Stem Cells Targeting Inflammation as Potential Anti-aging Strategies and Therapies

Rafael Gonzalez[1], Dave Woynarowski[2] and Luis Geffner[1]

[1]DaVinci Biosciences, LLC, Yorba Linda, CA, USA. [2]Dr Dave's Best, Fleetwood, PA, USA.

ABSTRACT: Human aging is associated with a vast array of clinical disorders that all relate to the body's inability to maintain homeostasis. In our bodies, the healing process requires tight control of the acute inflammatory response. When the levels of inflammatory markers such as interleukin-6, tumor necrosis factor alpha, and C-reactive protein are elevated, there is a direct correlation with several chronic diseases of aging such as cardiovascular disease, cognitive decline, and physical disability. Extensive studies have shown strong evidence that elevated levels of these pro-inflammatory mediators may predict disease and disability in the aging population. As there is no cure for aging, a key question is how to modulate the effects of inflammation on aging and how to maintain healthy aging. Stem cells offer alternative approaches for treating various diseases/disorders. The use of stem cells as immune system modulators has shown tremendous promise. Mesenchymal stem cells (MSCs) have specific immunomodulatory properties that may help control inflammation. Several animal studies demonstrate that intravenous infusions of MSCs can decrease the pro-inflammatory response while increasing the anti-inflammatory response. Moreover, human clinical studies using MSCs in autoimmune and other inflammatory diseases have demonstrated modulation of the inflammatory response. Therefore, the use of stem cells as anti-aging therapies may offer many an alternative method of slowing down or deterring several of the detrimental aspects of aging.

KEYWORDS: aging, inflammation, stem cells, immunomodulation, stem cell therapy, anti-aging

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CORRESPONDENCE: rgonzalez@dvbiosciences.com

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Aging

Medicine has focused for centuries on prolonging and maintaining a healthy life span. In the twentieth century, life expectancy has increased significantly due to improvements in the health care sector. Advances in neonatal care, control of infectious and transmissible diseases, preventative medicine, interventional cardiology, orthopedic surgery, and neurosurgery, among many other improvements in health care, are now not only prolonging lifespan but also improving the quality of life. It is now expected that there will be 1.2 billion people 60 years or older by the year 2025.[1]

As scientists and clinicians, we are witnessing a slow but steady paradigm shift in the way we view aging. Driven by the continuous elucidation of the various cellular and molecular signaling pathways that control the repair and degeneration pathways of the cell, we are able to extrapolate the role of various pathway aberrations that accumulate in aging cells and in entire organism as it ages.[2–6] The net result is a greater understanding that aging, or at least some components of the aging process, may be a "disease" and thus may present targets or opportunities for therapeutic treatments. Indeed, chronological aging is a strong predictor but not the cause of several diseases such as cardiovascular disease. Aging is also associated with increased development of cancer. Nearly one in two individuals between the ages of 40 and 80 years in industrialized nations has an overall lifetime risk of having cancer.[7]

The literature elucidated numerous mechanisms involved in aging such as DNA, mitochondrial and telomere damage, and free-radical accumulation, all leading to apoptosis and/or senescence of cells. Human aging is associated with a vast array of clinical disorders that all relate to the body's inability to maintain cellular and molecular homeostasis. Accumulation of radical oxygen and nitrogen species, which is the simple consequence of our dependence on these gases in our respiratory chain for a modicum of cellular turnover, has predictable age-related consequences on the cellular machinery. In addition, daily inescapable events such as exposure to ultraviolet (UV) rays from sun and exposure to viruses, bacteria, and parasites all have consequences in metabolic processes that lead to damaging agents (eg, reactive oxygen species). This leads to changes at the molecular, cellular, organismal, and systemic level that our bodies can no longer combat, and maintenance of homeostasis is disrupted or challenged.[8] At the systemic level, immune and inflammatory responses have been key contributors to aging and disease.[1,8–10] In this article, we will focus on the inflammatory response that contributes to aging.

