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Review Article

Muscle-bone crosstalk via endocrine signals and potential targets for osteosarcopenia-related fracture

Renwang Sheng [a,d,1], Mumin Cao [a,c,d,e,f,1], Mingyuan Song [a,d], Mingyue Wang [d], Yuanwei Zhang [a,c,d,e,f], Liu Shi [a,c,d,e,f], Tian Xie [a,c,d,e,f], Yingjuan Li [c,g], Jinyu Wang [b,c,d,**], Yunfeng Rui [a,c,d,e,f,*]

[a] Department of Orthopaedics, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, PR China
[b] Department of Rehabilitation, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, PR China
[c] Multidisciplinary Team (MDT) for Geriatric Hip Fracture Management, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, PR China
[d] School of Medicine, Southeast University, Nanjing, Jiangsu, PR China
[e] Orthopaedic Trauma Institute (OTI), Southeast University, Nanjing, Jiangsu, PR China
[f] Trauma Center, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, PR China
[g] Department of Geriatrics, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, PR China

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ABSTRACT

Background: Osteosarcopenia is a syndrome coexisting sarcopenia and osteopenia/osteoporosis, with a high fracture risk. Recently, skeletal muscle and bone have been recognized as endocrine organs capable of communication through secreting myokines and osteokines, respectively. With a deeper understanding of the muscle-bone crosstalk, these endocrine signals exhibit an important role in osteosarcopenia development and fracture healing.

Methods: This review summarizes the role of myokines and osteokines in the development and treatment of osteosarcopenia and fracture, and discusses their potential for osteosarcopenia-related fracture treatment.

Results: Several well-defined myokines (myostatin and irisin) and osteokines (RANKL and SOST) are found to not only regulate skeletal muscle and bone metabolism but also influence fracture healing processes. Systemic interventions targeting these biochemical signals has shown promising results in improving the mass and functions of skeletal muscle and bone, as well as accelerating fracture healing processes.

Conclusion: The regulation of muscle-bone crosstalk via biochemical signals presents a novel and promising strategy for treating osteosarcopenia and fracture by simultaneously enhancing bone and muscle anabolism. We propose that myostatin, irisin, RANKL, and SOST may serve as potential targets to treat fracture patients with osteosarcopenia.

The translational potential of this article: Osteosarcopenia is an emerging geriatric syndrome where sarcopenia and osteoporosis coexist, with high fracture risk, delayed fracture healing, and increased mortality. However, no pharmacological agent is available to treat fracture patients with osteosarcopenia. This review summarizes the role of several myokines and osteokines in the development and treatment of osteosacropenia and fracture, as well as discusses their potential as intervention targets for osteosarcopenia-related fracture, which provides a novel and promising strategy for future osteosarcopenia-related fracture treatment.

1. Introduction

In recent years, sarcopenia has been recognized as an age-related and progressive skeletal muscle disease characterized by accelerated muscle mass and function loss [1,2]. Osteoporosis or osteopenia is a systemic skeletal disease involving bone mass and micro-architecture loss [3]. In 2017, Duque and colleagues first coined the term “osteosarcopenia” to describe the simultaneous presence of sarcopenia and osteoporosis [4].

* Corresponding author. Department of Orthopaedics, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, PR China.
** Co-corresponding author. Department of Rehabilitation, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, PR China.
E-mail addresses: drwangjinyu@seu.edu.cn (J. Wang), ruiyunfeng@126.com (Y. Rui).
[1] These co-authors contributed equally to this study

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Sarcopenia and osteoporosis are regarded as a "hazardous duet" to increase fracture risk, and thus osteosarcopenic patients have a higher risk for fracture than healthy individuals and even those with sarcopenia or osteoporosis alone [5–8] (Fig. 1). Moreover, both clinical and animal studies have demonstrated that sarcopenia, osteoporosis, and osteosarcopenia are associated with impaired or delayed fracture healing [9–11], and fractured patients with osteosarcopenia exhibit increased mortality [12]. Currently, the treatment for fractures is mainly focused on bone, which is insufficient to promote fracture healing and functional recovery in osteosarcopenic patients. Developing a novel strategy that targets skeletal muscle and bone simultaneously is significant for osteosarcopenic patients with fractures.

