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Translational Article

Guest Editorial

Stem Cell Transplantation for Frailty

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It was reported over 50 years ago that old age is associated with depletion and loss of function of stem cells (1). Since that time, there has been extensive research confirming the deleterious effects of aging on all types of stem cells, and a growing belief that such age-related changes in stem cells further accelerate tissue and organismal aging (2–4). There are two major divisions of stem cells, embryonic stem cells and adult stem cells. Embryonic stem cells are only present at the embryonic state and are pluripotent, giving rise to any fetal or adult cell type. Similarly, inducible pluripotent stem cells have the potential to differentiate into cells of various lineages, and are thus similar to embryonic stem cells. Inducible pluripotent stem cells are derived experimentally from differentiated somatic cells usually involving activation of the "Yamanaka transcription factors" (Oct4, Sox2, Klf4, Myc; "OSKM") (5). In contrast, adult stem cells, or tissue-specific stem cells, have restricted lineage potential and are present in both the developing and adult organisms. Adult stem cells respond to tissue injury throughout life by proliferation and differentiation, leading to telomere attrition and eventually reduced proliferative capacity. Today, stem cells are considered to play a central role in aging and have been included among the Seven Pillars of Aging (6) and the nine Hallmarks of Aging (7).

Transplantation of stem cells has been trailed in humans since the 1950s in particular for myeloproliferative disorders where hematopoietic stem cell transplantation has become routine care. There have also been hundreds of early-phase clinical trials using mesenchymal stem cells (MSCs) for a wide range of disorders including graft-versus-host disease, autoimmune disease, and heart disease where both regenerative and immunomodulatory effects of MSC are harnessed (8). MSC can be harvested from the patients themselves (autologous stem cell transplantation) or from a donor (allogeneic stem cell transplantation). In older patients, allogeneic stem cells harvested from younger donors are preferable because age-related changes in stem cells make them less efficient for transplantation (9). MSC have a number of biological properties that make them attractive as therapeutic agents: they home to sites of inflammation and tissue injury after an intravenous injection; they differentiate into many cell types including muscle and bone; they secrete bioactive compounds that induce tissue recovery and suppress inflammation; and they avoid host immune responses because of their immunomodulatory effects (8).

The possibility that stem cells might be "vehicles for youthful regeneration of aged tissues" has been well recognized (3,10). Mesenchymal stem cells from young mice infused into old mice improved age-related osteoporosis and also increased life span (11). Transplantation of stem cells from young mice to old mice has also been reported to improve cardiac (12) and reproductive function (13). Apart from transplanting young stem cells, an alternative therapeutic approach is to improve the function of endogenous stem cells within old animals (10). For example, induction of the "Yamanaka factors" in a progeria mouse model reduced markers of aging and increased life span (14), whereas the embryonic stem cell gene, *Nanog*, reversed aging changes in MSC from old donors (15). In summary, there are age-related changes in stem cells; animal data indicating the beneficial effects of stem cell transplantation and/or activation in various aging conditions; and extensive experience with stem cell transplantation in humans. There is clearly an opportunity to now undertake clinical trials to explore the therapeutic potential for stem cell transplants for age-related conditions in older humans.

Frailty provides an ideal target for clinical trials of MSC transplantation and aging. Frailty in older humans is associated with reduced circulating MSC, while many of the clinical features of frailty involve mesenchymal tissues, that is, the musculoskeletal system (16). Frailty is a common syndrome in old age associated with high mortality and disability. It is diagnosed in humans using either Fried's frailty phenotype or Rockwood's frailty index or variations on these two approaches (17) and has also been recognized and

defined in older mice (18). In clinical practice, the diagnosis is often made based on clinical impression rather than any formal diagnostic process. The definitions of frailty overlap with definitions of aging and sarcopenia. Frailty can be considered to be the end-stage consequence of the biological processes of aging and accumulated chronic disease. Therapies that have been trailed include exercise, diet, vitamin D, and anabolic steroids but with little success (17).

In this issue of the *Journals of Gerontology*, two clinical trials are published on the effects of MSC transplantation in frail older humans, and these trials represent potential landmarks in the treatment of frailty. Both studies are early-phase trials of a small number of participants, designed primarily to assess safety, so conclusions about efficacy need to be treated with caution. Even so, the results are striking and, at minimum, pave the way for large randomized Phase III clinical trials. The studies have been titled CRATUS (the Greek God of strength and power) and the rationale, methods and design were published previously (19).

The first study was a Phase I open-label trial (20) where allogeneic MSC collected from the bone marrow of younger donors aged 20–45 years were used to treat 15 frail patients (average age 78 years) using a single infusion of either 50, 100, or 200 million cells. After 6 months, outcomes that improved included the 6-minute walk and tumor necrosis factor α (TNFα) levels, with variable improvements in forced expiratory volume in 1 second (FEV1), Mini-Mental State Examination (MMSE), and quality of life. No significant adverse effects were recorded, and only one patient developed antibodies that could potentially neutralize the outcomes.

The second study by the same group was a Phase II randomized, double-blinded trial of allogeneic MSC at two doses (100 or 200 million cells) versus placebo (21). The participants were 30 frail patients with an average age of 76 years. No therapy-related adverse effects were documented at 1 month. Improvements were reported for physical performance, the 6-minute walk test, short physical performance exam, FEV1, and TNFα mostly in the 100 million cell groups. The authors conclude that the treated groups had "remarkable improvements" in outcomes. There are always caveats associated with interpreting efficacy in small numbers of subjects, yet it is remarkable that a single treatment seems to have generated improvement in key features of frailty that are sustained for many months.

