Review Article

Stem Cell INVESTIGATION

Extracellular vesicles and aging

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Abstract: Aging and the chronic diseases associated with aging place a tremendous burden on our healthcare system. As our world population ages dramatically over the next decades, this will only increase. Hence, there is a great need to discover fundamental mechanisms of aging to enable development of strategies for minimizing the impact of aging on our health and economy. There is general agreement that cell autonomous mechanisms contribute to aging. As cells accrue damage over time, they respond to it by triggering individual cell fate decisions that ultimately disrupt tissue homeostasis and thus increase risk of morbidity. However, there are numerous lines of evidence, including heterochronic parabiosis and plasma transfer, indicating that cell non-autonomous mechanisms are critically important for aging as well. In addition, senescent cells, which accumulate in tissues with age, can display a senescence-associated secretory phenotype (SASP) that contributes to driving aging and loss of tissue homeostasis through a non-cell autonomous mechanism(s). Given the diverse roles of blood-borne extracellular vesicles (EVs) in modulating not only the immune response, but also angiogenesis and tissue regeneration, they likely play a key role in modulating the aging process through cell non-autonomous mechanisms. The fact that senescent cells release more EVs and with a different composition suggests they contribute to the adverse effects of senescence on aging. In addition, the ability of EVs from functional progenitor cells to promote tissue regeneration suggests that stem cell-derived EVs could be used therapeutically to extend healthspan. This review focuses on the potential roles of EVs in aging, the potential of EV-based therapeutic applications for extending healthspan and the potential for use of circulating EVs as biomarkers of unhealthy aging.

Keywords: Aging; extracellular vesicles (EVs); mesenchymal stem cells (MSCs)

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Aging

It is estimated that in the next 20 years, the number of individuals in the United States over the age of 65 will double, numbering more than 70 million individuals. Unfortunately, as we age there is an unavoidable and progressive loss of the ability to maintain tissue homeostasis under stress and an attrition of functional reserve. As a consequence, the incidence of numerous debilitating diseases increases nearly exponentially with age, including cardiovascular disease, neurodegeneration, diabetes, osteoarthritis, and osteoporosis. Over 90% of individuals >65 years of age have at least one chronic disease, while >70% have at least two. These chronic diseases account for 75% of our healthcare costs, amounting to approximately $3 trillion in costs last year alone. Indeed, chronic diseases of the elderly are the greatest healthcare burden in the United States and seriously impact the quality of life of a large segment of the population. Thus, there is a significant need to understand mechanisms driving aging and to develop novel therapeutics. Given the diverse roles of blood-borne EVs in modulating not only the immune response, but also angiogenesis and tissue regeneration, they likely play a key role in modulating the aging process. This review focuses on the role EVs could play in aging, their therapeutic application for extending healthspan and their potential for use as biomarkers of unhealthy aging.

Mechanisms underlying aging

Aging is a complex process involving a number of different pathways with both genetic and environmental components (1-5). Aging is thought to arise, in part, as a consequence of the accumulation of stochastic molecular and cellular damage. The precise nature of the damage responsible for aging-related degeneration remains poorly defined, but likely consists of mitochondrial dysfunction, elevated ROS, telomere attrition, changes in nuclear structure, accumulation of genetic mutations, or DNA, protein and membrane damage. Biological processes that underlie aging phenotypes and are also active at sites of etiology of most chronic diseases include: (I) chronic, low-grade, "sterile" inflammation; (II) macromolecular and organelle dysfunction resulting in changes in level or function of proteins, carbohydrates, lipids, mitochondria and DNA; (III) stem cell and progenitor cell dysfunction; and (IV) increased senescent cell burden. These four processes are linked in that interventions targeting one process also attenuate the others. For example, oxidative DNA damage increases stochastically in cells in different tissues, likely driven in part by increased mitochondrial ROS, resulting in the induction of cellular senescence. These senescent cells accumulate with age at sites of pathogenesis in chronic diseases (6,7). Reduction of the senescent cell burden can lead to reduced inflammation, decreased macromolecular dysfunction, and enhanced function of progenitors (8-10). Also, adult stem cells become dysfunctional with evidence of senescence with age, likely driven by macromolecular and organelle dysfunction (11). These four biological processes are also the key components of the seven pillars of aging, defined as adaption to stress, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis and stem cells and regeneration.