In the last two decades, accumulating evidence has revealed that skeletal muscle and bone can secrete myokines and osteokines respectively, to communicate with each other [13,14], which provides a new direction to elucidate the vicious loop between sarcopenia and osteoporosis, as well as the mechanisms of osteosarcopenia development. Various myokines (e.g., irisin) and osteokines (e.g., sclerostin, SOST) changed in response to risk factors of osteosarcopenia like aging, physical inactivity, and de-loading, accompanied by skeletal muscle and bone mass loss [15–18], indicating that these endocrine signals could be key mediators in osteosarcopenia development. In clinical practice, skeletal muscle is typically recognized as a source of vascular supply during fracture healing. Interestingly, emerging studies have shown that muscle-bone crosstalk via endocrine signals also regulates fracture healing processes [19]. Myokines (e.g., myostatin and irisin) and osteokines (e.g., SOST and the receptor Activator of Nuclear Factor κB Ligand, RANKL) are differentially expressed and secreted after fracture, and the intervention of these signals accelerated fracture healing [20–24]. In general, endocrine signals from the musculoskeletal system in response to various factors influence both muscle and bone metabolism, as well as the healing processes of fracture. Proper regulation of these signals can improve skeletal muscle and bone status in osteosarcopenia, as well as accelerate fracture healing.

In this review, we focused on several well-defined myokines (myostatin and irisin) and osteokines (SOST and RANKL) that showed great potential to treat osteosarcopenia and fracture simultaneously (i.e., osteosarcopenia-related fracture). We first summarized the crosstalk of skeletal muscle and bone via these biochemical signals and explored their roles in osteosarcopenia development and treatment. Secondly, we discussed how these signals responded to skeletal injuries and regulated fracture healing. Lastly, we summarized the potential systemic intervention of targeting these myokines and osteokines for osteosarcopenia-related fracture treatment.

2. Crosstalk of skeletal muscle and bone via endocrine signals in the development of osteosarcopenia

In muscle-bone crosstalk, skeletal muscle can secrete hundreds of myokines to positively (e.g., irisin, IGF-1, FGF2, decorin, and IL-6) or negatively (e.g., myostatin and FGF21) regulate bone metabolism, and bone can produce osteokines (e.g., OCN, RANKL, and SOST) to influence muscle metabolism inversely, as previously reviewed [5,14,17,25–27] (Fig. 2). Endocrine signals in muscle-bone crosstalk are influenced by various factors, such as aging, physical inactivity, nutrition intake, inflammation, and de-loading [14,18,28]. These factors are highly associated with sarcopenia, osteoporosis, and osteosarcopenia, and the interventions for these signals exhibit compelling effects to improve the mass and function of skeletal muscle and bone simultaneously [29]. Thus, it was reasoned that these biochemical signals in muscle-bone crosstalk are important mediators in osteosarcopenia development. Clarifying the roles of the changed myokines and osteokines facilitates to