MSC transplantation is a promising and innovative approach for the treatment of frailty in older humans, and we look forward to the results of Phase III clinical trials. That only a single treatment may be required with few if any adverse effects is of course especially appealing for older people, where the burden and adverse effects of treatments are always a major concern. We are very pleased that the authors chose to publish their groundbreaking trials in the *Journals of Gerontology* as this attests to the leading role this journal has developed as a platform for translational research in aging. Because of the far-reaching implications of this research, we are inviting researchers to submit articles for a special translational edition of the *Journals of Gerontology: Biological Sciences* and the *Journals of Gerontology: Medical Sciences* on stem cells and aging.

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Conflict of Interest

None reported.

References

1. Albright JF, Makinodan T. Growth and senescence of antibody-forming cells. *J Cell Physiol*. 1966;67(suppl 1):185–206. doi:10.1002/jcp.1040670415
2. Rao MS, Mattson MP. Stem cells and aging: expanding the possibilities. *Mech Ageing Dev*. 2001;122:713–734. doi:10.1016/S0047-6374(01)00224-X
3. Rando TA, Wyss-Coray T. Stem cells as vehicles for youthful regeneration of aged tissues. *J Gerontol A Biol Sci Med Sci*. 2014;69(suppl 1):S39–S42. doi:10.1093/gerona/glu043
4. Mistriotis P, Andreadis ST. Vascular aging: molecular mechanisms and potential treatments for vascular rejuvenation. *Ageing Res Rev*. 2017;37:94–116. doi:10.1016/j.arr.2017.05.006
5. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126:663–676. doi:10.1016/j.cell.2006.07.024
6. Kennedy BK, Berger SL, Brunet A, et al. Geroscience: linking aging to chronic disease. *Cell*. 2014;159:709–713. doi:10.1016/j.cell.2014.10.039
7. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153:1194–1217. doi:10.1016/j.cell.2013.05.039
8. Wang S, Qu X, Zhao RC. Clinical applications of mesenchymal stem cells. *J Hematol Oncol*. 2012;5:19. doi:10.1186/1756-8722-5-19
9. Tashiro J, Elliot SJ, Gerth DJ, et al. Therapeutic benefits of young, but not old, adipose-derived mesenchymal stem cells in a chronic mouse model of bleomycin-induced pulmonary fibrosis. *Transl Res*. 2015;166:554–567. doi:10.1016/j.trsl.2015.09.004
10. Neves J, Sousa-Victor P, Jasper H. Rejuvenating strategies for stem cell-based therapies in aging. *Cell Stem Cell*. 2017;20:161–175. doi:10.1016/j.stem.2017.01.008
11. Shen J, Tsai YT, Dimarco NM, Long MA, Sun X, Tang L. Transplantation of mesenchymal stem cells from young donors delays aging in mice. *Sci Rep*. 2011;1:67. doi:10.1038/srep00067
12. Edelberg JM, Tang L, Hattori K, Lyden D, Rafii S. Young adult bone marrow-derived endothelial precursor cells restore aging-impaired cardiac angiogenic function. *Circ Res*. 2002;90:E89–E93. doi:10.1161/01.RES.0000020861.20064.7E
13. Selesniemi K, Lee HJ, Niikura T, Tilly JL. Young adult donor bone marrow infusions into female mice postpone age-related reproductive failure and improve offspring survival. *Aging (Albany, NY)*. 2008;1:49–57. doi:10.18632/aging.100002
14. Ocampo A, Reddy P, Martinez-Redondo P, et al. In vivo amelioration of age-associated hallmarks by partial reprogramming. *Cell*. 2016;167:1719–1733.e12. doi:10.1016/j.cell.2016.11.052
15. Han J, Mistriotis P, Lei P, Wang D, Liu S, Andreadis ST. Nanog reverses the effects of organismal aging on mesenchymal stem cell proliferation and myogenic differentiation potential. *Stem Cells*. 2012;30:2746–2759. doi:10.1002/stem.1223
16. Gunawardene P, Bermeo S, Vidal C, et al. Association between circulating osteogenic progenitor cells and disability and frailty in older persons: the Nepean osteoporosis and frailty study. *J Gerontol A Biol Sci Med Sci*. 2016;71:1124–1130. doi:10.1093/gerona/glv190
17. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14:392–397. doi:10.1016/j.jamda.2013.03.022
18. Kane AE, Huizer-Pajkos A, Mach J, et al. A comparison of two mouse frailty assessment tools. *J Gerontol A Biol Sci Med Sci*. 2017;72:904–909. doi:10.1093/gerona/glx009
19. Golpanian S, DiFede DL, Pujol MV, et al. Rationale and design of the allogeneiC human mesenchymal stem cells (hMSC) in patients with aging fRAilTy via intravenoUS delivery (CRATUS) study: a phase I/II, randomized, blinded and placebo controlled trial to evaluate the safety and potential efficacy of allogeneic human mesenchymal stem cell infusion in patients with aging frailty. *Oncotarget*. 2016;7:11899–11912. doi:10.18632/oncotarget.7727
20. Golpanian S, DiFede DL, Khan A, et al. Allogeneic human mesenchymal stem cell infusions for aging frailty. *J Gerontol A Biol Sci Med Sci*. 2017;72:1505–1512
21. Hare JM, Tompkins B, Difede D, et al. Allogeneic mesenchymal stem cells ameliorate aging frailty: a phase II randomized, double-blinded, placebo controlled clinical trial. *J Gerontol A Biol Sci Med Sci*. 2017;72:1513–1521.