Autonomous and non-autonomous mechanisms of aging

There is compelling evidence to support the hypothesis that the underlying cause of aging is the cell autonomous, time-dependent accumulation of stochastic damage to cells, organelles and macromolecules. However, it is also clear from heterochronic parabiosis (12-17) and serum transfer (17,18) studies that cell non-autonomous mechanisms play important roles in suppressing or driving degenerative changes that arise as the consequence of spontaneous, stochastic damage. For example, using heterochronic parabiosis, it was demonstrated that factors in young blood rejuvenate certain cell types and tissues in old mice (12-17). These anti-geronic factors in young serum include GDF-11 and oxytocin (19). Treatment of mice with rGDF-11 (15,16,20), similar to heterochronic parabiosis, has rejuvenating effects on skeletal muscle, heart and brain, although these results are still controversial (21,22). Furthermore, factors in umbilical cord, but not adult, plasma function as synaptic plasticity-promoting proteins with TIMP2 demonstrated to increase hippocampal-dependent cognition (23). Conversely, factors in old blood can drive aging of certain cell types and tissues in young mice. These blood-borne pro-geronic factors include the chemokine CCL-11 (24) and β-2 microglobulin (25). In addition to these identified geronic factors, it is likely there are other circulating factors that also play key, cell non-autonomous roles in aging. Indeed, it is likely a combination of loss of anti-geronic factors and an increase in pro-geronic factors that drives aging. Given that almost all cell types release EVs, including stem/progenitor cells and senescent cells, it is likely that subsets of blood-borne EVs play key roles as both anti- and pro-geronic factors.

Cellular senescence

Senescence is a cell fate that involves loss of proliferative potential of normally replication-competent cells with associated resistance to cell death through apoptosis and generally increased metabolic activity. Frequently, senescent cells develop a senescence-associated secretory phenotype (SASP) characterized by increased release of pro-inflammatory cytokines and chemokines, tissue-damaging proteases, factors that can impact stem and progenitor cell function, hemostatic factors, and growth factors (8). Markers of senescent cells include increases in expression of the cell cycle regulators, p16INK4A and p21Cip1, of SASP factors (e.g., IL-6, IL-8, monocyte chemoattractant protein-1, plasminogen-activated inhibitor-1, and many others), increased senescence-associated β-galactosidase (SA-βgal) activity, senescent-associated distension of satellites (SADS), and telomere-associated DNA damage foci (TAFs), among others. Senescent cells that express the SASP thus can have substantial pathologic effects. In support of an important role for senescence in aging, selective killing of p16INK4a-positive senescent cells extended healthspan in transgenic mouse models (INK-ATTAC and p16-3MR mice) of accelerated aging

(26-30). Importantly, clearing senescent cells from aged INK-ATTAC mice improved age-related changes in metabolic function (9). Subsequently, it was demonstrated that chronic clearance of p16INK4a-positive cells in adult mice extends the median lifespan of naturally aged mice (27). Clearance of senescent cells in versions of this genetic model (INK-ATTAC and 3MR mice) or treating mice with novel senolytics extended healthspan (31,32), restored vascular reactivity (33), stabilized atherosclerotic plaques (34), improved pulmonary function (35), alleviated osteoarthritis (28), improved fatty liver disease (36) and improved lung function in a pulmonary fibrosis model (35). Conversely, injecting senescent cells is able to drive age-related diseases such as osteoarthritis (37). Thus, the increase in cellular senescence that occurs with aging appears to play a major role in driving life-limiting, age-related diseases (8,29,30,38-40). As discussed below, senescent cells release more EVs with a different composition, suggesting that EVs should be considered part of the SASP, important for conferring the adverse effects of senescent cells on aging.