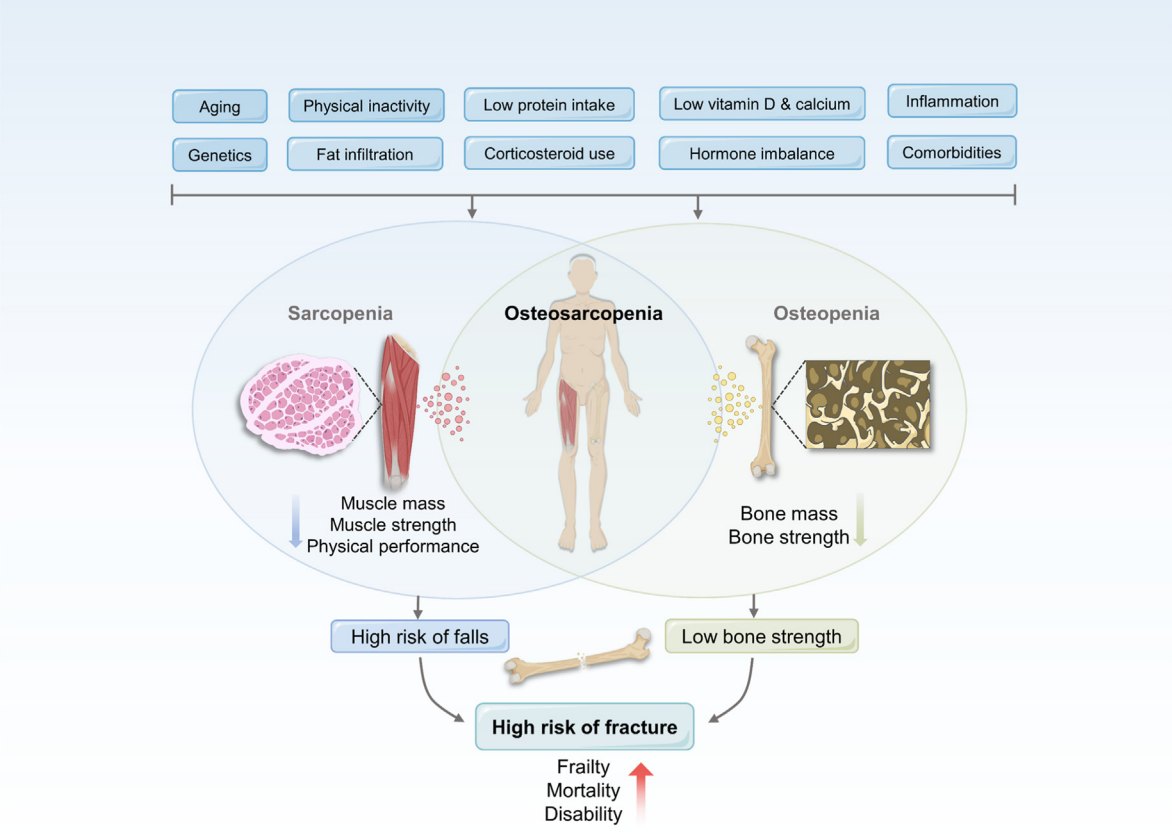

Figure 1. The risk factors, pathophysiology, and clinical outcomes of osteosarcopenia.

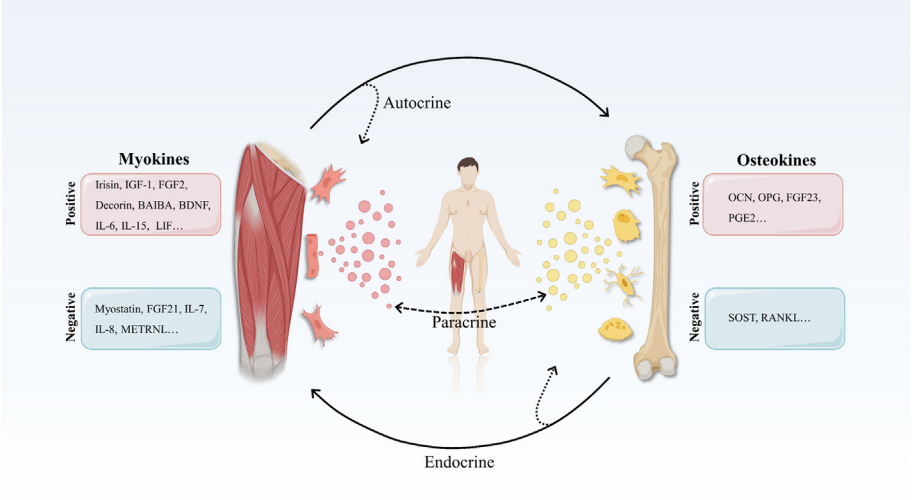

Figure 2. The crosstalk of skeletal muscle and bone via myokines and osteokines in different manners. The positive and negative myokines or osteokines for muscle and bone metabolism were summarized. Abbreviation: IGF-1, insulin-like growth factor 1; FGF2/21/23, fibroblast growth factor 2/21/23; BAIBA, beta-aminoisobutyric acid; BNDF, brain-derived neurotrophic factor; IL-6/7/8/15, interleukin 6/7/8/15; LIF, Leukemia inhibitory factor; METRNL, meteorin-like; OCN, osteocalcin; OPG, osteoprotegerin; PGE2, prostaglandin E2; SOST, sclerostin; RANKL, the receptor Activator of Nuclear Factor κB Ligand.

