Cellular senescence as a key factor in osteoporosis: the role of SIRT1

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ABSTRACT

Osteoporosis, a prevalent age-related condition, is characterized by decreased in bone mass and bone quality. Among the pathogenetic mechanisms, cellular senescence has been suggested to induce inflammation and affect bone cell function, contributing to bone fragility. In this context, sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase, emerges as a central regulator of musculoskeletal health, influencing osteoblastic differentiation, suppressing osteoclastic activity and maintaining bone mass by the deacetylation of critical targets. Interestingly, a close association was found between an elevated senescence-associated secretory phenotype and aged bone cells, confirming a role for senescence in bone aging. The aim of our minireview is to highlight cellular senescence as a key factor in osteoporosis, focusing on the central role of SIRT1 and exploring potential strategies to modulate its activity, including diet, exercise and pharmacological interventions. In conclusion, enhancing SIRT1 activity represents a potential therapeutic approach for age-related bone disorders, offering interesting perspectives for future research and therapeutic development.

KEYWORDS

SIRT1, osteoporosis aging senescence bone cells, diet, exercise, pharmacological interventions.

Introduction

Osteoporosis, a common age-related disorder, is characterized by a decrease in bone mass and quality, resulting in increased bone fragility and susceptibility to fractures [1,2]. It mainly affects older people, particularly postmenopausal women, as hormonal changes during menopause contribute to accelerated bone mass loss [3]. Pathogenetically, osteoporosis is known to be caused by altered bone turnover, leading to an imbalance between bone resorption and formation processes, resulting in reduced bone strength [4]. Although numerous studies have been conducted in this field, the underlying biological mechanisms have not been fully elucidated.

Cellular senescence, a process in which bone cells undergo age-related changes, has been suggested as a key factor in osteoporosis [5]. Age-related cellular senescence is a major risk factor for health, and it is characterized by several physiological changes, including DNA damage, telomere shortening, chromatin alterations, mitochondrial dysfunction, proteostasis imbalance and accumulation of reactive oxygen species (ROS). These factors cause irreversible cell cycle arrest and alterations in gene expression [6]. In addition, p21 and p16, known cyclin-dependent kinase inhibitors, have emerged as key regulators in this context, as they mediate cell cycle arrest and prevent the proliferation of damaged or dysfunctional cells [7].

Cellular senescence is known to involve a complex interplay of genetic and environmental factors that have a significant impact on bone cell function and viability [8], altering the function of osteoblasts, osteoclasts and myeloid progenitors, as well as promoting inflammation and impairing bone matrix synthesis [9]. Indeed, the accumulation of senescent cells in the bone microenvironment has been shown to promote a pro-inflammatory environment, further increasing bone loss. In addition, senescent cells secrete factors collectively referred to as senescence-associated secretory phenotype (SASP). These include interleukin 8, interleukin 1α, interleukin 1β, interleukin 6, epidermal growth factor and matrix metalloproteinase-1 (MMP-1), which can negatively affect neighbouring cells and interfere with bone homeostasis [10,11]. They are known to promote senescence of osteocytes (mature bone cells), inhibiting osteogenesis and promoting osteoclastogenesis, which in turn results in tissue dysfunction [12].

In addition, experimental studies in mouse models have found significantly elevated levels of SASP in osteoblastic progenitors, osteoblasts and osteocytes of aged mice compared with younger mice, suggesting that a subset of cells within the

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bone microenvironment may become senescent with ageing, thus contributing to age-related bone loss [13]. Therefore, understanding the molecular mechanisms underlying bone senescence is fundamental to developing effective strategies to prevent osteoporosis.

To date, much research has focused on sirtuins, molecules that can act on cellular ageing and promote longevity. Among these, sirtuin 1 (SIRT1) is the most studied in bone metabolism, and it plays a central role in normal skeletal development and homeostasis [14]. Based on this evidence, the aim of our mini-review was to provide a concise summary of the role of SIRT1 in bone health, exploring potential strategies for stimulating its activity in order to slow down the cellular senescence processes that underlie musculoskeletal disorders, such as osteoporosis.

SIRT1: function and mechanism of action

SIRT1, a member of the NAD^+-dependent deacetylase family, is known for its role in promoting longevity and mediating the effects of calorie restriction in various diseases, as well as in modulating cellular homeostasis by influencing processes such as DNA repair, apoptosis and inflammation [15,16]. In particular, SIRT1 is essential for musculoskeletal system development, its deletion having been demonstrated to induce significant mineralization defects leading to the development of osteoarticular diseases [17]. SIRT1 plays multiple roles in the regulation of bone health, influencing osteoblast differentiation, suppressing osteoclast activity, and intricately balancing the processes of bone formation and resorption [18]. Furthermore, SIRT1 plays a critical role in the maintenance of bone mass and structural integrity by triggering the deacetylation of key targets involved in bone metabolism, including forkhead box O (FoxO) family members and β-catenin [19].

