

Role and Mechanisms of Cellular Senescence in Bone Disorders

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Abstract. Osteopathologic diseases are caused by damage to the bones. The reason is that there is an imbalance in the extent of osteoclastic resorption and osteoblastogenesis. Changes in the harmony of osteoblasts, osteoclasts and osteocytes affect the structure and strength of bone. Cellular senescence is a kind of irreversible growth arrest that can be induced by external factors and damage. At this time, it is shown that there is continuous inhibition of mitosis and secretion of the senescence-associated secretory phenotype (SASP). Recently, studies have found that biological senescence is the main factor restricting the function and differentiation of osteoprogenitor cells. It promotes the development of bone abnormalities. This paper presents the basic ideas, clinical signs, triggers and biological effects of cellular senescence. The different roles of senescence in osteoblasts, osteoclasts and osteocytes are introduced. Based on the above, this paper introduces the present-day treatment methods for cellular senescence. It will also explore the possibilities, deficiencies and future research directions of such methods in the management of bone diseases. The above evaluation can help us better understand the significance of cellular senescence in osteopathy and be used to develop new precision pharmacology for it.

Keywords: cellular senescence, bone disorders, bone remodeling, bone cells

1. Introduction

With the rapid aging of the world, many older people are starting to develop osteoporosis. Osteoporosis is caused by a lack of normal bone remodelling in the body [1]. Generally speaking, the change in the skeleton does not significantly affect life and work. Its long-term effect is that bone resorption by osteoclasts outpaces bone formation by osteoblasts, leading to loss of bone mass [2]. However, if there is an imbalance, it will result in osteopenia and damage the trabecular bone structure, leading to osteoporosis [3]. Disruption of bone remodelling is related to many factors, such as reduced levels of sex hormones, cellular senescence, insufficient intake of calcium and Vitamin D through diet, abnormal mechanical stress, pro-inflammatory cytokines, drug effects, long-term illness, etc [4]. Among them, cellular senescence is considered an essential reason for the deterioration of bone with age [5].

Senescence is a state of cell quiescence that occurs due to many reasons or genotoxic damage. At this time, there is a permanent block in the cell cycle [6]. Hayflick and Moorhead first reported this in 1961. Hayflick and Moorhead found that fibroblasts from outside the body have a limited

capacity for division, and after a certain number of divisions, they enter a state of senescence [7]. Senescent cells have different characteristics in morphology, altered gene expression, irreversible G0/G1 arrest, and the formation of a metabolic paracrine environment (SASP); at the same time, there is degradation of protein macromolecules, rearrangement of energy metabolism, structural changes such as thinning and ballooning of the cell membrane, etc. These cells also have a more prominent SA- β -Gal staining and the activation of some cyclin-dependent kinase repressors, such as p16INK4a and p21Waf1/Cip1. SASP is relatively much more prominent than others; therefore, it is a key focus of senescence research. Senescent cells release all kinds of pro-inflammatory factors, chemokines, nutrients, and also produce matrix metalloproteinases that change the microenvironment of the surrounding area [8, 9]. Over the course of ageing, cells will accumulate more and more in organs; at the same time, the constant emission of SASP is responsible for chronic inflammation and eventual organ dysfunction [10]. There is an overgrowth of senile cells in the trabecular bone cavity of the musculoskeletal system, which results in reduced maturation of osteoblasts and inhibited bone formation; at the same time, SASP also increases osteoclast activity and thereby promotes bone disease [11].

Somatic senescence is one of the main pathological factors promoting the development of musculoskeletal diseases. Fully differentiated cells can suppress the normal function of bone marrow mesenchymal stem cell (BMSCs) and osteogenic and osteocytic groups by releasing SASP; this is known as "reduced ossification and increased bone resorption" [12-14], and it will disturb the dynamic balance of skeletal regeneration and cause various bone diseases such as fragility fractures and degenerative joint diseases [15]. With age, osteoblasts lose the capacity to form calcified matrix, and at the same time, senescence of osteoclasts is associated with increased bone resorption. Together, the two mechanisms cause an abnormal development of bone [13, 14]. Finally, based on the above, we will consider how the phenomenon of biological aging affects skeleton dysfunction.

