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Review Article

A Review of Stem Cells: Why Do We Age?

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Abstract

The answer to "why we age and how we stop it" is one of the most sought-after explanations of all time. The key to stopping, or at least slowing, the process of mammalian ageing begins by understanding the mechanisms behind it. The aim of this review is to shed light on the inner workings of stem cell ageing and extrapolate possibilities for health span extension. Understanding ageing (and not just as the process that brings us closer to death, but as a declining quality of life) at a deeper level not only allows for breakthroughs in slowing ageing, but also permits practitioners to recommend and personalize the best course of treatment for any disease or disability based on a patient's level of stem cell activity. The findings, in summary, indicate that stem cells themselves can be either the cause or the victim of ageing and there are multiple factors which determine the outcome. Whilst many stem cell types don't diminish in number over time, their function does decline. An ultimately, cell senescence is the most prominent key to understanding stem-cell associated ageing.

Keywords: Stem cells; Ageing; Regenerative medicine.

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Introduction

The problem of ageing has undoubtedly been a topic of research since the beginning of the study of human biology. Not only does one not want to age themselves, but to be able to prolong the life of a loved one is the greatest gift of all. According to the United Nations by 2050 one in six people, or 16% of the population, will be over the age of 65. This is a 7% increase from 2019 [1]. A multitude of disorders associated with ageing, including, but not limited to, decreased mobility, strength and cognition, and increased risk of cardiovascular complications, and osteoarthritis not only reduce the quality of life of individuals, but put an incredible monetary strain on society. A 2007 article by Burge et al. estimates 9 million people in the United States suffer age-associated fractures, yearly, accounting for a cost of US$20 billion [2].

The question remains, how do we stop it? Or at least, slow it down? Is there a method to determine the best possible course of treatment for a patient dependent on their stem cell activity? Understanding the mechanics of ageing is the key to finding answers, and what better place to start than at the beginning, the stem cell. Throughout this review the author aims to analyze key components of the stem cell state, such as apoptosis, senescence, and quiescence, and both the intrinsic and extrinsic factors affecting the ageing of numerous stem cell types.

Cell apoptosis, senescence and quiescence

It is a common assumption that ageing occurs as a result of cell apoptosis (programmed cell death), however, apoptosis occurs at a decreased rate in several types of cells as humans age [3].

Senescent cells, on the other hand, remain alive but much less functional and increase in number with age. Short, uncapped telomeres or stress-induced epigenetic alterations can cause this irreversible state of cell cycle arrest [4]. In this way senescence my inadvertently contribute to ageing, however, such arrest limits the malignant potential of cells and thus reduces mutations and suppresses formation of tumors [5]. Unlike apoptotic cells, senescent cells still retain the ability to influence their surrounding environment, modulating their niche through the "senescence-associated secretory phenotype" (SASP) which performs a key role in mediation of the pro-inflammatory status of hMSCs [6]. Sustained cell life and secretion of degenerative enzymes, tumour promoting mitogens, inflammatory cytokines, and growth factors triggers ageing of tissues and carcinogenesis [4,7].

Quiescence is also a state of cell-cycle arrest, but it is temporary and reversible, often occurring in muscle stem cells which are commonly reactivated for muscle injury repair and new muscle cell generation [8].