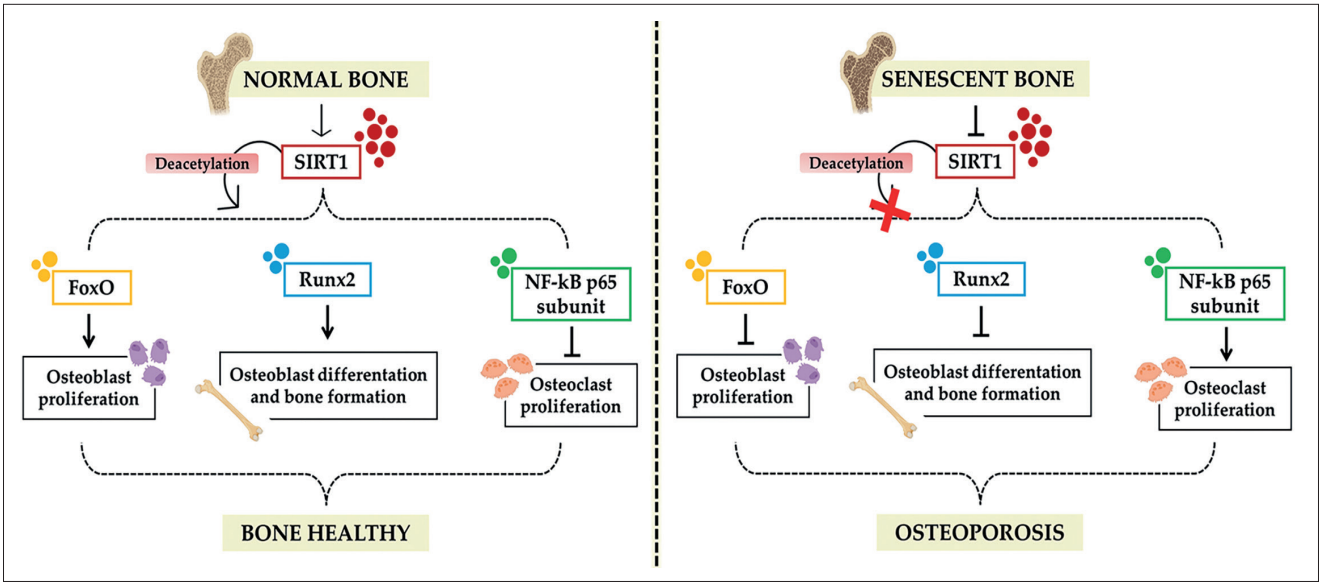
Interestingly, SIRT1 is known to promote bone formation through the activation of Wnt signalling pathways [20]. Indeed, FoxO deacetylation by SIRT1 prevents the binding of FoxO to β-catenin, increasing Wnt signalling and promoting osteoblastic proliferation [21]. In this context, Iyer and colleagues reported that SIRT1 deletion in osteoblast progenitors caused impaired bone formation, especially of cortical bone, suggesting a role for SIRT1 in the accumulation of cortical bone during skeletal growth and maintenance even in adults [21].

SIRT1 is also known to deacetylate runt-related transcription factor 2 (Runx2), a key transcription factor that regulates osteoblast differentiation and bone formation, enhancing its transcriptional activity and promoting osteoblastogenesis. This interaction influences the expression of osteogenic genes, promoting mineralization and bone integrity. Conversely, changes in SIRT1 activity may impact Runx2 function, contributing to skeletal abnormalities [22]. Not surprisingly, the interaction between SIRT1, Runx2 and osteoblastic activity confirms the existence of intricate regulatory mechanisms underlying bone homeostasis, paving the way for the development of potential therapeutic interventions for disabling conditions, such as osteoporosis and other bone disorders [23].

There is evidence demonstrating that SIRT1 plays a role in regulating osteoclastogenesis by interacting with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Specifically, SIRT1 negatively modulates NF-κB activity, deacetylating its p65 subunit and suppressing osteoclastogenic gene expression. This inhibition prevents osteoclast formation and bone resorption [24].