2. Physiological basis of bone cells

Maintaining the balance of bone cells is to regulate osteoblasts, osteoclasts and osteocytes [16]. Osteoblasts are the cells that produce new extracellular matrix of bone, and osteoclasts break down this material. Osteocytes are the primary cells in bones that perform various functions to regulate bone remodeling by sensing mechanical stress and changing their surroundings [17]. The three types of cells cooperate to keep the building in good condition through direct contact and the release of circulating chemokines [2, 18].

Osteoblasts are the cells of bone formation that originate from BMSCs; through the BMP/Wnt pathway, they develop along a particular transcriptional route under the control of Runx2 and Osterix [19]. Mature osteoblasts secrete alkaline phosphatase and regulate calcium ion concentrations to initiate and control bone mineralization; simultaneously, they release RANKL and OPG to orchestrate osteoclast differentiation [20]. Osteoclasts are bone-resorbing cells that originate from uncommitted progenitor cells; under the control of M-CSF and RANKL [2], they proliferate, migrate, fuse, differentiate, etc., and eventually form mature particles with the ability to break down minerals [21]. These are the resorption sites; they have ruffled borders and release proton pumps and lysosomal enzymes to forcibly degrade the extracellular skeletal framework and maintain the stability of the whole skeletal framework [22]. The two main types of cells involved in bone remodelling are osteoblasts and osteoclasts, and they are regulated by osteocytes [23]. Osteocytes are primary sensors of bone mechanosensing, bone modelling and the regulation of hormone systems and mineralisation and remodelling in the body [17]. Osteocytes reduce the formation of new bone by osteoblasts through the secretion of sclerostin and thus interfere with the Wnt/ β -catenin

pathway [24]. It also raises the RANKL/OPG ratio to promote the formation of osteoclasts and thus cause bone loss. Osteocytes are dense dendritic structures that can feel changes in the mechanical stress environment and then transmit these biophysical signals to all parts of the bone, along with releasing many factors that regulate the formation of new extracellular matrix by osteoblasts, the development of osteoclast precursors, changes in hematopoiesis in the bone, etc. Generally speaking, the three groups of cells are still healthy and lively compared with those in the entire skeleton [25, 26].

3. Basic characteristics and related research of cellular senescence

Senescent cells maintain a highly active metabolic state and are not subject to apoptosis due to the suppression of the pro-apoptotic pathway [27]. Changes in senescent cells affect all parts inside the bone structure, such as the cell membrane, cytoplasm, nucleus, mitochondria, lysosomes and secretory vesicles, etc. All of the vital organelles are functionally damaged; consequently, osteoblast activity decreases, osteocyte stimulation becomes irregular, and there is an increase in the aging and death of osteocytes, leading to age-related bone loss and osteoporosis [28].

We need to know that cellular senescence has essential roles in the body and promotes the first stages of skeletal damage repair [29]. First of all, SASP can move macrophages and fibroblasts to the site of injury and start an inflammatory response. It can stimulate the movement and division of osteogenic precursor cells to aid in the beginning of healing. At present, in the research on senescence, the traditional indicators and analysis methods are mainly SA- β -Gal staining, protein or mRNA expression of p16 and p21, quantitative assessment of SASP molecules, and immunofluorescence detection of DNA-damage markers such as phosphorylated histone H2AX [6, 30]. Together, the above indicators can help us know how many senescent cells are in a person's body or in lab cultures accurately.

Senescence has the opposite effects on all parts of the bone. Geriatric osteopenia will be induced and repair will be promoted in the early stages of bone injury. Therefore, to explore the heterogeneity of senescent cell populations is to find a way to understand the genes that affect bone strength and to identify disorders of the musculoskeletal system more precisely for treatment.

4. Effects of senescence on the functions of major bone cells

With the aging of osteoporosis, the rate of osteoclast activity has exceeded that of osteoblast formation, thus disrupting the process of bone remodelling and causing various bone diseases. [15] The three kinds of bone cells directly involved in the above biological processes are osteoblasts and osteocytes; a decrease in the number of osteoblasts and impaired osteogenic maturation result in insufficient bone mineralisation, and at the same time, there is an increase in the density and activity of osteoclasts which accelerates bone resorption. In addition, more osteocyte apoptosis and reduced cell function disrupt the proper regulation of skeletal homeostasis [13, 31].

