Bone and Arthrosurgery Science, 2026, Volume 4, Issue 3
http://ojs.bbwpublisher.com/index.php/BAS
Online ISSN: 2981-8222
Print ISSN: 3083-4856

Expanding Therapeutic Potential and Mechanisms of SIRT3 in Bone-Related Diseases through Mitochondrial Function Regulation

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Abstract: As a representative degenerative joint disease, the pathological mechanism of osteoarthritis has increasingly highlighted the critical role of SIRT3 protein in various bone-related disorders. Beyond its significant impact on osteoarthritis, mitochondrial dysfunction is closely linked to the pathogenesis of multiple bone diseases, including osteoporosis, osteonecrosis, bone erosion in rheumatoid arthritis, abnormal fracture healing, and bone tumors. This review systematically explores how SIRT3 regulates mitochondrial function, thereby influencing metabolic processes, apoptosis, autophagy, and senescence in various bone-related cells such as osteoblasts, osteoclasts, osteocytes, and chondrocytes. By conducting cross-disease comparative analysis, we reveal the central role of the SIRT3-mitochondrial function axis in maintaining skeletal homeostasis, providing important theoretical basis and research directions for the future development of broad-spectrum skeletal protection strategies targeting SIRT3.

Keywords: Sirtuin 3; Mitochondria; Osteoporosis; Osteonecrosis; Rheumatoid arthritis

Online publication: July 7, 2026

1. Introduction

Currently, Chinese manufacturing enterprises are experiencing a slowdown in growth and face issues such as the need for further optimization of their internal human capital structures. To address this situation, tax incentive measures such as additional deductions for R&D expenses can be implemented. By reviewing relevant domestic and international literature, a majority of scholars, such as Ma [1], argue that the policy of additional deductions for R&D expenses is a special provision established by the government aimed at

encouraging companies to increase their investment in R&D and support technological innovation. Studies by Guceril *et al.* [2] indicate that when companies benefit from tax reduction incentives, their investment behavior is significantly stimulated.

Bone and joint diseases represent a significant global health concern affecting individuals across all age groups, characterized by remarkable diversity and complexity. These conditions encompass both degenerative disorders such as osteoarthritis, as well as metabolic bone diseases (e.g., osteoporosis), inflammatory bone diseases (e.g., rheumatoid arthritis), traumatic bone injuries (including fractures and their complications), and various benign and malignant bone tumors. Although the etiologies and clinical manifestations of these diseases vary, recent studies suggest they may share certain common underlying pathophysiological mechanisms. Growing evidence indicates that mitochondrial dysfunction constitutes a pivotal shared biological basis, involving multiple aspects including abnormal energy supply, disruption of redox homeostasis, and disturbances in cellular metabolic regulation [1–4].

As a deacetylase primarily localized within mitochondria, SIRT3 is regarded as a core regulatory factor essential for maintaining cellular homeostasis. It plays a pivotal role in regulating cellular energy metabolism, enhancing cellular antioxidant stress resistance, and modulating the processes of apoptosis and autophagy [5–7]. Currently, researchers have preliminarily elucidated the protective mechanisms of SIRT3 in the progression of osteoarthritis, such as delaying disease progression by reducing chondrocyte apoptosis and inhibiting inflammatory responses [8]. However, for other types of bone and joint diseases, the specific functional mechanisms, expression changes, and potential therapeutic value of SIRT3 remain inadequately systematically summarized or thoroughly investigated.

Therefore, this article aims to provide a comprehensive review of the latest research advancements on SIRT3 in various bone-related diseases, analyze its expression patterns and biological functions under different pathological conditions, and further investigate whether it could serve as a common therapeutic target across diverse bone disorders, thereby offering theoretical support and novel research insights for future precision treatment strategies for bone and joint diseases.

2. The multicellular regulatory role of SIRT3 in bone homeostasis

Bone tissue, as a complex structure composed of various cell types, primarily includes osteoblasts, osteoclasts, osteocytes, and chondrocytes. Each of these cells performs distinct physiological functions and collectively maintains bone homeostasis. This homeostasis is sustained through a dynamic functional equilibrium among these cells; dysfunction in any cell type can lead to bone metabolic disorders. Studies have demonstrated that SIRT3, as a key deacetylase, exerts profound effects on the survival, differentiation processes, and functional performance of these critical cells in bone tissue by regulating mitochondrial function [9]. Specifically, SIRT3 plays a pivotal regulatory role in the biological activities of osteocytes by optimizing mitochondrial energy metabolism, antioxidant capacity, and apoptosis pathways.

2.1. Osteoblasts

As a key class of deacetylases, SIRT3 plays a pivotal role in the regulation of osteoblast function. It significantly enhances mitochondrial oxidative phosphorylation, improves energy metabolism efficiency, thereby robustly promoting ATP synthesis and supply, providing ample energetic support for the mineralization function of osteoblasts [10,11]. Meanwhile, SIRT3 also mitigates cellular damage caused by

oxidative stress by inhibiting the excessive accumulation of reactive oxygen species (ROS), significantly reducing the apoptosis rate of osteoblasts, thereby effectively promoting bone formation and maintaining skeletal homeostasis [12].