Aging and Inflammation

Evolutionarily, strong immune and inflammatory responses allowed early humans to survive to the reproductive age. However, these same response mechanisms lead to a variety of deleterious consequences now that humans routinely survive to older age.[11] Levels of inflammatory mediators typically increase with age even in the absence of acute infection or other physiologic stress.[12] In a highly intricate process, organs lose functionality and/or structural integrity both due to and leading to age-related diseases like atherosclerosis, dementia, and cancer. While the etiology of the aging process is not fully understood,[12] inflammation clearly plays a major role, inextricably linking inflammation and aging.[13,14]

Franceschi[15] and others have coined and used the term "Inflammaging" to describe the specific combination of events which accelerate the aging process. These events, which are provoked by a continuous load and stress, include the generation of damaged macromolecules and cells that accumulate with age, production of the harmful metabolites and byproducts of the body's microbial constituents, cellular senescence, and immunosenescence, to name a few.[10] These same events most certainly accelerate the diseases we commonly associate with aging such as heart disease, dementia, cancer, and degenerative joint disease. The susceptibility to diseases and death increases as a result of age-related changes in most physiological systems. Molecular inflammation is an important biological component of aging, and monitoring the molecules that mediate inflammation may be useful to assess the aging processes.[16] Specifically, monitoring blood levels of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) may give us the means to better understand the aging process. Indeed, increased blood levels of pro-inflammatory cytokines can be observed during aging, and high circulating levels of TNF-α and IL-6, even in healthy elderly populations, predict mortality independently of comorbidity.[17] Moreover, an inflammatory response appears to be the prevalent triggering mechanism that drives tissue damage associated with different age-related diseases.[18]

In our bodies, the healing process requires tight control of the acute inflammatory response. When inflammatory markers such as IL-6, TNF-α, and C-reactive protein (CRP) are elevated, there is a direct association with several chronic diseases of aging such as cardiovascular disease, cognitive decline, and physical disability. Extensive studies have shown strong evidence that elevated levels of these pro-inflammatory mediators may predict disease and disability in the aging population.[13,14] IL-6, which has been shown to have anti-inflammatory and pro-inflammatory properties, is a cytokine that is released by several cells such as vascular endothelial cells, adipocytes, and skeletal muscle cells.[19–21] The cytokine TNF-α is released mostly by macrophages and also by other cells such as lymphoid cells, mast cells, vascular endothelial cells, adipocytes, and neuronal tissue.[22–24] It is been shown in apparently healthy elderly people that levels of various cytokines—mainly IL-6 and TNF-α—are elevated even in the absence of any infection.[22,23,25–28] This is in contrast to levels in younger individuals, which maintain cytokines such as IL-6 and TNF-α tightly regulated.

In the liver, when elevations of the cytokine IL-6 occur, CRP, which is an acute phase protein, is produced. Various studies in disease and inflammation have focused on CRP, used clinically as a biomarker, or circulating plasma marker, of inflammation.[29–31] CRP activates the complement cascade and functions in innate immunity. As such, CRP is a marker of the general systemic response to insult through inflammation. CRP, through activation of the classical complement pathway and unregulated stimulation of the innate immune response, leads to tissue destruction and organ dysfunction, which potentiate age-related diseases.[13]

Inflammatory markers are associated with heart failure (HF) risk in the elderly.[32,33] A large amount of studies in cardiovascular disease indicate CRP as a predictor of the disease. More recent studies indicate that there are other predictors of cardiovascular disease in the elderly, such as the pro-inflammatory markers IL-6 and TNF-α. Increased CRP correlated with coronary heart disease (CHD) in men and women ≥65 years old in an evaluation of 10-year cumulative incidence of CHD.[29] The relative risk of CHD increased 1.45-fold when CRP (>3 mg/L vs <1 mg/L) was elevated. This is even after adjustments for the usual risk factors. Moreover, CRP appeared to be helpful in assessing the risk for both elderly men and women.[29] Congestive heart failure (CHF) risk increased by 68% and 60% per tertile increment of IL-6 and TNF-α, respectively, while levels of CRP serum ≥5 mg/dL were associated with an increased risk of 2.8-fold for CHF. IL-6 was the best predictor of HF out of the three biomarkers.[34]

