Mesenchymal stem cells (MSCs) have emerged as a promising tool in regenerative medicine because of their unique ability to modulate immune responses, rejuvenate damaged cells, and promote tissue repair. Found in many tissues, including bone marrow (BM), adipose tissue (AT), and the umbilical cord (UC), MSCs are multipotent cells capable of self-renewal and differentiation into osteoblasts, chondrocytes, and adipocytes.[3]

Their biological role involves sensing tissue injury, migrating to the site, modulating immune activity, and releasing



molecular signals that guide stem and progenitor cells in tissue regeneration.[5] MSCs have garnered substantial research interest as regenerative medicine therapeutics because of their unique biological function. Indeed, MSC-based therapies have shown promise in preclinical and early clinical studies across many diseases over the past 15 years.[8]

Limitations of Cell-Based Therapies

However, several limitations hinder broader adoption.[9] Systemic administration via intravenous infusion often results in MSC accumulation in the lungs, liver, and spleen, reducing availability at target tissues.[10,11] This is particularly problematic for treating diseases of the central nervous system (CNS), where MSCs cannot efficiently cross the blood-brain-barrier,[12] further restricting effective doses.

Direct delivery methods (e.g., intracerebral injection) improve targeting[11,13] but can be invasive and are not feasible for every patient. Immunogenicity is another concern. Although MSCs express low levels of HLA antigens, allogenic rejection can still occur, and their proliferative capacity poses a tumorigenic risk,[14] limiting repeat dosing.[15]

Paradigm Shift to MSC-EV Therapies

Mounting evidence suggests that much of MSC's therapeutic benefit is mediated by extracellular vesicles (EVs), which are nanoscale, membrane-bound packages containing bioactive cargo, such as growth factors, cytokines, lipids, mRNA, and

microRNAs, to target cells.[6] MSC-derived EVs offer a cell-free alternative that addresses these limitations.

EVs are generally classified into three main subtypes — exosomes (30–150 nm), microvesicles (100–1,000 nm), and apoptotic bodies (500–2,000 nm) — with exosomes being the most abundant subtype secreted by MSCs. Their small size allows them to circulate systemically with less accumulation in off-target tissues, and they can effectively cross the blood-brain-barrier enabling noninvasive delivery to the CNS.[16] Like cells, EVs are composed of a lipid bilayer but contain lower levels of HLA markers and have no replicative capacity, rendering them even less immunogenic and tumorigenic, which facilitates repeat dosing.[17]

From a manufacturing standpoint, EVs are much easier stored long term, allowing for off-the-shelf therapies. These benefits position MSC-EVs as a safer and more clinically versatile therapeutic while retaining the immunomodulatory and regenerative signaling capacities that make MSC therapies effective.

Mechanisms of MSC-EV Regeneration

Preventing Further Damage: Immunomodulation

Immunomodulation is a primary mechanism by which MSC-EVs exert their regenerative effects.[18] MSCs detect inflammatory cues in the tissue microenvironment through pattern recognition receptors, including toll-like receptors, and respond by secreting EVs enriched with anti-inflammatory molecules, including prostaglandin E2 and interleukin-10.[2] This cocktail suppresses SASP cytokines like TNFα and IL-6 by targeting pathways including NF-κB, JAK/STAT, and MAPK/ERK.[2,6]

Macrophages are reprogrammed from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype,[19,20,21] while dendritic cell maturation is inhibited, reducing T-cell-mediated responses and shifting the microenvironment toward an anti-inflammatory state.[22]

SASP cytokines also drive extracellular matrix (ECM) remodelling and fibrosis in conditions like OA.[23] MSC-EVs counteract this by reducing levels of tissue-degrading enzymes like matrix metalloproteinase-1 (MMP1),24 downregulating fibrosis-associated proteins like α-smooth muscle actin[25] and upregulating ECM structural components like collagen type II,[26] ultimately restoring tissue integrity. By reprogramming the immune environment, MSCs support a regenerative state, limiting further damage from activated immune cells.

Rejuvenating Senescent Cells: Activating Regenerative Signaling and Survival Pathways

Beyond inflammation control and ECM remodelling, MSC-EVs actively promote tissue repair by rejuvenating senescent cells and activating stem/progenitor repair pathways. MSC-EVs activate mTOR signalling to enhance cell proliferation and ERK signalling to promote cell migration toward injury sites.[2,6] They promote cell survival by upregulating anti-apoptotic genes like BCL227 and downregulating pyroptosis regulators, including caspase-1.[28]

Oxidative stress and mitochondrial dysfunction are reduced via EV-mediated delivery of antioxidant enzymes, functional mitochondria, and induction of endogenous antioxidant pathways.[29] These changes reduce SASP secretion, synergizing with the immunomodulatory effects. Once rejuvenated cells exit senescence, MSC-EVs activate tissue-specific repair pathways in stem/progenitor populations to allow tissue regeneration.

Therapeutic Potential of MSC-EVs

These molecular effects translate into the tangible therapeutic outcomes observed across a variety of conditions. While clinical studies on MSC-EVs remain limited — primarily in COVID-1930,31 — they are expanding as preclinical data continues to show efficacy in OA, respiratory diseases,[2] ND,[32] and CVD, amongst others.

The treatment of OA with MSC-EVs is currently the most well studied. OA progression is driven in part by pro-inflammatory M1 macrophage in synovial tissue.[33] MSC-EVs have been shown in preclinical studies to promote M2 macrophage polarization, reduce synovial inflammation, and stimulate chondrocyte-driven ECM formation via ERK, AKT, and Wnt5a signaling.[19–21]

Intra-articular injection in animal models preserved cartilage thickness and reduced joint degeneration,34 and a recent clinical trial in patients with knee OA reported significant improvements in both pain and functional outcomes following MSC-EV injection.35 During the COVID-19 pandemic, a phase 1 clinical trial involving intravenous MSC-EV administration in hospitalized patients showed enhanced oxygenation and decreased inflammatory markers, supporting their role in mitigating acute respiratory distress.[30,31]

"By reprogramming the immune environment, MSCs support a regenerative state, limiting further damage from activated immune cells."

The treatment of ischemic stroke is the most well studied ND treated with MSC-EVs. Preclinical studies demonstrated that MSC-EV treatment after ischemic stroke led to an increase in M2 macrophage, a reduction in pro-inflammatory cytokines, reduced apoptotic signalling, and an increase in angiogenesis.[37] A small phase 1 trial demonstrated that MSC-EVs are safe and potentially effective in patients undergoing decompressive craniectomy.[39]

The versatility of MSC-EV administration is exemplified by two studies using topical delivery. Dry eye symptoms in patients with the autoimmune condition Sjögren's syndrome showed improvements after topical application of Wharton's jelly-derived MSC-EVs, which were accompanied by decreased levels of SASP cytokines, including IL-6, in tear fluid.[36] In dermatology, AT-MSC-EVs moderately reduced melanin production in hyperpigmentation disorders.[38] Lastly, there are ongoing trials assessing MSC-EVs for burn wounds.[40]

MSC-EVs represent a paradigm shift in regenerative medicine. They capture the therapeutic benefits of MSCs while

avoiding their primary safety, delivery, and manufacturing limitations. By modulating inflammation, reversing cellular senescence, and activating tissue repair pathways, MSC-EVs have demonstrated broad potential across musculoskeletal, respiratory, neurological, autoimmune, and dermatologic diseases. The MSC-EV field is now moving toward larger and more rigorous clinical trials, which will be critical for validating their safety, efficacy, and long-term benefits.

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**See more references (26-40) online.*