elucidate the pathological mechanisms of osteosarcopenia, which can instruct future osteosarcopenia treatment. Focused on the potential intervention targets for osteosarcopenia-related fracture, we only discussed specific myokines (myostatin and irisin) and osteokines (RANKL and SOST) in response to sarcopenia, osteoporosis, and the two primary risk factors of osteosarcopenia including aging and physical inactivity in the present review.

2.1. Myokines

2.1.1. Myostatin

Myostatin, also named growth and differentiation factors 8 (GDF-8), is the first identified myokine that belongs to the transforming growth factor beta (TGF-β) superfamily. It has been recognized as a negative regulator of both skeletal muscle and bone [14]. Myostatin suppresses the proliferation and differentiation of muscle cells [30], and the increased myostatin is positively associated with muscle diffusion and damage, as well as sarcopenic status [31]. Similarly, myostatin is shown to suppress osteogenesis and promote osteoclastogenesis, leading to decreased bone formation and increased bone resorption [14,32]. Moreover, myostatin can target various bone cells, including BMSCs, osteoblasts, osteocytes, and osteoclast, suggesting its important role in regulating bone metabolism in muscle-bone crosstalk [15].

Up to now, the association of skeletal muscle mass and serum myostatin level has been widely investigated in community residents and patients with severe heart, lung, kidney, and liver diseases, while the reported association was complicated and controversial [33–38]. Kuriyama et al. and Yasar et al. found that a high serum myostatin level was associated with low skeletal muscle mass in community residents, sarcopenic patients with chronic kidney diseases, and male patients with chronic obstructive pulmonary diseases [34,38,39]. In contrast, other studies reported that lower serum myostatin levels could contribute to increased skeletal muscle wasting in patients with severe liver diseases and heart failure [35–37]. These disparate results highly suggested that increased myostatin could be not a primary cause of sarcopenia or osteosarcopenia [40] and could be caused by different features of study cohorts (e.g., age, sex, basic diseases) and various measurements for myostatin and skeletal muscle mass. Strikingly, increasing studies have indicated that serum myostatin level was changed in response to aging and sex, which seemed to be a critical factor that influenced age-related myostatin changes and skeletal muscle loss [33,41]. Bergen III et al. investigated the myostatin levels in subjects of different age and sex in a random cohort of Rochester and found that the increased serum myostatin with age could result in skeletal muscle loss in women, which possibly contribute to their higher sarcopenia incidence [41]. However, they discovered that the younger men had a significantly higher circulating myostatin level than the older men with or without sarcopenia, indicating that myostatin could serve as a homeostatic regulator of skeletal muscle mass in men [41]. Consistently, Peng et al. found that low serum myostatin levels of healthy community-living older residents were associated with skeletal muscle mass loss only in men but not women [33]. Generally, sarcopenic and older women probably had increased circulating myostatin concentrations that could result in the further loss of skeletal muscle mass [41,42], which should be clarified by future studies.

Although the relationship between skeletal muscle loss and myostatin level was not fully covered, high myostatin levels were reported to be positively associated with low cortical bone thickness in middle-aged community residents [39]. Thus, the increased myostatin levels in response to aging or skeletal muscle loss (especially in women) could accelerate osteosarcopenia development. In addition, acute or long-term physical activity was found to inhibit myostatin secretion into circulation, while physical inactivity and bed rest induced an inversed effect [43–45]. Importantly, myostatin inhibition has shown great potential to improve both skeletal muscle and bone mass in osteosarcopenia [46,47]. Lee et al. found that systemic inhibition of myostatin/activin A signaling prevents the loss of skeletal muscle and bone during spaceflight in mice [46]. Bialek et al. also demonstrated that a soluble myostatin decoy receptor (ActRIIB-Fc) increased the mass of both muscle and bone in mice [47]. Taken together, myostatin secretion in skeletal muscle is influenced by age, physical activity, and muscle mass, and the increased myostatin negatively regulates muscle and bone metabolism, leading to muscle and bone mass loss, which can be reversed or rescued by myostatin inhibition.