Finally, SIRT1 has been suggested to contribute to mitochondrial function maintenance by reducing oxidative stress, a key factor in cellular senescence [25]. In fact, SIRT1 activates antioxidant proteins through protein deacetylation, promoting cellular resilience against ROS. On the other hand, oxidative stress can compromise SIRT1 activity, triggering a feedback mechanism through which a reduction in SIRT1 functionality contributes to increasing oxidative stress, accelerating cellular senescence [25]. Not surprisingly, this dual role makes SIRT1 a potential target for interventions aimed at mitigating bone senescence in osteoporosis.

Figure 1 The role of SIRT1 in healthy and senescent bone.



SIRT1 and osteocytes

The intricate regulation of bone homeostasis involves various factors, among which SIRT1 emerges as a key player in osteocyte function. Osteocytes, through their paracrine signalling, significantly influence both osteoblasts and osteoclasts. Sclerostin, a crucial molecule derived from osteocytes, negatively modulates bone formation by antagonizing the Wnt signalling pathway [26]. Kim *et al*. identified a pathway by which the enzyme deubiquitinase ubiquitin-specific peptidase 4 (USP4) stabilizes histone deacetylase SIRT1 via phosphorylation mediated by casein kinase 2 (CK2). SIRT1 acts as a positive regulator of bone mass and suppressor of sclerostin expression [27]. Genetic deletion of Sirt1 leads to low bone mass, whereas the activator of SIRT1 preserves it in aged mice. CK2, by inhibiting USP4, reduces SIRT1 expression, increasing osteocyte differentiation. In line with this, another study investigated the role of advanced oxidation protein products (AOPPs) in age-related bone loss. AOPPs, known inducers of oxidative stress, exacerbated bone loss in aging mice by enhancing resorptive activity and diminishing bone formation [28]. This effect was associated with elevated sclerostin levels and reduced SIRT1 expression. *In vitro* experiments demonstrated that AOPPs induced ROS production, leading to increased sclerostin expression via SIRT1 downregulation. Co-treatment with ROS inhibitors or SIRT1 activators ameliorated bone mass and microstructure in AOPP-exposed mice, suggesting a potential therapeutic strategy [28]. These findings suggest that modulation of SIRT1 and sclerostin are a promising avenue for therapeutic intervention.

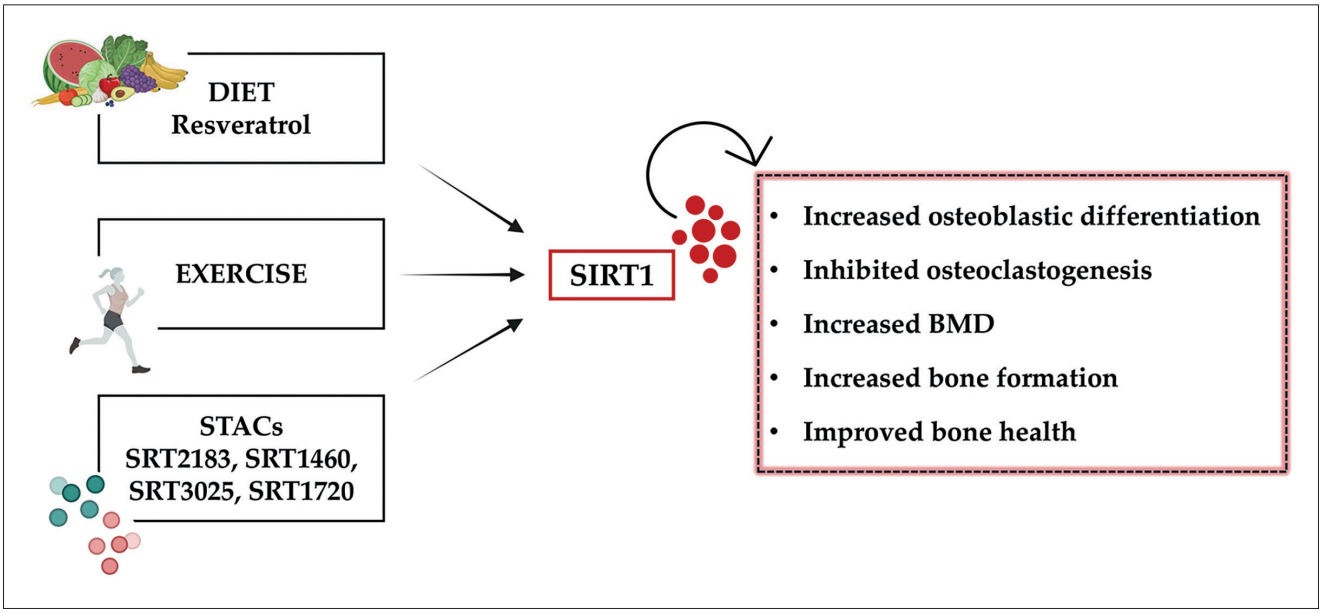
Potential strategies to regulate SIRT1 activity

Several factors, including diet, exercise and pharmacological interventions are known to influence SIRT1 expression and activity.