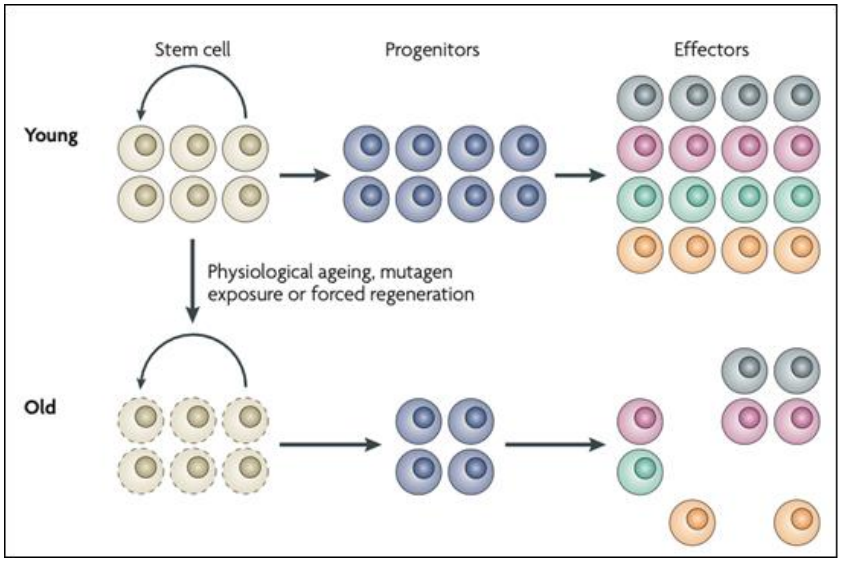

Figure 1: How stem cells age. Curved arrows represent self-renewal. Whilst stem-cell number does not necessarily decline with age, function, or the ability to produce progenitors (blue) and differentiated effector cells (different colors), does decline [5].

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Ageing by cell type

Mesenchymal stem cells

According to Murray, et al. [9], mesenchymal stem cells (MSCs) are "multipotent stromal cells that can differentiate into a variety of lineages, including osteocytes, adipocytes, and chondrocytes". Further, for the purpose of their review, Sethe, et al. [4] defined MSCs as "post-embryonic, bone-marrow derived cells, naturally capable of multipotent differentiation into connective tissue of non-haematopoietic lineage, in particular bone, ligaments, tendons, fibres, cartilage, and adipose tissue". Arnold Caplan coined the term "mesenchymal stem cell" in 1991 [10] to describe these cells. Whilst most commonly isolated from bone marrow, MSCs can also be taken from umbilical cord blood, connective tissue, skin, synovial fluid, and the placenta. The differentiation potential of MSCs into osteoblasts and adipocytes is stimulated by Nitric Oxide (NO) [11].

Research into the use of human mesenchymal stem cells (hMSCs) for treatment of a variety of diseases is extensive and ongoing with 1014 registered clinical trials as of July 2021 [12]. Bone marrow-derived mesenchymal stem cells (BM-MSCs) have been shown to be involved in bone, skin, liver, and muscle cell regeneration, and are the most commonly utilised in stem cell engineering [4,13]. However, the lifespan of these cells presents a substantial hurdle for culture expansion [6].

It has been determined that MSCs are both the subject to and the cause of ageing in an organism. MSCs experience time-related stress such as oxidative damage from reactive oxygen species (ROS), genetic abnormality, and reduced differentiation capacity as a result of quiescent surrounding tissue and are thus subject to ageing. On the other hand, as time goes on, the ability for MSCs to replenish progenitor cells decreases leading to functional deterioration. Hence, MSCs themselves are also causes of organismal ageing [4]. Whilst young hMSCs tend to possess anti-inflammatory properties, aged hMSCs are prone to pro-inflammatory expressions. MSC extracellular vesicles (carrying mRNAs, microRNAs, and proteins) from a 72-year-old donor displayed decreased immunosuppression when compared to those of a 25-year-old [6]. Further, older BM-MSCs produce increased amounts of IL-6 [4], the effector of inflammation [14].

Haematopoietic stem cells

Sufficient production of blood cells is maintained by Haematopoietic Stem Cells (HSCs) [15]. It is believed that HSCs can not only sustain blood cell production for the duration of the life of an organism but can also extend past the lifespan of the host [16]. By the same token, a 1979 study conducted by Harrison [17] demonstrated that HSCs can be transplanted into multiple consecutive recipients and continue to function for more than eight years, far exceeding the lifetime of the original donor.