Stem cells and aging

A characteristic of aging is the loss of regenerative capacity, leading to an impaired ability to respond to stress and therefore increased morbidity and mortality. This has led to the hypothesis that aging is caused, in part, by the loss of functional adult stem cells necessary for maintaining tissue homeostasis. Indeed, mice greater than 2 years of age have a significant reduction in the number and proliferative capacity of different adult stem cell types. For example, there are age-related changes in bone marrow-derived mesenchymal stem cells (BM-MSCs) including loss of proliferation and differentiation potential and increased senescence. Similarly, MSCs derived from the bone marrow of patients with Hutchinson-Gilford Progeroid Syndrome, a disease of accelerated aging, are defective in their ability to differentiate (41). In addition, muscle derived stem/progenitor cells (MDSPC) are adversely affected in accelerated and natural aged mice, displaying loss of proliferation and ability to differentiate in culture (11,42). Importantly, this dysfunction was demonstrated to directly contribute to age-related degenerative changes since intraperitoneal injection of only 106 functional, young MDSPCs was sufficient to extend healthspan and lifespan in two different mouse models of accelerated aging (11). Only a few of the injected, labeled MDSPCs were found in different tissues with no evidence of differentiation, suggesting that the therapeutic effect of MDSPCs is likely mediated by secreted factors that act systemically in a cell non-autonomous manner. Consistent with this hypothesis, co-culture of young, functional MDSPCs with old MDSPCs in a transwell system resulted in improvement in the ability of the old MDSPCs to proliferate and differentiate (11). At least part of this activity co-purifies with EVs.

Injection of young, functional BM-MSCs into rats has been shown to extend their lifespan. Ubiquitously located throughout the body, MSCs can act locally through chemotactic-induced migration from the perivascular niches in response to stress or injury as well as systemically through the secretion of various soluble factors such as chemokines, cytokines and extracellular vesicles (EVs). Tasked with maintaining the HSC niche through the regeneration of an extracellular matrix comprised of osteoblasts, adipocytes and endothelial cells (43-45), MSCs also maintain tissue homeostasis through modulating HSC function. In addition, MSCs are vital in maintaining blood vessel integrity through promotion of angiogenesis and thus are essential for systemic wound healing and tissue regeneration. Lastly, MSCs have a profound capacity to modulate the immune system, therefore modulating the immune response to stress and injury by regulating the pro-inflammatory response of macrophages and prohibiting lymphocyte proliferation (46). MSCs derived from old mice are defective in their ability to differentiate and undergo senescence more rapidly in culture.

EVs

EVs are comprised of both microvesicles, released from the plasma membrane by shedding, and nanovesicles or exosomes, generated by reverse budding of multivesicular bodies (MVBs) (47,48). These different types of EVs are characterized predominantly by their size, with exosomes ranging from 30 to 100 nm and microvesicles usually being larger than 100 nm. Although their contents likely differ, both small and large EVs are enriched for a subset of diverse proteins, lipids, messenger RNAs (mRNAs), and non-coding RNAs (ncRNAs), such as miRNAs, which are derived from the parental cells. EVs have a variety of reported functions and some of their better-documented activities are associated with some form of immune regulation (47,48). EVs from both immune and non-immune cells, such as MSCs and endothelial cells, contribute to antigen-specific and non-specific immune

regulation (47-49). Depending upon the context and vesicle type, EVs can stimulate or suppress the immune responses to infections with viruses and microbial pathogens as well as cancer.

EVs derived from stem cells also have significant ability to repair damaged tissue (50). For example, EVs derived from marrow or adipose MSCs affect the phenotype and induce healing of many different tissue and cell types, including liver (51), heart (52), pulmonary epithelial cells and kidney (53,54) as well as promote angiogenesis (55,56). Consistent with these regenerative capacities of stem cell EVs, a recent study demonstrated that implantation of healthy hypothalamic stem/progenitor cells into the hypothalamus leads to the slowing of ageing (57). Moreover, it was demonstrated that the functional hypothalamic stem/progenitor cells release exosomes into the cerebral spinal fluid that likely contribute to slowing aging through transfer of miRNAs (57). Conversely, it has been demonstrated that senescent cells release more EVs and with a different composition (58-60), likely contributing to the SASP. Taken together, these results suggest that functional stem/progenitor cell-derived EVs are able to extend healthspan and lifespan whereas senescent cell-derived EVs could function as pro-geronic factors.

