How mesenchymal stem cells affect longevity

Introduction

Mesenchymal stems cells (MSCs) are multipotent stromal cells with multilineage differentiation potential.[1] Classically they were isolated from bone marrow[2] but the current concept of MSCs has now broadened to include other tissue cells with varying multipotency.[3] MSCs are an attractive target for longevity research because they are easily harvested, rapidly expanded in vitro,[4] and their transdifferentiation potential suggests promising clinical applications in regenerative therapy.

Aging of an organism correlates with physiological decline.[5] Molecular mechanisms malfunction and disrupt cellular function, ultimately leading to systemic decline. Death occurs when the organism can no longer maintain homeostasis in the face of degradation.[5] Regeneration, in contrast, is the reversal of molecular aberrations and the replacement of lost functional units.[5] Regenerative therapy aims to delay death in addition to extending physiological competency; it aims to extend both lifespan and healthspan.[5]

In companion animal medicine, the emphasis of therapy is on healthspan (or 'quality of life'). In a 2017 study into companion animal deaths at a clinic in New Zealand, 91% of dogs that died between July 2012-June 2014, were euthanized. Of those, the highest number (32%) were euthanized as a result of decreased quality of life due to degenerative joint disease.[6] Because euthanasia is a veterinary treatment option, diseases such as osteoarthritis, inflammatory bowel disease, and keratoconjunctivitis sicca that are not life-threatening in humans can be in companion animals.

The present article will review the longevity literature and describe how MSCs play a role. The next section covers the mechanisms of stem cell aging, followed by a review of experimental studies evaluating the effect of MSCs on lifespan.

Mechanisms of stem cell aging

Stem cells experience age-related functional decline when their regenerative capacity decreases.[7] They become more susceptible to oxidative stress, accumulate toxic aggregates, and eventually succumb to apoptosis, necrosis or autophagy.[8] This process is thought to occur as a result of several mechanisms: microenvironment influence, DNA damage, mitochondrial dysfunction, epigenetic alterations, and telomere attrition.[8,9]

The stem cell microenvironment, or niche, has been a focus of particular interest. In addition to intrinsic self-regulation, stem cells receive signals from regulatory cells within their niche.[10,11] When the niche cells age, their numbers decrease and proinflammatory cytokines such as IL-6 and TNF-α increase.[8] Concentrations of circulating factors such as insulin, IGF-1, and TGF-β change, causing niche cells to malfunction and send altered signals to the stem cells.[9] While MSC transplantation focuses on replacing aged MSCs, future therapy may focus on manipulating the microenvironment to regenerate existing stem cells and prolong life.[10,12]

The effect of MSC transplantation on lifespan

In disease states, the indirect effect of MSC transplants on lifespan is clear; by slowing disease progression, MSC transplants prolong life. In humans, this effect has been described in conditions as varied as amyotrophic lateral sclerosis,[13] t-cell lymphoma,[14] and Crohn's disease.[15] A similar diversity of animal diseases improve with MSC transplants: intervertebral disc disease,[16–18] diabetes mellitus,[19] and osteoarthritis.[20–25] More recently, however, research has focused on whether MSC transplantation prolongs life in aged but otherwise healthy animals.

MSCs slow aging by enhancing cell and tissue regeneration and by improving organ function but the mechanisms are unknown.[26] Studies have demonstrated improved cardiac function,[27] postponed reproductive failure,[28] delayed lung, kidney, and colon pathology,[29] and improved offspring survival.[28] Increased lifespan is seen in mice after the administration of MSCs from young donors.[26]

In a 2011 study, researchers aimed to evaluate the effect of allogeneic MSCs on the progression of osteoporosis in old female mice.[26] The mice were irradiated then transplanted with MSCs from either young or old donor mice. In addition to slowing the progression of osteoporosis, the transplants from young donors prolonged lifespan by 125 days (890 days compared with 765 days in the control group, $P = 0.009$).[26] The lifespan of the mice that received BMSCs from old donors and the lifespan of the control group were the same ($P = 0.846$).[26]

Young rats showed similar improvements when two types of MSC transplants were compared.[30] Human amniotic membrane-derived mesenchymal stem cell transplants were compared with adipose tissue-derived mesenchymal stem cell transplants.[30] Both extended lifespan (23.4% for amniotic membrane-derived mesenchymal stem cells and 31.3% for adipose tissue-derived mesenchymal stem cells).[30] Additionally, cognitive and physical functions improved in both groups.[30]