2.2. Osteoclasts

SIRT3 may significantly influence the differentiation process and bone resorption activity of osteoclasts by regulating mitochondrial energy metabolism and oxidative stress pathways [13,14]. However, there remains considerable controversy regarding its specific mechanisms of action. Different studies indicate that it may exert diametrically opposed regulatory effects under varying conditions, demonstrating complex bidirectional regulatory characteristics [15].

2.3. Osteocyte

As essential mechanoreceptors within bone tissue, osteocytes play a pivotal role in sensing mechanical stimuli and regulating bone metabolism. The mitochondrial function of osteocytes is critical for maintaining their normal survival and signaling capacity, involving multiple aspects such as energy metabolism, calcium ion homeostasis, and oxidative stress regulation. Studies have demonstrated that SIRT3 may effectively delay the aging process of osteocytes by modulating mitochondrial dynamic equilibrium and autophagic activity [16]. Specifically, SIRT3 promotes a dynamic balance between mitochondrial fusion and fission, enhances the capacity of mitochondria to clear damaged organelles through autophagy, thereby improving mitochondrial function and reducing oxidative damage, ultimately contributing to the maintenance of osteocyte homeostasis and physiological functions [17].

2.4. Chondrocytes

Multiple studies have conclusively demonstrated that the OA (osteoarthritis) model reveals the significant protective effects of SIRT3 protein on chondrocytes, which effectively delays the progression of cartilage degeneration through multiple mechanisms including reduction of oxidative stress and inhibition of inflammatory responses [18]. Furthermore, given its pivotal regulatory role in cartilage metabolism, SIRT3 may also play significant biological functions in various other cartilage-related disorders, such as the repair of cartilage tissue damage and the initiation and progression of chondromas, demonstrating broad potential research value and application prospects [8].

3. Expansion of the mechanism of action of SIRT3 in common bone-related diseases

3.1. Osteoporosis

Osteoporosis is a chronic metabolic bone disease characterized primarily by a significant reduction in bone mass and degeneration of bone tissue microstructure, with its core pathogenesis stemming from a functional imbalance between osteoblasts and osteoclasts. SIRT3 may play a crucial regulatory role in this process through multiple molecular pathways [19]. On one hand, SIRT3 enhances the mitochondrial bioenergetic metabolic efficiency of osteoblasts, promotes bone matrix synthesis and mineralization processes, thereby significantly improving bone formation capacity [20,21]. On the other hand, it can inhibit excessive differentiation and bone resorption activity of osteoclasts by regulating glucose metabolism and

reactive oxygen species levels within them, thereby preventing accelerated bone loss [22]. Furthermore, SIRT3 specifically activates the critical SIRT3-FOXO3a signaling axis, enhancing the antioxidant defense mechanisms of various cells in bone tissue, effectively eliminating excess free radicals, and reducing osteocyte apoptosis induced by oxidative stress [23]. The aforementioned multiple mechanisms work synergistically and collectively to regulate the dynamic balance of bone metabolism from both the promotion of bone formation and the inhibition of bone resorption, ultimately contributing to slowing or even reversing the progression of osteoporosis.

3.2. Osteonecrosis

Bone necrosis, as a severe skeletal disorder, is typically closely associated with multiple factors such as ischemia and prolonged use of hormonal medications. In the early stages of the disease, a pivotal pathological event is the onset of mitochondrial dysfunction, which directly impairs the normal metabolism and function of osteocytes. SIRT3 is believed to play a significant protective role in combating bone necrosis [24]. Its mechanisms of action primarily include the following aspects: First, SIRT3 effectively maintains the stability of mitochondrial membrane potential, thereby inhibiting the apoptosis process mediated by the mitochondrial pathway [25]. Secondly, it significantly enhances the activity of mitochondrial autophagy, promoting the timely clearance of damaged or dysfunctional mitochondria and preventing their accumulation from causing further cellular damage [26]. Furthermore, SIRT3 can enhance ATP production efficiency by optimizing energy metabolism pathways [27], thereby enabling osteocytes to better adapt to adverse microenvironments such as hypoxia and improving their survival capacity under stress conditions.

3.3. Rheumatoid arthritis bone erosion

Rheumatoid arthritis is a chronic autoimmune disease characterized primarily by persistent synovitis and progressive bone erosion. Recent studies have revealed that the mitochondrial-associated protein SIRT3 may play a significant regulatory role in the pathogenesis and progression of this disease through multiple mechanisms [28]. SIRT3 may maintain cellular energy metabolic homeostasis by inhibiting mitochondrial functional impairment in chondrocytes and osteoblasts within the inflammatory microenvironment, thereby delaying the deterioration of joint structure [29]. Additionally, SIRT3 can regulate the mitochondrial metabolic status of various immune cells, including macrophages, influencing their polarization and function, thereby modulating the progression of inflammatory responses [30]. Furthermore, SIRT3 can also inhibit the activation of NF-κB through the SIRT3-NF-κB signaling pathway [31]. It reduces the release of downstream inflammatory factors, ultimately mitigating the extent of inflammatory bone destruction. These mechanisms collectively demonstrate the multifaceted protective role of SIRT3 in the pathological process of rheumatoid arthritis.