2.1.2. Irisin

Irisin is a cleaved product of its precursor, fibronectin type III domain containing 5 (FNDC5), which is produced by the contracted skeletal muscle and released into circulation during exercise [27]. Due to the positive roles of irisin in regulating muscle and bone anabolic metabolism, its biological effects in muscle-bone crosstalk are widely investigated [18,48]. Bone is recognized as the primary target organ of irisin, and irisin mainly promotes bone anabolic metabolism via increasing bone formation and decreased osteoclast activities [27,29].

The majority of studies found that the patients with sarcopenia or osteoporosis have a significantly lower serum irisin than the healthy controls whether other diseases existed or not, indicating the high sensitivity of irisin in response to skeletal muscle and bone disorders [49–53]. Thus, it has been recognized as a predictive marker for sarcopenia, osteoporosis, and osteosarcopenia [49,53,54]. Aging and physical

inactivity are two important risk factors for osteosarcopenia, and it was observed that serum irisin levels decreased with them [55,56]. It is worth noting that the decreased circulating irisin might further accelerate muscle and bone loss in osteosarcopenic patients, while irisin administration shows the potential to rescue these processes. Zhu et al. found that irisin deficiency decreased bone density and delayed the development and mineralization of bone from the early stage to adulthood in mice [57]. In contrast, exogenous irisin treatment not only improved skeletal muscle mass and strength but also increased bone mass and strength by promoting osteogenesis and reducing osteoclast activities [29,58]. Several studies also found that irisin administration could promote the healing of dystrophic skeletal muscle, and prevent muscle atrophy and bone loss in hind-limb-suspended mice [23,59]. Collectively, these findings highly suggested that irisin from skeletal muscle played a critical role in regulating muscle and bone metabolism, and the irisin changes in response to sarcopenia, aging, and reduced physical activity could induce or accelerate osteosarcopenia development.

2.2. Osteokines

2.2.1. RANKL

RANKL is a soluble ligand that inhibits osteogenesis but promotes osteoclast differentiation, which is mainly located in osteoblasts and osteocytes. RANKL is a member of the OPG/RANKL/RANK system, which has been widely reported to regulate osteoclast biology including development, activation, and function [60]. In this system, RANKL can bind to its receptor RANK, which subsequently activates various downstream signaling molecules, including colony-stimulating factor 1 receptor (CSF-1) and nuclear factor kappa B (NF-κB) receptors, initiating osteoclast differentiation. On the other hand, osteoprotegerin (OPG) also is a soluble receptor of RANKL that can decrease the binding of RANK and RANKL, consequently inhibiting osteoclastogenesis [60]. Previous studies demonstrated that OPG/RANKL/RANK axis dysfunction or RANKL over-expression caused osteoporosis while RANKL inhibition rescued osteoporosis \and increased bone mass and strength [15,60]. RANKL was also reported to be expressed in skeletal muscle, where its activation suppressed myogenic differentiation and induced muscle atrophy by regulating the NF-κB signaling pathway [61,62], indicating that the OPG/RANKL/RANK axis participated in the crosstalk of bone to muscle [15]. Besides, the skeletal muscle could secrete OPG, and OPG deficiency and RANKL/OPG imbalance induced selective atrophy of fast-twitch IIb myofibers in mice [63]. Collectively, these findings indicated that OPG/RANKL/RANK system was probably involved in the crosstalk from bone to muscle during osteosarcopenia development.

