International Journal of
Stem Cells & Research

Review Article

Reprogrammed Stem Cells and Ageing Suppression -

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Submitted: 25 July 2020; **Approved:** 29 July 2020; **Published:** 30 July 2020

Cite this article: Laugi H. Reprogrammed Stem Cells and Ageing Suppression. Int J Stem Cells Res. 2020; 4(1): 006-008.

ABSTRACT

Stem cells seem boon to biological science. They are the special cells that give rise to a number of different cells thereby performing specialized functions. For instance, a single stem cell can be specialized to perform functions of nerve cells, blood cells, osteoblast, etc. after undergoing genetic reprogramming. Haematopoietic Stem Cells (HSCs), found in bone marrow, can be reprogrammed to perform functions of nerve cells and so on. Despite several complications seen in stem cell therapy, these cells have created a new platform for the treatment of a number of dreadful diseases like cancer, diabetes, cardiovascular diseases, sight loss, memory loss, Alzheimer's disease, etc. They are used in checking the efficiency of new drugs. As for example, a drug prepared by a researcher to cure a nerve disease can test on nerve cells created from stem cells in a lab before undergoing human trials. Recent discoveries in the field of stem cell therapy have revealed further chances of extending lifespan using reprogrammed stem cells.

Hypothalamus is a multi-tasker. It controls hunger, memory, temperature, sleep, etc. Recent discovery has revealed that it plays significant role in controlling ageing. The continuous supply of neural stem cells to it, keeps us young. Molecular pharmacologist Dongsheng Cai from the Albert Einstein College of Medicine in Bronx says, "The number of hypothalamic neural stem cells declines in an animal with increase in age." This is how ageing occurs. If we supply neural stem cells to the hypothalamus to replace damaged cells, we control ageing and extend lifespan. Tests in mice have proved this. Cai and his team used a toxin to destroy 70% of neural stem cells in mice. This caused mice to live few months less. To see if an opposite effect was also possible, the team injected hypothalamic neural stem cells taken from new born mice into brains of two groups of mice. One of these groups was made up of normal old mice; the other had had the hypothalamus disrupted by the toxin. The treated animals lived significantly more than the untreated, enjoying a lifespan 15% longer than the untreated animals. Hence, this therapy creates a new way to extend lifespan [1].

Mechanism of Cellular Ageing

When stem cells divide, their telomeres shorten, and cells stop dividing and die. When a subset of HSCs was taken from adult bone marrow and cord blood, telomere of HSC taken from adult bone marrow was found to be shorter than that from cord blood. This shows that a progressive decline in telomere length occurs with age in these cells [2]. Telomerase is a reverse transcriptase protein encoded by TERT (Telomerase Reverse Transcriptase) gene and a template RNA TERC (Telomerase RNA Component). This enzyme prevents this decline in stem cells by lengthening telomeres, but the decrease in activity of this enzyme has been reported in ageing process [3]. When mice are engineered to lack telomerase, their telomeres shorten, and the animals age much faster than the normal mice. In somatic cells, there is decrease in the activity of this protein after birth. Hence, telomere length is gradually shortened after cell division thereby triggering cellular senescence. In Embryonic Stem

Cells (ESCs), this protein is activated and hence maintains telomere length. Although telomere shortening occurs even in most of the stem cells, rate is quite slow than other normal somatic cells [4].

Effects of Ageing on Stem Cells

Ageing is responsible for most of the human diseases. About 150000 people die every day across the globe. Among them, roughly two-third die due to age related diseases. Stem cell research has become focal point of biomedical research since 1998, when Dr. James Alexander Thomson made scientific breakthrough in successful generation of ESCs lines from human blastocytes. Stem cells replenish dying cells and regenerate damaged tissues throughout the life. However, these cells appear to age with the person. As they age, their functional ability also deteriorates. Several factors contribute to ageing associated stem cell dysfunction and hence, ageing-induced-diseases.

Changes in microenvironmental factors like hormonal, immunologic and metabolic disorders with age affect stem cell function. Ageing related tissue degeneration like osteoporosis is due to impaired Mesenchymal Stem Cell(MSC). Metabolic alterations of hyperglycemia and hyperinsulinemia are important pathologic factors in ageing and MSC dysfunction. In human, sex hormones especially estrogen production alters with age leading to several serious diseases. Estrogen deficiency changes MSCs to adipocytes [5].

Ubiquitin-proteasome system is the major protein degradation system in the cell. Specifically, the proteasome helps to clear abnormal proteins and degrade short lived proteins. An age related decrease in proteasome activity weakens cellular capacity to remove oxidatively modified protein and causes different diseases [6].