Increased levels of circulating pro-inflammatory mediators also play a role in accelerating the disease progression of atherosclerosis and peripheral artery disease (PAD). Studies in PAD demonstrate a significant association between fibrinogen, CRP, IL-6, and IL-1 receptor antagonist.[35] In another PAD study, there was a significant risk association between IL-6 and tumor necrosis factor receptor 2 in PAD patients.[36]

Levels of IL-6 and TNF-α circulating in the blood stream have been shown to be elevated in type 2 diabetes patients.[37] CRP also plays a role in the development of diabetes. In the development of type 2 diabetes, increased levels of CRP and IL-6 were found to be independent risk predictors, while high levels of CRP predicted short-term incidence of the disease.[38] Interestingly, individuals with increased CRP were twice as likely to have type 2 diabetes.[39] Several studies including The Rotterdam Study, CHS, Nurses' Health Study, WHIOS, and WHS have all reported increased CRP as a predictor of type 2 diabetes even after adjustment for possible confounders such as obesity.[31,39–42]

Chronic low-grade inflammation plays a critical role in frailty.[43,44] Frailty encompasses an increased vulnerability to stress with old age. It causes a decline in strength and unintentional weight loss. Patients with frailty syndrome report fatigue, slow walking speed that increases the risk of injuries due to falls, and an inability to perform physical activity. This leads to frequent hospitalizations, disability, and eventually death.[45] A major component of frailty is sarcopenia (age-related loss of muscle mass, strength, and function).[46,47] People with the highest tertiles of circulating IL-6 levels were 1.76 times more likely to develop mobility disability.[48] It has been shown that higher levels of IL-6 and TNF-α, individually and jointly, are associated with lower muscle mass and strength. This leads to a tendency for older people to develop sarcopenia.[27] In another study with a 30-month follow-up period, it was demonstrated that higher levels of these cytokines led to a higher incidence of mobility limitation.[49] Strong associations were found between muscle decline and elevated TNF-α and its soluble receptors in a study investigating the correlation between inflammatory markers and changes in muscle mass and strength.[50] Moreover, it was found that increased IL-6 and CRP levels significantly and independently were linked to poor physical performance and muscle strength in the elderly.[51] Similar studies illustrate that increased levels of IL-6 are an independent predictor of handgrip and muscle power.[52] Data from the Women's Health and Aging Study (WHAS) demonstrate that older women with higher levels of IL-6 experienced a more drastic decline in walking ability and had an increased risk of developing physical disabilities than women with lower levels of IL-6.[53] The MacArthur Studies of Successful Aging also indicate a correlation between elevated levels of IL-6 and CRP with poor performance on walking speed and grip strength tests.[54] These studies all point to inflammation being strongly related to frailty syndrome, which leads to impaired mobility, disability, loss of muscle mass, and strength with age.

Chronic low-grade inflammation plays a role in Alzheimer's disease (AD), vascular dementia, and dementia. In the Health ABC study, investigators found that patients with increased levels of IL-6 and CRP performed poorly on cognitive test and had a greater risk of cognitive decline. After adjusting for confounding variables, the association decreased in the comparison of baseline performance, but the association remained significant in the comparison of decline between individuals with the highest and lowest tertiles of circulating inflammatory markers. Cognitive decline was significantly more likely for individuals in the highest tertile than in the lowest tertile, with the adjusted odds ratio (OR) of 1.34 and 1.41 for IL-6 and CRP, respectively.[55] In a separate study with the same cohort, it was found that metabolic syndrome contributes to cognitive impairment; however, this finding was based on stratified analysis and was observed only in the group with both metabolic syndrome and high levels of inflammatory markers.[56] In the MacArthur Studies of Successful Aging, elevated levels of IL-6 were found to be linked to poor cognitive function in the elderly and was shown to independently predict increased risk for cognitive decline in longitudinal follow-up at 2.5 years (highest tertile OR = 2.03) and 7 years (highest tertile OR = 1.90).[57] Patients with dementia, AD, and vascular dementia have similarly elevated cytokines levels; the fact that levels of these markers are elevated before the onset of clinical symptoms suggests that these cytokines may be ideal to assay in patients who are asymptomatic and high-risk.

