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Invited Contribution

Potential of Stem Cell-Based Therapy to Restore Function in Aging Systems: Are We There Yet?

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Abstract

While there is extensive interest in geroscience approaches to health and disease, few basic science discoveries have made their way into clinical trials. Herein, we comment on cell-based therapies, in which supplementing robust stem cell capacity to aged systems theoretically could lead to sustained improvement. This exciting approach has undergone translational development, and we highlight studies targeting a single system and others aimed at treating overall aging frailty by restoring the aged stem cell niches that underly diminished endogenous regenerative capacity.

Keywords: Aging, Clinical trials, Intervention, Rejuvenation, Stem cells

Adult stem cells are responsible for the maintenance and repair of systems throughout aging, and these cells exhibit declining endogenous capacity to heal tissues and maintain organ homeostasis in aged organisms (1). Thus, aged stem cells may not retain the full capacity they had in youth to stoutly preserve, repair, and maintain their host system against the ailments of time. Studies of these rare cells in aging organisms have identified critical alterations in their functional potential and altered phenotypes that parallel well within the range of the age-associated characteristics of the tissue or system where they reside. For example, in the hematopoietic system, the aged stem cell compartment becomes less heterogeneous and dominated by cells that have a proclivity to differentiate into cells of the myeloid lineage. In mouse models, transplants of these aged stem cells show cell-autonomous maintenance of the lineage-biased differentiation commitment. In humans, a similar phenomenon occurs with clonal expansion of hematopoietic stem cells (HSCs) that have an acquired selective advantage, often attributed to mutations in key epigenetic regulators (2, 3). These aberrations ultimately can affect the entire hematopoietic system and contribute to age-associated disease (4). In the musculoskeletal system, aging phenotypes of skeletal muscle wasting, or sarcopenia, have been associated with decreased numbers and less potent functional activation of the muscle stem cells (MuSCs). The loss of potential in the MuSCs contributes to the inability of muscles to retain or reverse age-associated loss of muscle mass, driven by myocyte loss (5). In skin, where some of the most apparent age-associated physical changes can be recognized, including hair loss, increased skin fragility, delayed wound healing, and the increased occurrence of skin cancer, all phenotypes are associated with changes in the skin-specific stem cells (including hair follicle, epidermal, sweat duct, and sebaceous stem cells) (6).

In murine models, there have been some therapeutic successes reported when aged systems have an influx of stem cells with restored or robust function. One such study showed that ex-vivo treatment of aged MuSCs with a small-molecule inhibitor and a culturing on a porous hydrogel substrate was able to restore potential to the aged MuSCs, and the improved potential was able to impart restored muscle repair when these cells were transplanted into injured, aged muscle (7). Another exciting study on aged MuSC rejuvenation recently reported that transplantation of aged MuSCs pulsed with transient expression of iPSC reprogramming factors was able to repair injured muscled from aged mice at a rate similar to young MuSCs. These data were also translated in human studies where aged human MuSCs were transiently reprogrammed and transplanted back to the aged donor and showed increased new tissue formation (8). On the flip side of these very positive results of improved muscle repair from reprogrammed

MuSCs in the aged environment, HSCs transplants into aged mice did not have such promising results. In transplants of young, robust HSCs into aged recipient mice, studies report that the aged niche, where the donor stem cells home to in the bone marrow, have negative effects on the robust stem cells populations, altering the cell-intrinsic potential of the transplanted HSCs (9, 10). Thus, in aged individuals, there may be complex interactions between intrinsic stem cell alterations and the systemic alterations that both need to be addressed for more effective stem cell therapies.

In human aging interventions that have shown promise, there may be synergy between both the direct effects on stem cells potential and indirect effects altering the niches and/or systemic factors to alleviate age-associated phenotypes (11). Many aging interventions target different pathways, a common effect reported in studies with mitigated aging phenotypes in humans is a reduction in circulating inflammatory cytokines. Reducing the overall levels of inflammation may alleviate some of the systemic stress on stem cells niches. Such reduction of inflammation has been reported in a wide variety of aging interventions including treatments with resveratrol (12), NAD^+ supplementation (13), senolytics (14), and caloric restriction (15). Along similar lines, but directly using stem cells/cell-based therapy, the concept of rejuvenating aged niches and recapitulating their bioactivity has been tested using allogeneic bone marrow-derived mesenchymal stem cells (MSCs) in the CRATUS phase I and II trials (16, 17). Individuals participating in these trials were of an average age of 78 and had mild clinical frailty. Evidence of bioactivity of MSC infusions was suggested by increases in 6-minute walk distance and reductions in circulating levels of TNF-α (an inflammatory cytokine). Importantly, these early findings are being built upon by ongoing larger clinical trials being conducted of MSC infusions in individuals with aging frailty that will enlarge the clinical database of this therapeutic approach and help better define cellular, metabolic, and biochemical markers of bioactivity (18, 19).

These promising results from MSCs transplants in aged individuals marry the concepts of restoring the environment as well as providing healthy donor stem cells to maintain these positive benefits. Thus, these stem cell transplants may not only be supplementing the system with additional, youthful stem cells, but also "restoring the soil" of the aged environment. Thus, the treated individuals may not only be less frail, but may also have a more hospitable niche for other stem cell treatments. By mitigating the more hostile, aged environment, there may be a new opening for harnessing the power of other adult stem cell therapies. The critical step in establishing this therapeutic principle is the systematic conduct of well-powered clinical trials, designed with appropriate enrollment criteria and end-points that could lead to approvals by regulatory agencies.

As we piece this puzzle together through sound scientific discovery, we are beginning to understand the distinct properties of these systems during aging, and how interventions with robust beneficial potential in animal models could be translated to humans. However, we must ensure that well-designed clinical trials are conducted to effectively pave the way. Unfortunately, the robust potential of stem cells and the desire to obtain new therapies or rejuvenation has led to predatory practices touting amazing results in unvalidated, unapproved stem cell uses (20). This can range from the, likely harmless, face creams imbued with stem cells claiming to rejuvenate aged skin to potentially harmful practices of non-FDA-approved therapies to "cure" diseases.

Harnessing the full potential of stem cells could lead to the mitigation of most aging phenotypes but, like most things worthwhile, we need to be patient to develop the most robust effects with these therapies. It will likely require the cooperation between multiple players—whether combinations of stem cell transplants or coordination between stem cell transplants and other pharmacological interventions. However, we may be just at the beginning of understanding these complex interplays, and thus it remains critical for leaders in the field to encourage and develop rigorously designed, and appropriately powered clinical trials that assess the safety and risk potential and, most importantly, provide the best opportunity to lead to effective and exciting novel therapeutic tools.

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Conflict of Interest

J.M.H. is a cofounder, board member, and paid consultant of Longeveron Inc. J.M.H. is also an inventor of technology licensed to Longeveron Inc. This relationship is reported to the University of Miami, and a management plan is in place. The University of Miami is an equity owner in Longeveron, which has licensed intellectual property from the University of Miami. I.B has no conflicts to disclose.

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