Certain dietary components, such as resveratrol, a natural polyphenol found in red grapes and wine, activate SIRT1, offering a potential avenue for therapeutic intervention [29]. In particular, resveratrol enhances SIRT1-mediated deacetylation, promoting osteoblast differentiation and inhibiting osteoclast formation [30]. In this context, Wang and colleagues, evaluating the action of resveratrol on ovariectomized rats, observed a correlation between high-dose resveratrol administration and reduced bone loss in ovariectomized rats versus untreated animals [31]. Specifically, the treated group was characterized by significantly higher femoral SIRT1 levels in association with higher bone mineral density (BMD), as well as higher levels of osteoprotegerin and β-catenin in the serum and lower expression of NF-ϰB. Including this element in the regular diet could therefore help maintain SIRT1 activity and mitigate bone senescence [32]. However, further research and *in vivo* studies are needed to establish the positive role of resveratrol, assumed through the consumption of foods that contain it, such as red wine [33]. It is known that excessive alcohol consumption can induce liver cirrhosis and cancer. Indeed, Vieira et al. established that in women, regular alcohol consumption is a risk factor for the development of breast cancer [34].

Interestingly, regular exercise has been associated with increased expression of SIRT1 and correlated with the activation of signalling pathways that help to regulate bone cell function [35]. From a mechanistic perspective, physical activity can stimulate the production of factors that activate SIRT1, providing a natural and accessible means of supporting bone health [36]. In this regard, Zhu *et al*. recently observed a significant improvement in bone health in 12-month-old mice subjected to treadmill running training for 8 weeks [37]. In particular, at the end of the training cycle, a significant increase in BMD was observed, in association with an up-regulation of autophagy in bone cells compared with control animals. Activation of autophagy has been shown to play a critical role in bone quality as its up-regulation results in a significant increase in osteoblast differentiation and reduced bone loss [38]. Notably, absence of

Figure 2 Potential strategies to promote SIRT1 activity in bone homeostasis.



the benefits of exercise when the *SIRT1* gene is deleted in bone marrow mesenchymal stem cells suggests a role in mediating physiological adaptations of bone tissue to exercise [37].

Finally, recent evidence has highlighted the existence of potential pharmacological agents capable of directly modulating SIRT1 activity. Small molecules and compounds designed to activate SIRT1 have shown promise in several preclinical studies, emerging as potential therapies aimed at counteracting the effects of senescence in osteoporosis [15]. In this context, synthetic SIRT1 activators (STACs) have attracted more attention than natural STACs due to their greater potency, bioavailability and specificity. Some preclinical studies have shown promising results using synthetic STACs, including SRT2183, SRT1460, SRT3025, and SRT1720 [39]. However, further research is needed to fully understand their effectiveness and safety in human applications.

Finally, regulation of NAD^+, the common co-substrate of SIRT1, has been proposed as an alternative method to modulate SIRT1 levels [15]. With aging, there is a progressive decline in NAD^+ levels, leading to a decrease in SIRT1 activity and an increased susceptibility to disease. Therefore, SIRT1 activity could be restored by increasing NAD^+ using NAD^+ precursors, such as nicotinamide and nicotinamide mononucleotide. Other strategies to increase NAD^+ levels include stimulation of NAD^+ synthesis and inhibition of NAD^+ degradation [40]. Importantly, numerous synthetic compounds capable of modulating the enzymes responsible for the synthesis or degradation of NAD^+ have been reported, offering potential avenues for therapeutic interventions aimed at supporting optimal SIRT1 function and improving age-related health problems.

Conclusions

The discovery of the intricate role of SIRT1 in osteoporosis provides valuable insights into the molecular mechanisms underlying bone senescence. Undoubtedly, SIRT1 emerges as a central regulator in maintaining bone health, influencing the functions of osteoblasts and osteoclasts and orchestrating the balance between the processes of bone formation and resorption. Strategies designed to enhance SIRT1 activity, which include dietary components, regular exercise, and/or pharmacological interventions, show promising therapeutic potential for attenuating age-related bone disorders, such as osteoporosis. Finally, the exploration of synthetic activators of SIRT1 and the modulation of NAD^+ levels offer interesting prospects for future therapeutic research and development.

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