4.1. Specificity of osteoblast senescence and dysfunction in bone formation

Bone-forming cell senescence is involved in the change of bone structure, and there are irregular patterns of mineralisation. Sustained loss of osteoblast function will gradually result in osteopenia, and many different reasons have been found; among them, there is vital-signal transduction, nuclear regulation, redox imbalance and disruption of regional communication [13]. One of the reasons for the aging of osteocytes may be changes in the regulatory network of p53/p21 or p16/Rb, as well as

mitochondrial damage and genome instability caused by an increased amount of reactive nitrogen species [32, 33]. In addition, osteocytic senescence is related to the development of mesenchymal stem cells (MSCs), which are derived from them. Senescence-modified MSCs have reduced osteoblast function and secrete basic senescence factors such as p53/p21 and p16/Rb; their SASP secretion is altered, they exhibit increased oxidative stress and mitochondrial dysfunction, impaired autophagy, etc. Senile osteoblasts secrete a large amount of pro-inflammatory cytokines, catabolic enzymes and growth factors in the form of SASP; as a result, the normal osteogenic function of cells is impaired, their niche environment is altered, and this may trigger the formation of a destructive cycle and lead to bone loss [13].

4.2. Specificity of osteoclast senescence and imbalanced bone resorption function

During bone aging, there is a significant increase in the number and lifespan of osteoclasts; thus, the rate of bone resorption now exceeds that of new bone formation by a large margin. An asymmetry in these acts as one of the main reasons for the start and progression of osteoporosis [14]. Active osteoclasts increase the dissolution of cancellous bone; thus, the bone becomes weaker, more prone to fractures or even completely lost [34], and this has weakened the structure of the whole skeleton. The above are all different. First of all, with age, the proportion of survival factors in the BCL-2 group among osteoclasts increases, and thus they do not undergo normal cell death; therefore, osteoclasts can remain active for a longer time [35]. At the same time, there is an irregular activation of the RANKL/RANK/OPG and nuclear factor- κ B (NF- κ B) signalling cascade and release of SASP by adjacent senescent cells in the osseous microenvironment [36]; this also promotes osteoclast differentiation and activity indirectly and thus leads to bone mineral loss. Chemokines secreted by older osteoclasts, such as IGF-1, can change the differentiation of adjacent bone-forming cells and thus advance the process of osteopenia [37].

4.3. Specificity of osteocyte senescence and its core role in maintaining bone homeostasis

In the late stage of life, osteocytes in older people promote the loss of skeletal structure through various ways, such as SASP and intercellular communication and EVs; thus, there is an overall disturbance in skeletal strength [38, 39]. At this time, osteocytes are still under the uniform control of the main signaling pathway, genes and an inflammatory environment [40]. The activation of the p53/p21, p16/Rb and NF- κ B pathways can lead to cell cycle arrest and physiological decline of osteocytes, chromosomal abnormalities affect the sensitivity of osteocytes to senescence, and at the same time, SASP released by senescent osteocytes promotes their own disintegration and increases the fragility of the skeleton. As a result of the above changes, senescent osteocytes have shown all sorts of symptoms, such as a decrease in cell size, fragmentation or damage of dendritic protrusions, simplification of the lacunar-canalicular system, and an increase in the levels of necroptosis and senescence [39, 41]. As a result, the injury may develop into osteoporosis and weak bones with age [42].

Therefore, clinical treatment of ageing bone and related musculoskeletal diseases should no longer be based on only one pathway of cellular signals. Therefore, the first purpose of the intervention will be to regulate the intricate cooperation of osteoblasts, osteoclasts and osteocytes. The aim of this paper may be to increase the precision of aged-part detection and raise the exclusion rate simultaneously. At the same time, new strategies will be developed to alter the local microenvironment of mature cells and modify their original function to solve the problem of poor bone stability [15].

5. Therapeutic strategies targeting cellular senescence

Elimination of senescent cells is now an urgent problem in the study of aging, and efforts are being made to remove these aged cells or reduce their harmful paracrine activities through medical and technological means [43]. Therefore, it may be that age-related diseases will be delayed or reduced. To stop the bone loss of older age caused by osteoporosis, it may be necessary to eliminate senescent cells from the bone microenvironment [44].