Recently, several studies have shown the possible influence of OPG/RANKL/RANK imbalance in osteoporotic patients on disturbing skeletal muscle homeostasis [64,65]. Xu et al. found that the women with postmenopausal osteoporosis had a significantly increased serum RANKL level and RANKL/OPG ratio compared to healthy controls [64]. Wang et al. also reported that the osteoporotic bone tissues exhibited a notably higher RANKL but lower OPG expression than the non-osteoporotic ones in fracture patients [65]. Besides, Xu and colleagues found that the patients with rheumatoid arthritis had higher osteoporosis incidence. They presented an increased RANKL level, a reduced OPG level, as well as a higher RANKL/OPG ratio in the circulation compared to the healthy controls [66]. These findings highly suggested that osteoporosis could result in the dysfunction of the OPG/RANKL/RANK axis, which has been demonstrated to induce skeletal muscle atrophy [63]. Meanwhile, OPG immunoglobulin fragment complex (OPG-Fc) injections for anti-RANKL treatments were shown to rescue the force and function of atrophic muscles and improve muscle integrity and regeneration after injury [67]. In addition, aging and physical inactivity were shown to increase serum RANKL/OPG levels, which also could induce osteosarcopenia incidence by negatively regulating both skeletal muscle and bone [15,68].

Taken together, these results supported that the OPG/RANKL/RANK axis imbalance could be caused by osteoporosis, aging, and physical inactivity. The disturbed OPG/RANKL/RANK axis could further trigger pathological changes in skeletal muscle and cause muscle mass and function loss in osteosarcopenia development. Strikingly, denosumab (Damb), a RANKL antagonist that was widely accepted for osteoporosis treatment, was demonstrated to also effectively rescue muscle function and increase muscle mass and strength [69], exhibiting the great potential for osteosarcopenia treatment.

2.2.2. SOST

SOST is a glycoprotein that mainly originates from mature osteocytes, and it has been recognized as a member of bone morphology protein (BMP) antagonists to suppress the Smad phosphorylation induced by BMP and canonical WNT signaling pathway [15]. In addition to the effects on suppressing bone formation and promoting bone resorption, SOST also exhibited a negative influence on skeletal muscle mass and function [15]. In previous studies, SOST inhibited the WNT3a-mediated signaling pathway, which suppressed the myogenic differentiation of C2C12 myoblasts and their crosstalk with osteocytes [70]. Thus, SOST is a potential osteokine secreted by osteoporotic bones to regulate skeletal muscle metabolism and homeostasis during osteosarcopenia development.

The association between serum SOST level and osteoporosis was controversial [71]. Several studies reported that lower bone mineral density (BMD) in osteoporotic patients was positively correlated with higher serum SOST levels [72,73]. In contrast, previous studies in Turkish, Chinese, and Spanish populations revealed a negative association between serum SOST levels and BMD in osteoporotic patients. Although their association was difficult to clarify, it was observed that SOST inhibition could effectively increase BMD in osteoporotic patients [71,74], indicating that SOST changes in response to osteoporosis were not facilitated to bone formation. In addition, a higher serum SOST level was shown to be positively correlated to older age and reduced physical activity, as well as lower skeletal muscle mass, which confirmed the role of the increased SOST level in accelerating osteosarcopenia development [15,75,76]. Furthermore, SOST deficiency or inhibition could lead to an increased lean body mass in older mice, with enhanced muscle regeneration and restored muscle function, while SOST overexpression causes the opposite effects [77,78]. Taken together, the changed serum SOST level in response to osteoporosis, aging, and physical inactivity could induce skeletal muscle mass and function loss, contributing to osteosarcopenia development. SOST inhibition also seemed to be an attractive effect to treat or rescue osteosarcopenia.

3. Skeletal muscle and bone secrete myokines and osteokines to regulate fracture healing

Clinically, it is well-accepted that skeletal muscle plays a crucial role in fracture healing. In the Gustilo-Anderson open fracture classification scale that is commonly applied to clinical practice for more than 4 decades, the severity classification of open fracture is mainly dependent on soft tissues, and the skeletal muscle is the primary tissue of them. It is also widely recognized that skeletal muscle can provide a vascular supply for nutrition and oxygen changes and supplies muscular osteoprogenitor cells to accelerate fracture healing [19]. However, increasing studies highlighted the important roles of myokines in fracture healing [79–81]. Kaufman et al. and Utvag et al. found that bone synthesis was enhanced by skeletal muscle-derived molecules while fracture healing was inhibited after a large muscle segment incision [79,80]. Lee et al. collected conditioned medium (CM) from the cultured C2C12 myoblasts and myotubes to investigate the muscle-bone interaction. They found that myotube CM suppressed bone resorption via inhibiting osteoclast differentiation, and enhancing pre-osteoblast viability and migration but suppressing its apoptosis, thereby promoting calvaria bone formation [81]. Besides, various myokines, including irisin, myostatin, IGF-1, and inflammatory factors (e.g., IL-1, IL-6, and TNF-α) were found to be differentially expressed or secreted in fractured patients [19,82].