Data from a number of studies in the elderly population have shown a strong correlation among multiple chronic diseases, disability, and elevated inflammatory markers, which are now considered strong predictors of all-cause mortality. When circulating levels of IL-6 are elevated, there is a strong correlation with death for various causes and we can strongly predict death in the near future.[58,59] There is also a strong correlation with CRP and early death.[14] In the Iowa 65+ Rural Health Study, which consisted of 1,293 elderly, healthy, nondisabled people, there was a 2× greater risk of death for those in the highest quartile of IL-6 versus the lowest quartile, while when both IL-6 and CRP were elevated, there was 2.6 times greater risk of death.[60] Indeed, elevated levels of both IL-6 and TNF-α were correlated with increased risk of death among the elderly.[61] Because these markers do not appear to be specific for any one disease or cause of death, these elevations can be viewed as reflecting a fundamental aspect of the aging process.

The cumulative effects of this complex interplay form the basis of aging. As there is no cure for aging, a key question is how to modulate the effects of inflammation on aging and how to maintain healthy aging. As we develop more understanding of aging, we continue to explore specific ways to intervene in the processes we know are at the root of aging and its accompanying diseases, at least in the Western society.

Stem Cells

In order to remain healthy, all human beings must maintain homeostasis. When replacing lost tissues, cells, or damaged organs, stem cells intervene.[62] Stem cells are undifferentiated cells with the ability to replicate indefinitely, or as needed. Stem cells may be classified according to their differentiation potential:

1. Totipotent, which are able to produce all embryonic and extra-embryonic tissue, ie, all tissues that form an individual;
2. Pluripotent, which have the ability to differentiate into any tissue from all three embryonic layers except placenta;
3. Multipotent, which have the ability to differentiate into two or more different cell types;
4. Unipotent, which only give rise to one cell type, by dividing themselves, such as the skin cells.

A stem cell is able to divide indefinitely to produce in each cycle two cells: a cell identical to itself throughout the life of the individual, and the other that will differentiate to different types of specialized cells, not only morphologically but also functionally, and that integrate to the target tissue, either in the presence or absence of damage.[63–65] Stem cells may be isolated from several locations including the blastocyst, fetal tissue (various organs of such), umbilical cord blood/tissue, and adult tissues (bone marrow, liver, fat, brain, muscle, and other tissues).

The most studied adult stem cell that was first isolated from the bone marrow is the hematopoietic stem cell (HSC); its role in our hematopoietic system has been well elucidated ever since the 1950s.[66] More recently, mesenchymal stem cells (MSCs), also first isolated from bone marrow, constitute approximately 0.001% of the mononuclear cells in the bone marrow of adults. These stromal cells, first characterized by Friedenstein et al, were described as adherent cells in vitro of fibroblast morphology and nonhematopoietic.[67–69] Caplan coined the term "mesenchymal stem cells" and was the first to describe that these cells have therapeutic potential.[70] Currently, MSCs can also be obtained from adipose tissue,[71,72] dental pulp,[73] and umbilical cord tissue,[74] to name a few. MSCs are now one of the most investigated adult stem cell types due to their inherent properties and regenerative potential in the clinic.

In order to standardize criteria for MSCs, in 2006 the International Society of Cellular Therapy (ISCT) proposed the following to define them: MSCs should be adherent in cell culture; express markers CD90, CD73, and CD105; test negative for hematopoietic markers CD34, CD45, markers for monocytes, macrophages, and lymphocytes; and be able to differentiate in vitro into osteoblasts and adipocytes under standard culture conditions.[75] In recent years, various surface markers have allowed us to identify and isolate MSCs. These markers include SH2, SH3, CD29, CD44, CD73, CD90, and CD105 cells. In addition, it has been demonstrated in vitro that MSCs are able to differentiate into mesodermal tissues such as osteoblasts, chondroblasts, adipocytes, and skeletal myoblasts.[76,77]

MSCs have the ability to migrate and target specific tissues. This nesting property (homing) by chemotaxis is an event that allows cells to migrate from a remote area in the body to find a damaged organ or tissue in a specific site.[78] Nesting is an important key in regenerative cell therapy and function. It is the mechanism by which MSCs are infused intravenously and reach the affected areas of the body to perform its regenerative functions.