Whilst HSCs might be able to maintain continuous blood cell production in laboratory settings, they are still not immune to ageing. It is understood that during ageing the quantity of effective cells decreases and the hematological system compensates with increased HSC numbers, possibly resulting in an increased risk of blood-cancer and cardiovascular disease caused by this "age-related clonal hematopoiesis" [7,18]. Moreover, normal ageing induces a skewed

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differentiation potential with HSCs favouring the myeloid lineage over lymphoid, thus aligning with observed immune system deterioration and lower incidence of acute lymphoblastic leukemia (juvenile-associated disease) versus higher prevalence of acute myeloid leukemia in old age [7,19,20]. HSC ageing is caused predominately by intrinsic factors [16]. This concept is supported by Rossi et al. and their findings that the aged phenotype is maintained by old HSCs in young hosts [21].

Intestinal stem cells

Gut epithelium renewal is maintained by Intestinal Stem Cells (ISCs). In typical circumstances the ageing of ISCs is largely linked to environmental stress response pathway activation, however, cell-intrinsic factors, like mitochondrial dysfunction, might also contribute [7].

In a 2008 study on the ageing Drosophila gut, Biteau et al. discovered that the number of ISCs in the flies increased with age but was accompanied by functional deterioration [22]. They found that interventions that stress the gut, such as bacterial infection, increase ISC numbers, supporting the hypothesis that ISC ageing is driven, at least in part, by environmental circumstances. Intrinsically, the high proliferation rate of ISCs is supported largely by oxidative phosphorylation which puts the cells at risk of oxidative damage and cellular dysfunction [23]. Also, age-associated changes in stem cell function could be underpinned by mitochondrial decline [24]. Interestingly, Rera, et al. demonstrated that upregulation of the Drosophila transcriptional coactivator dPGC-1, or spargel, increases mitochondrial gene expression and activity, defends against "age-related loss of intestinal homeostasis and integrity", and ultimately prolongs median life span [25].

Skin stem cells

Hair Follicle Stem Cells (HFSCs) and Melanocyte Stem Cells (MelSCs). Hair follicle stem cells (HFSCs) and melanocyte stem cells are responsible for hair growth and melanocytes (which produce the pigment of the skin, eyes, and hair [26]) respectively. The cycle of rest and activity of HFSC function is the cause of one of the most common signs of ageing, hair loss [27]. Whilst the number of HFSCs remains relatively constant with age, extended periods of recess underlie loss of function. The causes of such decline, as described by Schultz et al, include "increased sensitivity to DMPs (inhibitors of anagen entry), increases in JAK-STAT signalling and a decline in Notch signalling" [7,27,28].

Unlike HFSCs, MelSC population decreases considerably with age. However, not from expected causes like apoptosis or senescence, but instead as a result of abnormal differentiation into mature melanocytes. Hair greying, another obvious indication of ageing, arises from an inadequacy of critical genes which results in a loss of MelSCs into the melanocyte niche and/or apoptosis [29]. Similar effects are observed post ionizing radiation exposure promoting belief that hair greying may be caused by genotoxic stress. Hair colour may potentially be able to be conserved by reducing such stress or suppressing melanocyte differentiation [7,29].

Osteogenic stem cells

Osteoblasts, responsible for bone formation and maintenance [30], develop from

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osteogenic progenitor cells (OPCs), which themselves emerge from undifferentiated marrow stromal mesenchymal stem cells (MSCs) [31]. A study on 4-month-old and 24-month-old BALB/c mice conducted by Bergman et al. [31] found¬ that the primary MSC cultures from the elder mice had 41% less OPC colonies per marrow cell. They stated that, "on average, 30.9 million marrow cells per femur were harvested from the older animals, whole only 21.5 million cells per femur were harvested from younger animals", thus revealing that for each marrow cell in an older animal there are fewer stem cells with osteogenic potential than in younger animals. This clearly a contributor to age-related bone loss, which is also observed in humans. In addition, Hu, et al. [32] researched MSC differentiation and discovered that with age, MSCs preferentially differentiate into adipocytes, rather than osteoblasts, reducing new bone formation and increasing marrow fat accumulation. This reduced differentiation into osteoblasts results in decreased bone density and leads to osteoporosis. According to a 2004 report from the Surgeon General [33], osteoporosis is the most common cause of fractures. The risk of such factors increases with age and is most severe in women with around 4 in 10 Caucasian women aged over 50 in the United States experiencing a hip, spine, or wrist fracture at some stage. This puts an incredible burden on the health system with the estimated direct cost of osteoporosis to be US$2.77 billion in Australia alone in 2017 [34].