Circulating, blood-borne vesicles

EVs are found in blood and circulate throughout the body, presumably serving as a form of cell-to-cell communication at a distance. Given that EVs contain RNA, proteins and lipids derived from the cell of origin, components of circulating EVs are being used as markers of disease. For examples, tumor associated proteins such as EGF-R (glioblastoma) (61) or oncogene mRNAs (62) have been found in cerebral spinal fluid or blood-derived EVs respectively whereas the protein glypican-1 is found in circulating EVs from patients with pancreatic cancer (63). Also, circulating EVs have important biological activities (47,48). Serum-derived EVs from mice bearing tumors were able to suppress tumor antigen-specific responses (64-66). Similarly, intradermal immunization with a specific antigen resulted in the presence of MHC Class II+ EVs in the serum able to suppress antigen-specific immune responses in a mouse delayed type hypersensitivity (DTH) footpad model (67). More recently, it was demonstrated that EVs from human serum can promote vascular remodeling and prevent muscle damage in a mouse model of acute hind limb ischemia (68).

Taken together, these observations strongly suggest that EVs play important roles in immune regulation and tissue regeneration. More importantly, these results suggest that circulating EVs in the blood could contribute to cell non-autonomous mechanisms of aging. Indeed, given that EVs are important for cell-to-cell communication between neighboring cells and cells at a distance, transferring not only RNA, but also proteins, lipids and metabolites, they are well-positioned to play key pro- and anti-geronic roles with aging.

EVs as biomarkers of aging

EVs can act as a biomarker, specifying the progression of the disease state of the cells in which they originate. For example, EVs from the serum of aged rats have been shown to have reduced CD63 and increased acetylcholinesterase (AChE) levels compared to young controls. Interestingly, exercise in the aged animals altered the CC63 and AChE levels. The miR-183 cluster, comprised of miR-96, miR-182 and miR-183, increases with age, at least in EVs derived from bone marrow (69). Interestingly, transfection of a miRNA-183-5p mimic was shown to reduce cell proliferation and increase senescence in bone marrow stem cells, suggesting the bone marrow EVs from aged animals could suppress osteogenesis. In addition, increased levels of proBDNF and BDNF were found in circulating L1CAM+ EVs, derived from neuronal cells (70). Individuals with higher EV BDNF levels had slower walking speeds (70). In prostate cancer patients on dietary protein restriction, an increase in the levels of leptin receptor in total plasma EVs and, in particular, the L1CAM+ EV subset was observed (71). There also was a change in the phosphorylation status of the insulin receptor signal transducer protein IRS1 in L1CAM+ EVs (71). These results suggest that protein restriction could improve insulin and leptin sensitivity. In a recent study, the levels of circulating EVs in plasma were shown to decrease in a cross-sectional and longitudinal study. Here it also was demonstrated that plasma EVs from older individuals had increased MHC-II expression on monocytes and were more readily internalized by B cells (72). This uptake of the plasma EVs results in activation of not only B cells, but also monocytes (72). Thus circulating EVs in aged individuals likely can modulate the immune response.

Summary

Given the observations that heterochronic parabiosis

and plasma transfer can slow aging in old animals and accelerate aging in young animals, circulating factors act as anti and pro-geronic factors to modulate aging. The fact that EVs are released by many cell types *in vivo* and play important roles in cell-to-cell communication make EVs the perfect candidates for key geronic factors. Indeed, blood-borne EVs have been shown to modulate not only the immune response, but also promote angiogenesis and tissue regeneration. In addition, cellular senescence contributes to driving aging through release of soluble factors, as demonstrated by the fact clearance of senescent cells extends general healthspan. Since senescent cells release more EVs than non-senescent cells in culture and potentially in vivo, EVs likely are part of the SASP, contributing to the age-related pathologies driven by cellular senescence. Conversely, the ability of EVs from functional progenitor cells to promote tissue regeneration suggests that stem cell-derived EVs could be used therapeutically to extend healthspan. Taken together, there is substantial circumstantial evidence that EVs play key roles in aging and that regenerative EVs could be used to extend healthy aging. Finally, given the likely role of EVs in aging, components of EVs, in particular EV subsets such as L1CAM+ EVs, could be developed as biomarkers of unhealthy aging.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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