Experimental models have shown that MSCs are able to regenerate damaged or injured tissues such as bone, cartilage, liver, and myocardium.[79] Both in vitro and in vivo models have demonstrated the plasticity of MSCs, giving rise to non-hematopoietic cells such as myocytes, tenocytes, and nerve cells.[64,74–77,79] The MSCs used in patients modulate immune responses, such as in collagen diseases, multiple sclerosis, bone marrow transplantation, or graft versus host disease (GVHD).[80–83]

Mesenchymal Stem Cells and Immunomodulation

MSCs have specific immunomodulatory properties. First, MSCs are non-immunogenic cells that express few major histocompatibility complex class I (MHC I) antigens. This is important, as pro-inflammatory mediators in the innate response play a role in the initial steps of rejection prior to a T-cell response.[84] Second, MSCs do not express either MHC II antigens or costimulatory molecules, rendering them incapable of activating a T-cell response. MHC II antigens are essential to initiate both humoral (activation of B lymphocytes and secretion of antibodies) and cellular (activation and proliferation of cytotoxic T lymphocytes) immune response activation. MSCs inhibit mixed lymphocyte reactions and inhibit T-cell proliferation induced by allogenic or cell mitogenic factors. Moreover, MSCs regulate the immune system by increasing the regulatory T-cell response and decreasing pro-inflammatory mediators such as TNF-α, interferon gamma (IFN-γ), and IL-4.[85] Thus, MSCs may come from an unrelated donor and be used to induce an immunomodulatory effect.[86] Finally, MSCs have been approved for pediatric GVHD and are in clinical studies for adult indications of such.[87,88] The use of MSCs for GVHD clearly demonstrates that MSCs have immunomodulatory properties.

MSCs work in a paracrine manner to foster endogenous repair. Paracrine stimulation is a cellular communication whereby chemical messengers such as cytokines, chemokines, and growth factors exert effects on neighboring cells. Studies demonstrate the wide array of chemokines, cytokines, and growth factors that are released directly or indirectly by MSCs (Table 1). While MSCs can have both pro-inflammatory and anti-inflammatory properties,[89,90] most of the

Table 1. Effects of MSCs on immune system.

DIRECT	INDIRECT	ROLE
IL-10↑	IL-10↑	Anti-inflammatory
IL-6	IL-6	Pro-inflammatory/Anti-inflammatory Control
TGF-β1↑	TGF-β1↑	Anti-inflammatory
	TNF-α↓	Pro-inflammatory
PGE2↑		Anti-inflammatory
	IFN-γ↓	Pro-inflammatory
IL-1ra↑		Anti-inflammatory
	IL-4↑	Anti-inflammatory
IL-8↑	IL-8↑	Anti-inflammatory
Soluble HLA-G↑		Anti-inflammatory
	IL-5↓	Pro-inflammatory

Note: Direct release of molecules secreted by MSCs or Indirect release via other cell types.[81,87,92,107]
Abbreviations: IL-10, Interleukin 10; IL-6, Interleukin 6; TGF-β1, Transforming growth factor beta 1; TNF-α, Tumor necrosis factor alpha; PGE2, Prostaglandin E2; IFN-γ, Interferon gamma; IL-1ra, Interleukin 1 receptor antagonist; IL-4, Interleukin 4; IL-8, Interleukin 8; HLA-G, Human leukocyte antigen G; IL-5, Interleukin 5.

literature concurs with the anti-inflammatory and immunosuppressive properties of MSCs. For instance, through interactions with dendritic cells, natural killer (NK) cells, and T helper cells 1 and 2, MSCs are associated with decreased levels of the pro-inflammatory cytokines TNF-α, IL-12, IFN-γ, and IL-5 and increased levels of the anti-inflammatory cytokines IL-10 and IL-4.[81] In addition, MSCs directly secrete the anti-inflammatory cytokines IL-10, TGF-β, LIF, soluble HLA-G, and the IL-1 receptor antagonist, among others.[87,91,92]