Neural stem cells

The entire nervous system is produced during development by Neural Stem Cells (NSCs) [35], a population of quiescent cells found in the neurogenic niche of the sub granular zone of the dentate gyrus [36]. Age-related cognitive impairment may be underlined by a decreased production of new neurons in the adult hippocampus as a result of a diminishing number of NSCs due to their differentiation into astrocytes. Trauma, seizures, and disease trigger cell division which may also contribute to accelerated NSC loss [36]. Whilst other stem cells in vitro experience impaired function with age, this is not the case for NSCs. This is highly suggestive that cell-extrinsic factors are the major contributors to NSC ageing and a subsequent decline in function [7].

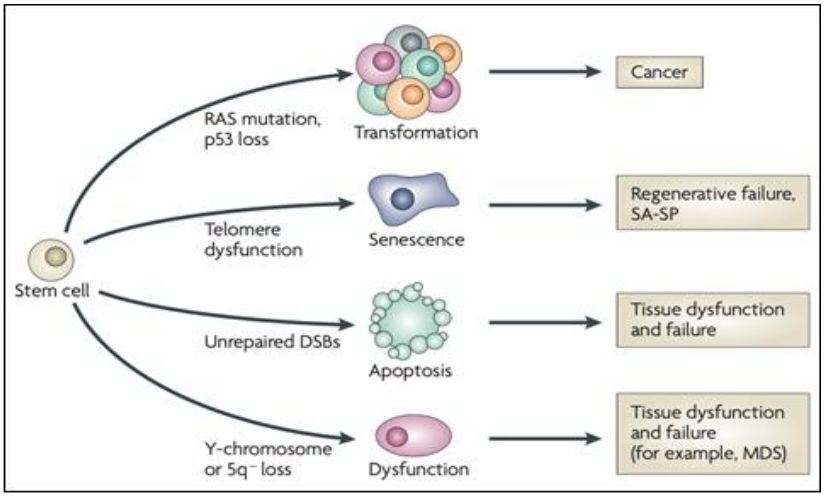

Figure 2: Fates of damaged stem cells [5].

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Other factors affecting stem cell ageing

Epigenetic

The term "epigenetic drift" describes the progressive, linear alterations to DNA methylation with ageing, thus the changing of stem cell fate and proliferation. Strategies to target the ageing epigenome have been developed to revitalise stem cells in the elderly and improve health-span [37].

Damage accumulation and telomere shortening

Unrepaired genomic damage accumulation, according the 'DNA-damage accrual' model of ageing, can result in cell transformation, senescence, apoptosis, or dysfunction [5]. Whilst DNA has a remarkable ability to self-repair, often mutations slip through the cracks. Suggestions have been made that the process by which some stem cells undergo self-repair could in fact expose them to oncogenic mutations, particularly quiescent cells which rely on the "error-prone non-homologous end joining pathway for repair of double stranded breaks" [38]. A 2010 study conducted by Mohrin et al. examined forced proliferation in mice HSCs post exposure to DNA-damaging radiation and found the animals showed reduced mutational events [39]. This suggests, according to Liu et al. that "in certain instances a break from quiescence that enables engagement of the high-fidelity homologous recombination pathway can help to maintain stem cell genomic integrity" [38]. A tell-tale sign of ageing in humans is telomere shortening, a particular kind of DNA damage [5,7]. Osteoblasts, myocytes, and chondrocytes all display age-related telomere shortening [4]. Telomeres protect the ends of chromosomes and are maintained by telomerase, which prevents telomere shortening and thus cell senescence by adding telomeric repeats onto the ends of chromosomes during DNA replication [40, 41]. Cell activity ceases and senescence begins once telomeres reach a certain length [4]. Preventing telomere shortening his is both the key to solving ageing, and the reason for the long-life of cancer [40]. In a study conducted by de Jesus et al., increased supply of the enzymatic subunit of telomerase, reverse transcriptase (TERT), when performed in the correct cancer-preventing environment, demonstrated expected telomere maintenance and a prolonged median lifespan in mice [42].

