Stem Cells, Aging, Challenges and the Way Forward

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Short Communication

Stem cells are wonderful biological gifts of nature for renewal and regeneration of cells and tissues as well as rejuvenation of organisms. They are naturally endowed with immense potential for self-renewal and differentiation of almost all types of cells, therefore, are able to perform repair of damaged tissues and maintain tissue homeostasis. This precise task of tissue homeostasis is accomplished by continuous secretion of various cell growth factors and replacement of damaged/dead cells by proliferation of resident stem cells in the tissues. The damaged site of the tissue can also attract stem cells from other sites of the body. This is carried out by a mechanism of chemotaxis, which involves a gradient of diffusible chemoattractant molecules secreted by the damaged cells and their cognate receptors present on the surface of the stem cells. The microenvironment of the site of tissue repair also play important role in this process. However, as organisms age, the stem cell-based tissue replenishment mechanism slows down considerably, thus allowing cellular accumulation of damaged DNA and other biomolecules, resulting into various degenerative pathologies such as Alzheimer’s disease, Parkinson’s disease, Amyotrophic lateral sclerosis, diabetes, Multiple system atrophy, Rheumatoid arthritis, Muscular dystrophy etc in the concerned nervous, metabolic, bone and muscle tissues of the body respectively [1-2]. These progressive degenerative diseases, in turn, alter the microenvironment of the tissues even more, which further affects the stem cell differentiation and/or trans-differentiation-based tissue regeneration and repair processes as the deteriorated niche alters the stem cell maintenance and function, causing them to undergo quiescence, dormancy and apoptosis. Ever expanding research has revealed the crucial role played by lack of function of stem cells in aging of organisms. The important question, in this context is whether stem cells affect aging or aging affects stem cells remains to be fully understood. But most probably, it could be both ways depending on the biological context and age of an organism. However, there is no ambiguity about depletion of stem cells reservoir as a function of age. Aging induces a paradigm-shift in intrinsic, extrinsic and systemic signalling in cells, changing the overall molecular landscapes and functions of tissues, in turn, it cumulatively drives the loss of stem cell number and function. For example, the aged human brain has been found to possess significantly lower number, yet functional, of neuronal progenitor cells compared to the young brain. Moreover, these few cells were found to be inclined more towards glial differentiation rather than neuronal differentiation, suggesting reasons for cognitive and memory decline in aged individuals [3]. Besides, stem cell functions also change as they try to keep pace with ever-changing structure, growth, maintenance and regeneration demands of aging tissues. For example, during embryonic development, stem cells divide very rapidly to fulfill the responsibility towards growing tissues and organs. But as the organism advances in age, except for few tissues like bone marrow, intestinal surface and hair follicles, the stem cells slow down their division and undergo quiescence otherwise they would lead to abnormal growth and cancer. Stem cell quiescence may be caused by age-induced change in the microenvironment or any other patho-physiological condition. Although stem cell quiescence protects it from functional exhaustion and accumulation of damaged DNA, it also allows persistence of mutations as the cells with damaged DNA continue to live within the tissue, affecting the working of normal fraction of stem cell population [4]. Like neural stem/progenitor cells, other category of stem cells, such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), melanocyte stem cells also undergo age-dependent decline in terms of function and abundance. Apart from stem cell quiescence, other mechanisms, such as terminal differentiation, apoptosis, and differential niche-based selection pressure may also lead to decline in stem cell pool of an organ, compromising its regenerative and repair ability [5].

Regenerative properties of stem cells may be restored by many ways, alleviating the age-associated pathologies, reducing the multiple risk factors and extending the health-span of organisms. Transplantation of stem cells from young to old/aged organisms have been found to reduce the oxidative damage to the somatic tissues, restoring the intrinsic regenerative potential...
and tissue homeostasis. The testimony of tissue regenerative and clinical potential of stem cells is evidenced in the historic market authorization of stem cell therapy Prochymal® (remestemcel-L), world’s first approved stem cell drug under Health Canada’s Notice of Compliance with conditions (NOC/c) pathway. Prochymal, an intravenous formulation of mesenchymal stem cells (MSCs) as its active ingredient, is made from the bone marrow of healthy donors aged in between 18-30 years. For preparation of prochymal, MSCs are isolated from a healthy donor’s bone marrow, cultured under properly maintained aseptic conditions. Developed by Osiris Therapeutics, Canada, Prochymal is currently available in several developed countries such as United States under Expanded Access Program, and being used for the treatment of acute graft-versus-host disease (GvHD) in children unresponsive to currently available treatment, including steroids [6]. Similarly, Hematopoietic stem cells (HSCs) the blood and immune cells forming stem cells have shown great promise in treatment of several age-based degenerative and immunological diseases, including multiple sclerosis (MS). In clinical trials, autologous hematopoietic stem-cell transplantation (aHSCT) has shown durable response, lasting even for more than 14 years in patients with MS. In addition, post-hoc result analysis showed very positive and encouraging findings in terms of reduced sickness and remarkable neurological recoveries [7]. Similarly, the recombinant colony stimulating factor (CSF) has been used in clinic to boost lymphocyte count in patients with blood cancer and reduced immunity.

Designing stem cell based treatment regime for age-associated disorders are quite challenging tasks for the researchers and clinicians around the world. Because aging is a dynamic biological process, which needs an insightful understanding about ever-changing structural and functional landscapes of various tissues and organs as the organisms age. These progressively deteriorating changes vary enormously among organs and from one individual to another, making the entire process even more difficult and cumbersome. The variations in regenerative and functional decline are, among others, attributed to the varying abundance of long-lived tissue stem cells endowed with the capacity to produce requisite daughter cells as and when need arises.

Though there have been empirical discovery of multiple promising nonclinical and clinical findings, we still have a long way to travel before we could realize the potential of stem cell therapy so much so that they can be completely integrated in treatment regime of age-associated diseases and disorders. To do so, we need to leverage various research findings to develop greater insights into age-related disease aetiologies, and devise compatible and holistic cell/tissue based therapy accordingly. Considering aforementioned promises and challenges presented by stem cells, cell therapy and regenerative medicine, we need to be very careful and cautious while designing stem cell-based therapy for treating age-associated degenerative diseases. However, this field provides enormous opportunity for biology, medicine and industry to work together for science, innovation, business, service and clinical practice for a better future.

References