Kovina *et al* found that MSC transplantation prolongs life even without the myeloablative conditioning traditionally used in bone marrow transplants.[31,32] Following bone marrow transplants from syngeneic young mice, the lifespan of non-myeloablative older mice increased by 31 ± 5% and their survival time from the beginning of the transplantation increased 3.25 ± 0.3 fold.[31] Importantly, the increased lifespan was accompanied by a subjectively observed good quality of life.[31] These results support findings from a 2013 study by the same researchers where mean survival time increased by 39 ± 4% in mice following MSC transplantation.[32]

The promising results of the 2019 study are unfortunately devalued by flaws in the paper. Its conclusions are undermined by the disparity in group sizes (the control group contained 20 mice, whereas the experimental group contained 51), the lack of control injections, the lack of a myeloablative control group, and the classification of injection-related embolic deaths as natural deaths. Most importantly, the results are reported differently in different sections of the paper; mice lifespan is variously reported as having increased by 28 ± 5%, 31 ± 5% and 30%, and the survival time as having increased by both 2.8 ± 0.3-fold and 3.25 ± 0.3-fold. Additionally, minor typographical and referencing errors appear and no *P* values

are provided. Taken together, these issues suggest that the article may not have undergone a rigorous and ethical peer-review process.

Multiple studies nonetheless demonstrate the lifespan-increasing effect of MSCs, as previously discussed.[26,29,30,33] Most notably, allogeneic MSC transplants improve markers of frailty in humans.[34] Frailty syndrome is characterized by age-related decrease in physical endurance and strength.[35] In addition, patients have raised inflammatory biomarkers and often experience a reduced lifespan.[35]

The randomized, double-blind phase 2 study compared allogeneic MSC transplants of either 100 million or 200 million cells with placebo. No treatment-associated serious adverse events were seen in either group after 30 days. Immunologic markers of frailty improved in both groups and physical performance improved in the 100 million group.[34] The reason for the dosing response was unclear, but researchers aim to clarify the results in a future study.[34]

While multiple studies describe the lifespan-increasing properties of MSC transplantation, MSC lysate administration does the opposite.[36] Middle-aged rats injected with adipose-derived MSC lysate (a solution of cell contents instead of entire transplanted cells) have a shorter average lifespan, decreased activity, and greater bone loss compared with those injected with saline.[36]

Previous studies found that both MSC and MSC lysate transplants improved glycemic control in mice fed a high-fat diet.[19,37] So it is possible that, while fat loss during youth is beneficial, weight loss in the latter stages of life is not.[36] Researchers postulate that MSC lysate favors cell regeneration without promoting cell clearance, creating a disparity between the two processes, and thereby shortening lifespan.[36]

MSCs and cancer

The role of MSCs in tumor pathogenesis is controversial, but MSCs appear to contribute to tumor progression. Tumors induce an inflammatory microenvironment similar to injury and MSCs are recruited to tumor sites with great affinity.[4] From there, they exert both direct and indirect actions on cancer cells, and immunomodulatory effects on tumor progression.[4] Studies suggest MSCs promote various stages of tumor pathogenesis, contributing to proliferation, invasion, metastasis, and angiogenesis.[4,38,39] As a result, MSC transplants may shorten lifespan due to their stimulatory effects on oncogenesis.

The evidence is, however, conflicting. Although the majority of studies show that MSCs stimulate oncogenesis,[4] some show that MSCs inhibit tumor progression.[40–46] The discrepancy in results may relate to disparity in experimental conditions (treatment endpoints, tissue origins, donor variability, injection sites, and transplant timing).[4,39] Given the conflicting results, it is unclear whether MSCs enhance or inhibit tumor pathogenesis[39] but they may do both. More research is needed into how MSCs affect cancer and whether transplants can shorten lifespan.

Summary

MSC transplantation is a promising avenue for regenerative medicine research. Studies show encouraging results in disease conditions in both humans and animals. This is particularly important in veterinary medicine as the conditions that respond to MSC transplants can be life-limiting in companion animals. In healthy animals, overwhelmingly, studies show a lifespan-enhancing effect with MSC transplantation. Despite the present uncertainty regarding the role MSCs play in oncogenesis, MSC therapy is considered a safe and exciting avenue of therapeutic research, promising to enhance both healthspan and lifespan.

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