Reactive oxygen species

Free radical emissions, Reactive Oxygen Species (ROS) or otherwise, have been interpreted as simultaneously a result and cause of both in vitro and in vivo ageing. While ROS contribute positively to numerous systems, such as activation of repair mechanisms in traumatic bone injury, they are undoubtedly damaging, especially to MSC-dependent regeneration [4]. Produced predominately as an electron by-product of mitochondrial oxidative phosphorylation [13], ROS have been shown to induce senescence in specific cell systems [5]. In 1972, Harman linked free-radical production to the process of ageing describing a ruthless cycle of cellular damage accumulation and decreasing mitochondrial stability which ultimately increase ROS production. Such an elevation prompts further destruction of cellular macromolecules and disruption of mitochondrial oxidative phosphorylation, all of which eventually elicit cellular decomposition [43,44].

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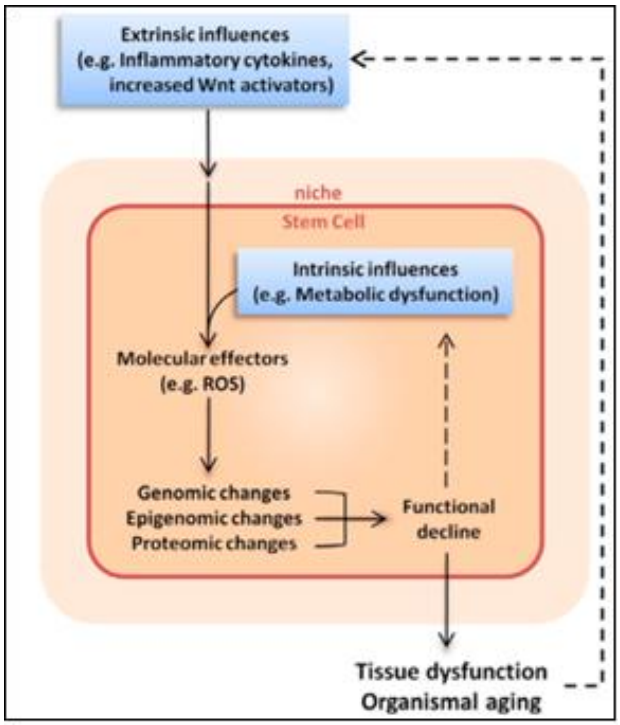

Figure 3: Extrinsic and intrinsic influences on stem cell ageing [38].

Antioxidants

An increased level of antioxidants has been reported to be advantageous for the ageing of MSCs [4]. Zou et al. [45] observed a sustained lifespan and improved rate of growth of hMSCs in cultures supplemented with antioxidants.

TGF-β

Mitogen agent transforming growth factor-β (TGF-β) [14] which hinders satellite cell regeneration and proliferation was found to be elevated in old mice [44,46]. Alterations in TGF-β signaling cause aged satellite cells and HSCs to display altered differentiation potential and impairs the function of NSCs [7].

Increased TGF-β pushes satellite cells in the direction of a fibrogenic lineage as opposed to myogenic, presenting a possible explanation for muscle fibre size reduction and diminished capacity for recovery from injury in the elderly [8].

Hormones

Changes in hormone levels of estrogen, testosterone and leptin impact the function of MSCs [6]. A decline in estrogen as a result of ageing has been linked to a loss of skeletal muscle [47], whilst testosterone has been perceived to support MSC proliferation [48]. Finally, released by adipocytes, leptin has been shown to induce senescence in chondrogenic progenitor cells by activation of proteins p53 and p21 possibly increasing MSC potential and bone integrity. This could be important in Osteoarthritis treatment procedures [49-51].