Mitochondrial dysfunction triggers imbalance between Oxidative Phosphorylation (OXPHON) and glycolysis. ATP synthesis is associated with mitochondria. In OXPHON, oxygen is needed to receive electrons from protein complexes. This allows more electron and high energy molecules to be passed along, and maintains hydrogen pumping to produce ATP. When we run out of oxygen and produce lactic acid, fermentation takes place. Fermentation starts only after glycolysis, replacing citric acid cycle and OXPHON to produce ATP [7]. These are controlled by both mitochondrial DNA and nuclear genomic DNA leading to epigenetic alterations as shown in figure. DNA contains all the information required by cell to perform specialized functions, so DNA damage leads to cellular senescence and death triggering depletion of stem pool.

Ageing Suppression

Ageing induces stem cell dysfunction. It has been one of the severe problems especially in the developed countries due to busy lifestyle, though not severe in developing countries like Nepal. How to suppress ageing? is one of the challenges seen in medical field. Research is going on to solve this mystery.

What we can do to suppress this is the use of Induced Pluripotent Stem Cells (IPSCs). These are a type of stem cells that can be generated from adult stem cells undergoing genetic editing and reprogramming. So, IPSCs can be reprogrammed to edit genetic defects that are responsible of premature and hasty ageing. This helps in rejuvenation of senescent cells. We can use these cells to understand the dynamics of Parkinson's disease, Alzheimer's disease, etc. As for instance, dystrophin connects cytoskeleton of a muscle fibre with extracellular matrix. Ageing affects this. What we can do to cure this is use of reprogrammed stem cells to express PAX7. This will surely help in myogenesis and the cells can be differentiated into muscle cells.

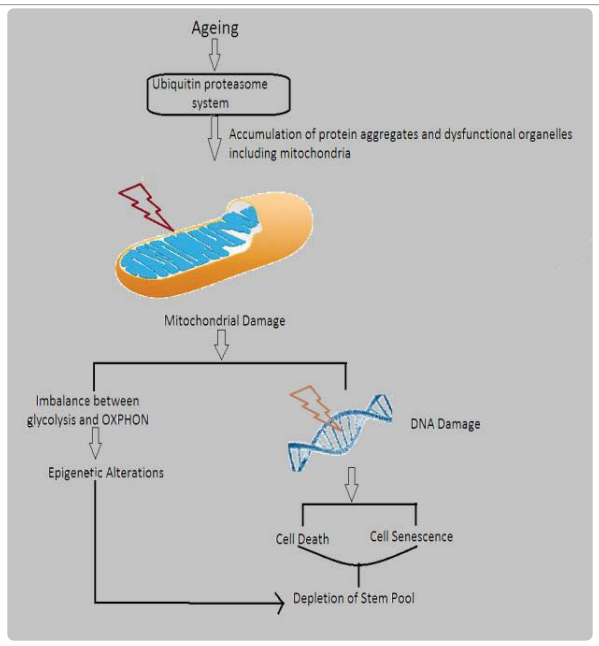

Figure 1: Ageing affects stem cells.

Likewise, genetic editing is to be done to reprogrammed stem cells to differentiate into beta cells which will increase the production of insulin thereby helping to control diabetes. Besides, these cells can be differentiated into cardiac cells to replenish and rejuvenate the defective cells of the heart and hence it can be repaired. It is beneficial to use RNA coding to produce telomere extending protein in in vitro human cultured cells. This mechanism can further be used in the manufacture of telomerase activation drugs. After studying the mechanism in the lab, this can be tested in human body to produce telomerase. This helps to increase the length of telomere thereby suppressing ageing and reducing age-induced health disorders. Klotho also suppresses ageing. A better understanding of potential effects of this protein on stem cells and ageing provides novel insights into cellular and molecular mechanism of ageing and diseases. Therefore, it is the need of the time to alter genomic sequences of genetic code of stem cells to reprogramme these cells to produce this protein.

CONCLUSION

Ageing brings a number of serious disorders in our body. There is decrease in the ability to replenish the damaged or injured cells, with age. It takes more time to heal a wound in old people than children. Besides, ageing causes cardiovascular diseases, cancer, type 2 diabetes, Alzheimer's disease, hypertension, osteoporosis, Age-Related Macular Degeneration (AMD), memory loss, etc. Stem cells act as panacea to all these major health disorders. We grow old partly because our stem cells grow old with us. The functions of aged stem cells become impaired because of cell intrinsic pathways and environmental changes. Altering the genomic sequences to reprogramme stem cells to perform specialized functions thereby suppressing ageing helps to regain the natural ability of all the cells of our body. It is the need of the time to understand the mechanism of producing proteins like Klotho, telomerase, etc that suppress ageing. With stem cell therapy and all its regenerative benefits, we are better able to prolong human life than at any time in history.

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