A typical pathological feature of the aging skeleton is the excessive accumulation of senescent cells. First, some chemicals have been developed that disrupt the life cycle of these abnormal cells, such as BCL-xL and PI3K δ . Also suppress the production of SASP by old cells that is harmful to the surrounding microenvironment. After that, various carriers or other techniques can be employed to extend the lifespan of anti-senescence therapy. Different kinds of elderly people will have different types of changes [45, 46].

5.1. Senolytics

Currently, the main way to treat cell aging is by means of drugs. The main therapeutic compounds can be divided into three types. Firstly, dasatinib in combination with quercetin is a well-known senolytic agent that can reduce tyrosine kinase activity and also inhibit the PI3K/AKT pathway by inhibiting phosphatidylinositol 3-kinase (PI3K). Then, Bcl-2 subunit inhibitors such as ABT-263, ABT-737 and WEHI-539 are employed to destroy senescent cells by targeting the increased anti-apoptotic factors BCL-2, BCL-xL and BCL-w that can be found in these cells; thus, the balance of apoptosis is disturbed. Finally, there are some other organic compounds that have weak senolytic activity, such as fisetin, curcumin and resveratrol; they can reduce senescent cells to a certain extent by decreasing oxidative stress and regulating all kinds of longevity signal transduction pathways. It is still needed that new drugs be developed which can precisely target the survival pathway of senescent cells. BCL-xL is overexpressed at all stages of senescence to inhibit apoptosis, and PI3K δ is necessary for the survival of senescent cells, so the amount of senescent cells can be reduced by regulating both [47-49].

5.2. Reversal of cellular senescence

In addition to medical therapy, the rejuvenation of senescent cells is also an aging study direction. Blocking SASP secretion will not decrease the number of senescent cells directly; it is only to prevent the release of harmful paracrine factors. Therefore, through regulation of the main SASP signal pathway, that is to say NF- κ B and the mammalian Target of Rapamycin cascade, chronic inflammation and organ damage can be effectively reduced [46]. For example, there are some occasional repairs to the genomic Myc oncogenes, Krüppel-like factor 4, SRY-box transcription factors 2+4 and octamer-binding transcription factor 4; they have shown the fixability of cellular dysfunction and general degeneration that occurs at the late maturation stage [50]. In addition, to rejuvenate or strengthen the function of mitochondria in old cells, one can regulate oxidative phosphorylation and prevent the accumulation of mitochondrion-derived reactive oxygen species; therefore, it is also one of the indications of senescence [51].

5.3. Limitations and future perspectives of therapeutic strategies

Although strategies to eliminate senescence foci are not in line with traditional hormone therapy, they will be able to meet the medical needs of modern society. Still, there are many problems with managing cellular ageing. Specifically, senescent cells are very diverse. All kinds of cells and different inducing factors lead to various senescence phenotypes, so a single clinical protocol cannot be used to completely eliminate or regulate senescence [52]. The first problem is that there are no reliable methods to accurately identify and eliminate old osteoblasts, osteoclasts or osteocytes in the bone tissue completely. In addition, there are no specific molecular markers that can differentiate senescent bone cells from healthy bone cells well [53, 54]. Therefore, in the future, we will do our best to improve the accuracy of the treatment and use all kinds of measures. First, there are some relatively trustworthy indicators of senescence. Then, by means of combination of anti-senescence drugs, senomorphic chemicals and directed-delivery systems such as nanostructured architectures, both pharmacological effect and cell targeting can be improved. It may help build cooperative therapeutic protocols that can deal with the different characteristics of senescent cells [55-57].

6. Conclusion

With the progression of cell senescence, homeostasis of bone remodeling is disrupted, and a state of "reduced mineralisation - increased resorption" occurs; this is the primary cause of skeletal diseases. Although there are treatments for age-related diseases, such as senolytic therapy and inhibition of SASP, they have not been applied to elderly patients because they have high variability in different groups of older people and lack precise indicators for early detection. In the future, it is necessary to develop good combination treatment plans and further study osteocyte ageing in order to achieve personalised management of musculoskeletal diseases in older adults.

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