Several animal model studies demonstrate the anti-inflammatory properties of MSCs. In a rat liver injury model, administration of MSC-conditioned media decreased blood levels of the pro-inflammatory mediators IL-1β, TNF-α, and IL-6 and increased the levels of the anti-inflammatory mediator IL-10.[93] Moreover, in liver fibrosis models, intravenous infusion of MSCs decreased the levels of IL-1β, TNF-α, TGF-β, and IL-6 while increasing IL-10.[94] In a study using a bleomycin-induced lung injury, intravenously infused MSCs significantly decreased inflammatory cell infiltrate and decreased IL-1, IL-6, and TNF-α cytokines.[95] In a rat traumatic brain injury model (TBI), intravenous infusion also decreased brain inflammatory cell infiltration, microglia, and apoptotic cell numbers. Moreover, there was a significant decrease in the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and IFN-γ and the chemokines MCP-1, MIP-2, and RANTES. In contrast, the anti-inflammatory cytokine IL-10 was significantly increased.[96] These studies support the notion that MSCs may regulate the inflammatory response in various diseases.

Clinically, MSCs have proven to regulate the inflammatory response in autoimmune diseases and other inflammatory diseases. In a study with 172 rheumatoid arthritis (RA) and 16 systemic lupus erythematosus (SLE) patients, there was a reestablished balance in immune response from a pro-inflammatory to an anti-inflammatory state following allogenic MSCs infusion.[97,98] In addition, the RA study demonstrated a significant decrease in IL-6, TNF-α, and CRP levels.[98] In patients with ankylosing spondylitis with high disease activity, infusing allogenic MSCs decreased CRP and ankylosing spondylitis disease activity CRP levels.[99] Patients with luminal Crohn's disease refractory to biologic therapy showed similar results. In a study by Forbes et al, MSC therapy correlated with improved quality of life and improved CRP levels.[100] Taken as a whole, these studies illustrate the immunity-modulating effects of intravenous infusion of MSCs.

Conclusions and Prospects

While inflammatory cytokine levels increase inevitably to some degree with age, healthy aging, which has been defined as aging without overt disease and without loss of physical or cognitive function, is associated with smaller increases of inflammation factors over time and with a lower inflammation status.[101] Inflammation has an undeniable role in the aging process. Analyses of the combined effects of inflammation on the genome, the epigenome, the mitochondria, and the various intracellular structures and membranes have identified multiple areas for potential intervention.[1–3,8–12] These interventions include specific exercise programs, diets and nutritional supplements, and specific cell-based therapies including platelet-rich plasma (PRP) and stem cells as both mitigating agents in disease and the aging process.[102–104]

The use of stem cells as immune modulators has shown tremendous promise. We now understand that the fate of the stem cells, which we introduce as therapies, is actually of secondary importance to the role they play in eliciting favorable changes in the immune response—primarily by generating anti-inflammatory and thus "antiaging" cytokines and chemokines (Table 1). Stem cells may have the appropriate properties to serve as anti-aging therapies (Fig. 1). They function in cell replacement strategies and most importantly have immunomodulatory effects that can control the detriments of a pro-inflammatory response. The question remains as to what source of stem cells to choose for optimal results and whether stem cells from aged or diseased individuals are effective. Work must continue to characterize each of the specific stem cell types and determine their own unique regenerative applications. Further evaluation of specific stem cell sources is also necessary to define the best sources for individual therapies. Finally, additional work is required to understand the differences and similarities in the aging process of somatic cells and stem cells, each in the context of the human organism. As with any therapy, stem cells may also come with limitations. As we age, so do our stem cells, and their quantity also declines. Moreover, these older stem cells may not be effective in controlling the immune system since they are aged. Therefore, there is a need for using an allogeneic stem cell product from umbilical cord tissue or a healthy donor. While more studies are needed, MSCs currently appear to be the most broadly applicable and easily accessible cells for regenerative and anti-aging therapies. MSCs demonstrate the potential to suppress the inflammatory response, which in turn may mitigate pain. Hence, an improvement in quality of life is obtained. Stem cells have not cured any diseases, yet they have increased the quality of life for many suffering from various diseases.[99,105,106] Most importantly, they have been proven to be safe.[97–99,105,106] Controlled studies in the aging population are needed in order to justify the use of MSCs as an anti-aging strategy. These future studies would examine biomarkers of longevity or inflammation in order to evaluate the efficacy of stem cells as potential anti-aging strategies and therapies.