3.4. Fracture healing

Fracture healing is a complex biological process involving multiple interconnected stages such as inflammation, repair, and remodeling, which requires substantial energy expenditure. During this process, SIRT3 may exert positive effects through various mechanisms: for instance, by promoting the proliferation and differentiation of osteoblasts and chondroblasts, accelerating intracartilaginous ossification, and effectively improving mitochondrial function, thereby providing critical support for callus formation and

mineralization [32]. These effects contribute to enhancing the efficiency and quality of fracture healing, highlighting the potential significance of SIRT3 in bone metabolism regulation [33].

4. The cross-disease potential and challenges of SIRT3-targeted therapy

Based on the aforementioned mechanisms, SIRT3 agonists, lifestyle interventions, and gene therapy strategies not only hold promise as novel therapeutic approaches for osteoarthritis (OA) but may also be extended to various other bone-related disorders. For instance, SIRT3 agonists such as resveratrol and quercetin may exert protective effects in conditions like osteoporosis and osteonecrosis by regulating mitochondrial function, inhibiting oxidative stress, and suppressing inflammatory responses [34,35]. Meanwhile, non-pharmacological interventions such as moderate exercise and scientifically guided caloric restriction have been demonstrated to exert positive effects on various skeletal disorders—including reduced bone mass and bone microstructural degeneration—by activating the SIRT3 pathway and regulating bone metabolic balance [9,36]. Furthermore, with continuous advancements in gene editing and vector technologies, SIRT3 gene therapy strategies utilizing lentiviruses or AAV vectors have demonstrated precise and highly effective therapeutic potential in localized bone disorders such as osteonecrosis, delayed fracture healing, and bone defect repair [37].

However, this field still faces numerous scientific and technological challenges. Firstly, the precise mechanisms of action of SIRT3 in different types of osteocytes (such as osteoblasts, osteoclasts, and bone cells) remain incompletely understood, and its biological effects may exhibit cell-specificity [9]. Secondly, while systemic administration of SIRT3 agonists has demonstrated metabolic improvement effects in animal models, their long-term impacts on systemic energy metabolism, insulin sensitivity, and other organ functions require careful evaluation. Finally, targeted delivery systems for various skeletal disorders—including tissue-specific promoters, nanocarriers, and localized sustained-release technologies—still require further optimization to enhance therapeutic precision and safety.

5. Conclusion and prospects

As a core regulatory factor governing mitochondrial function, SIRT3 not only plays a pivotal role in osteoarthritis but also demonstrates significant potential in the treatment of various bone-related disorders such as osteoporosis, osteonecrosis, and bone tumors [9]. It exerts regulatory effects through multiple biological mechanisms, including modulating cellular energy metabolism processes, enhancing antioxidant defense capacity, inhibiting abnormal apoptosis, and promoting protective autophagy, thereby maintaining homeostatic balance within bone tissue.

These mechanisms suggest that SIRT3 holds significant promise as a shared therapeutic target for multiple bone disorders. Future research should focus on several key directions:

First, it is essential to elucidate the cell-specific mechanisms of SIRT3 in different types of bone diseases and clarify its distinct regulatory networks in osteoblasts (which form new bone), osteoclasts (which resorb bone), and chondrocytes (which maintain cartilage). Uncovering these cell-type-specific roles will facilitate the development of more targeted therapeutic interventions.

Second, it is essential to develop advanced drug delivery systems that specifically target bone tissue to improve therapeutic precision and reduce systemic side effects. Current challenges include off-target effects

and limited bioavailability in bone microenvironments, which could be addressed by nanoparticle-based carriers or bone-homing peptide conjugates that selectively accumulate in skeletal tissues.

Third, it is essential to actively advance preclinical animal studies using disease-relevant models (such as ovariectomized mice for osteoporosis) and subsequent translational clinical research to systematically verify the actual therapeutic efficacy and safety of SIRT3 agonists. Rigorous study design and standardized outcome assessment will be critical for successful clinical translation.

In-depth investigation of the SIRT3-mitochondrial function axis not only improves our understanding of the shared pathophysiological mechanisms underlying multiple bone disorders, but also provides critical scientific evidence and research directions for developing novel "one-target, multiple-disease" therapeutic strategies that target the same molecular target. This approach has the potential to treat osteoporosis, osteoarthritis, and bone fractures through a unified mechanism, reducing the need for polypharmacy.

Funding

This work was supported by the Guangxi Natural Science Foundation Project (Grant No. 2025GXNSFHA069045).

Disclosure statement

The authors declare no conflict of interest.

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