American Journal of Aging Science and Research

Di Bernardo, Am J Aging Sci Res
2020; 1(1): 7-8.

Editorial

Effect of senescence on behavior of mesenchymal stromal/stem cells

Giovanni Di Bernardo*

Department of Experimental Medicine, Biotechnology and Molecular Biology Section, University of Campania "Luigi Vanvitelli,", Naples, Italy

*Author for correspondence:
Email: gianni.dibernardo@unicampania.it

Received date: May 27, 2020
Accepted date: May 28, 2020

Citation: Di Bernardo G. Effect of senescence on behavior of mesenchymal stromal/stem cells. Am J Aging Sci Res 2020; 1(1): 7-8.

During lifespan the homeostasis and repair of organs and tissues are guaranteed by the adult stem cell population. Among them, mesenchymal stromal cells (MSCs), which contain a subpopulation of multipotent stem cells, are emerging as promising candidates for cell therapy of numerous diseases. MSCs are non-hematopoietic cells capable of self-renewal and differentiation into osteocytes, adipocytes, and chondrocytes. They can be isolated and expanded from the stroma of many organs and tissues such as bone marrow and adipose tissues [1]. According to the criteria establish from International Society for Cellular Therapy (ISCT), MSCs are characterized by their capability to adhere to plastic under standard culture conditions; their positivity to surface markers CD105, CD90, and CD73 and, negativity to MHC-II, CD11b, CD14, CD34, CD45, and CD31; their robust differentiation potential into various tissues of mesodermal origin. Nevertheless, the isolation of MSCs according to ISCT criteria does support the purification of homogenous MSC populations, it produces heterogeneous, nonclonal cultures of stromal cells containing stem cells with different multipotential properties, committed progenitors, and differentiated cells [2]. Besides the multilineage differentiation capacity and the considerable potential for in vitro expansion, MSCs have a remarkable immunoregulatory and anti-inflammatory properties, they can secrete trophic factors that favor tissue remodeling and have the ability to reach the site of injury. These peculiar properties made MSCs useful candidates for the treatment of various congenital and acquired diseases [3].

It is well known that cell therapy protocols require hundreds of million MSCs per each treatment and, consequently, these cells need to be expanded *in vitro* for many times before being implanted.

This necessary procedure that ensures the required number of MSCs pose an important issue. The lack of standardized procedures regulating *ex vivo* growth greatly affects MSC biological properties. It has been widely demonstrated that *in vitro* expansion of MSCs can give rise to replicative senescence.

Senescence is the permanent cell cycle arrest accompanied by resistance to apoptosis that occurs in response to excessive intracellular or extracellular stress or damage and determine the loss of cellular functions over time. Although senescent cells undergo irreversible growth arrest, they are metabolically active and are characterized by specific attributes, such as enlarged and flattened morphology, high β-galactosidase activity, telomere dysfunctions, senescence-associated heterochromatin foci, impairment of DNA repair mechanisms, changes in metabolism and alterations in gene expression. Moreover, senescent cells secrete a myriad of factors, including inflammatory cytokines, growth factors, matrix metalloproteinases and mitogens, which are indicated as the senescence-associated secretory phenotype (SASP) [4].

Senescence is a dynamic and multistep process that starts from a pre-senescent status and goes on until it reaches full senescence. The passage from early to full senescence is characterized from transient to a stable cell-cycle arrest sustained by P16-RB and/or P53–P21 pathways. The progression to full senescence is also accompanied by chromatin remodeling and changes in SASP production [5]. The precise SASP components depend on both the cell type and nature of the senescence stimulus. Recent studies have proposed that SASP may contribute to cellular proliferative arrest through autocrine/paracrine pathways. Secreted factors can regulate the senescence response and may represent a danger signal that sensitizes normal neighboring cells to senesce. Therefore, senescent cells must be

avoided in any cell batch destined for clinical application in order to preserve their therapeutic potential. Nowadays, the milestone in MSC research field is the discovery of senescence markers able to determine the quality of the *in vitro* cells destined for clinical use.

Growing evidence has indicated that beside the *in vitro* replicative senescence, MSCs may undergo senescence *in vivo*. Since MSCs constitute a reservoir of precursor multipotent cells ensuring the homeostasis and repair of adult organs and tissues, their senescence is considered partly responsible for organismal functional decline during chronological aging. In addition to declining function in many organs, aging is frequently associated to long-term disability and morbidity. Frailty, declining cognitive function, diabetes, kidney failure, sarcopenia, osteoporosis, loss of physiological resilience and many other ailments are common as organisms age. It has been reported that the selective elimination of dysfunctional senescent cells extends median life span and prevents or attenuates age-associated diseases in mice. To date the researchers' effort is focused on the development of senolytic drugs able to eliminate the dysfunctional senescent cells. Senolytic drugs specifically target senescent cells by inducing apoptosis of senescent but not non-senescent cells.

Both *in vivo* and *in vitro* MSC senescence can strongly affect cell properties with important clinical implications. It has been widely reported that the development of robust senescence and aging markers necessarily requires a comprehensive profile of SASP composition. Indeed, several stress evoke a senescence and a SASP response, which in turn give rise multiple phenotypes associated with aging. Moreover, a deep understanding of mechanisms involved in the development and progression of MSC senescence and the set-up of standardized methods to monitor it by also represent a critical issue. The identification of senolytic drugs able to eliminate senescent cells or to revert senescent phenotypes seems to be of particular interest. Reliable senolytic agents might be useful for the treatment of age-related diseases and for MSC rejuvenation, thus allowing to reduce or bypassing expansion limitations.

References

1. Squillaro T, Peluso G, Galderisi U. Clinical trials with mesenchymal stem cells: an update. Cell Transplantation. 2016 May;25(5):829-48.

2. Galderisi U, Giordano A. The gap between the physiological and therapeutic roles of mesenchymal stem cells. Medicinal Research Reviews. 2014 Sep;34(5):1100-26.

3. Castro-Manrreza ME, Montesinos JJ. Immunoregulation by mesenchymal stem cells: biological aspects and clinical applications. Journal of immunology research. 2015; 2015:394917.

4. Özcan S, Alessio N, Acar MB, Mert E, Omerli F, Peluso G, Galderisi U. Unbiased analysis of senescence associated secretory phenotype (SASP) to identify common components following different genotoxic stresses. Aging (Albany NY). 2016 Jul;8(7):1316.

5. Alessio N, Capasso S, Ferone A, Di Bernardo G, Cipollaro M, Casale F, et al. Misidentified human gene functions with mouse models: the case of the retinoblastoma gene family in senescence. Neoplasia. 2017 Oct 1;19(10):781-90.