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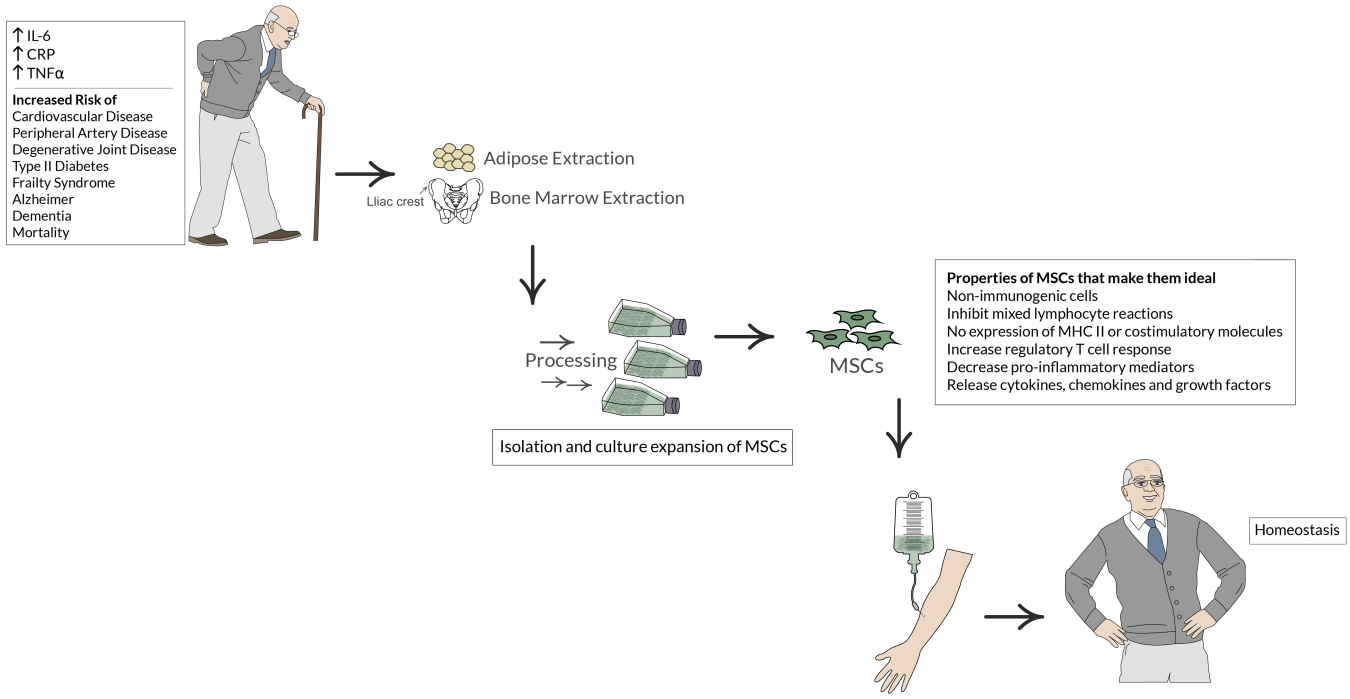

Figure 1. Potential of mesenchymal stem cells as anti-aging strategies.
Notes: Elderly individual with increased IL-6, CRP, and/or TNF-α has either a bone marrow or adipose extraction. The tissue is processed to isolate the mesenchymal stem cells and culture-expand them. The cells are introduced intravenously.
Abbreviations: IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; CRP, C-reactive protein; MHC II, major histocompatibility complex II.

Author Contributions

Conceptualization and writing: RG, DW, LG. First draft: RG. Drafting of the figure and table: RG. Jointly developed the structure and arguments for the paper: RG, DW, LG. All authors reviewed, prepared, and approved the final draft.

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