REJUVENATION RESEARCH
Volume 19, Number 1, 2016

DOI: 10.1089/rej.2015.1676

Aging of Stem and Progenitor Cells: Mechanisms, Impact on Therapeutic Potential, and Rejuvenation

Jasmin Nurkovic,[1] Vladislav Volarevic,[2] Majlinda Lako,[3] Lyle Armstrong,[3] Nebojsa Arsenijevic,[2] and Miodrag Stojkovic[2,4]

Abstract

It was once suggested that adult or tissue-specific stem cells may be immortal; however, several recently published data suggest that their efficacy is limited by natural aging in common with most other somatic cell types. Decreased activity of stem cells in old age raises questions as to whether the age of the donor should be considered during stem cell transplantation and at what age the donor stem cells should be harvested to ensure the largest possible number of viable, functional, and non-altered stem cells. Although stem cells remain active into old age, changes in stem cells and their microenvironments inhibit their regenerative potential. The impact of aging on stem cell populations differs between tissues and depends on a number intrinsic and extrinsic factors, including systemic changes associated with immune system alterations. In this review, we describe key mechanisms of stem and progenitor cell aging and techniques that are currently used to identify signs of stem cells aging. Furthermore, we focus on the impact of aging on the capacity for proliferation, differentiation, and clinical use of stem cells. Finally, we detail the aging of embryonic, mesenchymal, and induced pluripotent stem cells, with particular emphasis on aging mechanisms and rejuvenation.

Introduction

In the early 1960s, the aging process of cells was first described in a seminal study by Hayflick and Moorhead in which they observed that normal human fibroblasts were able to enter a state of irreversible growth arrest after serial cultivation under *in vitro* conditions.[1] Medvedev's attempt[2] to simplify the theory of aging resulted with more than 300 different ''theories.'' Fortunately, recent advances have resulted in a significant simplification of the theoretical underpinnings of aging research, and this, combined with the greatly increased power of experimental techniques to investigate the phenomenological complexities of the senescent phenotype, has cleared a path toward better understanding of the aging process.[3] Nevertheless, the intrinsic complexity of aging remains a significant challenge to understand how cell aging is caused.

Today, aging is still an unclear phenomenon in human biology. Moreover, there is sound scientific evidence that stem cells are aging. The latest findings raise new questions as to whether the age of the donor should be considered during the transplantation of stem cells and to define the best procedure for obtaining the largest possible number of stem cells *in vitro*. Because of the high expectations regarding the therapeutic application of stem cells, inevitably, in the context of normal aging, several important questions arise that we will try to answer in this review.

Mechanisms of Stem Cells Aging

There are several factors that contribute to stem cell aging—shortening of telomeres, de-repression of the gene locus *INK4a/ARF* and cell cycle regulators, accumulation of DNA damage, epigenetics, changes in mitochondrial structure, signaling pathways, as well as systemic factors.

Shortening of telomeres

Telomeres are nucleoprotein complexes at the chromosome ends. They consist of linear arrays of repeat sequences that are 5–15 kb in humans but considerably larger in mice.[4] In many human somatic tissues, a decline in cellular division capacity with age appears to be linked to the fact that the telomeres get progressively shorter as cells divide. The reason for this is the absence of the enzyme telomerase,

[1]Stem Cell Laboratory, Department of Biomedical Sciences, State University of Novi Pazar, Novi Pazar, Serbia.
[2]Centre for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia.
[3]Institute of Genetic Medicine, International Centre for Life, Newcastle University, Newcastle upon Tyne, United Kingdom.
[4]Spebo Medical, Leskovac, Serbia.