Caloric Restriction (CR) and P16INK4a

Caloric restriction (CR), without malnutrition, is a well-supported intervention for increased longevity in

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multiple species [7]. CR has been shown to significantly ease ageing in mice and combat the age-related rise in senescence markers, such as P16INK4a [5]. Reduced levels of P16INK4a enhance stem cell function and prevent cell senescence [38,52].

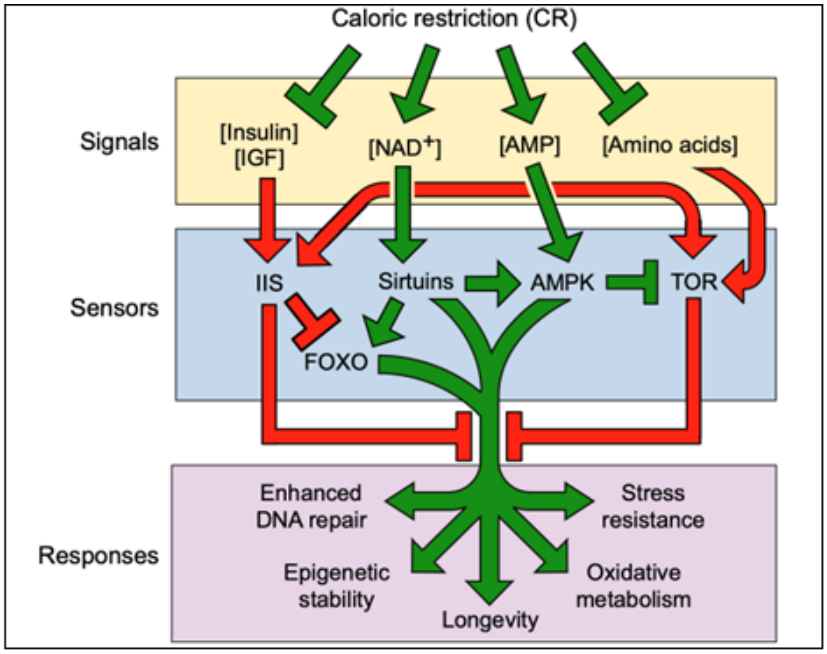

Figure 4: By Schultz & Sinclair; "The molecular effects of caloric restriction. Caloric restriction causes reduce levels of insulin, IGF and amino acids, and increased levels of NAD+ and AMP. These changes are sensed by the insulin-IGF signaling (IIS) pathway, target of rapamycin (TOR), sirtuins and AMP kinase (AMPK), resulting in enhanced DNA repair, stability of the epigenome, stress resistance, oxidative metabolism and ultimately, longevity. All of these signals, sensors and responses regulate stem cell behavior. Green arrows represent interactions that promote longevity and related phenotypes, and red arrows are interactions that suppress these phenotypes" [7].

Conclusion

The factors that influence the ageing of stem cells are extensive and complex. Understanding the mechanisms behind stem cell ageing, and the ageing of an organism is no easy feat. The author concludes that reactivation of senescent cells, or suppression of senescence itself, whilst simultaneously keeping unwanted mutation in check is one of the most promising avenues for extending quality of life. Methods involving reducing ROS and leptin, inducing Caloric Restriction and management of telomere length target the entire senescent cell population impacting all facets of biological life and well-being.

Simultaneously, awareness of an individual's stem cell activity before treatment, especially when considering regenerative methods which work to enhance the body's natural processes, is essential in accurately understanding treatment effectiveness. Thus, not only does stem cell research, particularly around ageing, develop methods for prolonging of lifespan, it enables more constructive avenues for maintaining health span.

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Disclaimer

Dr Gordon Slater is a medical director of Integrant Pty Ltd, an orthobiologics company. He also has a pecuniary interest in Regen-U, Australia.

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