Therefore, myokines are critical muscle-derived biochemical signals that influence fracture healing. Of course, the impaired or surrounding healthy bone tissues responded to skeletal injuries and secreted several osteokines like RANKL and SOST to regulate fracture healing locally [20,83]. Therefore, the systematic intervention for these biochemical signals of the musculoskeletal system provided new opportunities to accelerate fracture healing.

Up to now, myokines (irisin and myostatin) and osteokines (RANKL and SOST) have been demonstrated to regulate the multiple fracture healing processes, and corresponding interventions show compelling therapeutic effects, which will be discussed in the following.

3.1. Myokines

3.1.1. Myostatin

Several studies reported that myostatin responded to fracture and was differentially expressed during fracture healing [22,84]. Cho et al. found that myostatin expression in transcription level increased and peaked on day 1 after fracture, indicating its early response to injuries in the fracture healing cascade [84]. Elkasrawy et al. discovered that a strong and intense myostatin staining was localized at the impaired muscle fibers 12–24 h after a deep penetrant musculoskeletal injury. Myostatin staining was subsequently shown in the chondrocytes of soft callus, suggesting that the secreted myostatin by skeletal muscle could target these chondrocytes [22]. Furthermore, they demonstrated that exogenous myostatin treatment induced the decrease of callus cartilage and total bone volume in a dose-dependent manner. Several studies further demonstrated that myostatin deficiency or inhibition induced blastema formation in the early inflammation stage after fracture, and promoted bony callus formation with improved bone volume and strength [85,86]. These findings demonstrated that myostatin secretion by skeletal muscle was increased in response to musculoskeletal injuries, and myostatin inhibition could effectively promote fracture healing.

Interestingly, Sun et al. found that low-intensity pulsed ultrasound (LIPUS) inhibited myostatin expression in impaired quadriceps and promoted the new bone remodeling with increased osteoblast proliferation and reduced myostatin receptor expression, and recombinant myostatin proteins blocked these effects, indicating that LIPUS could promote bone healing via inhibiting myostatin expression [87]. Similarly, Zhang et al. found that the sarco-osteoporotic mice and sarcopenic mice had an increased myostatin expression after fracture and showed impaired fracture healing, while low-magnitude high-frequency vibration (LMHFV) could rescue this impaired fracture healing via myostatin suppression, with the enhanced callus formation and remodeling, as well as improved bone microarchitecture and strength [11]. These studies provided several convenient and safe approaches to physically regulate myostatin expression for better fracture healing.

In summary, myostatin, as a negative regulator of both skeletal muscle and bone, increased in response to musculoskeletal injury. The increased myostatin level suppresses the formation of fibrocartilage callus and bone tissues. Importantly, myostatin expression can be inhibited by both physical and pharmacological treatments, which effectively accelerates fracture healing by promoting callus formation and remodeling. Therefore, myostatin could be considered a potential molecular target for future fracture treatment.

3.1.2. Irisin

Bone was the primary target organ of irisin, and recombinant irisin could improve cortical bone geometry and enhance bending resistance and strength to fracture in young mice [27,29], indicating the possible role of irisin in accelerating fracture healing. Specifically, several studies revealed that serum irisin level was inversely associated with osteoporosis, fracture, and even fracture history [82,88,89]. Metzger et al. found that irisin could decrease the osteoclast surfaces and osteocyte-derived pro-inflammatory factors, as well as increase bone formation rate [90]. Grano and colleagues demonstrated that recombinant irisin administration promoted bone formation and bony callus remodeling, accelerating fracture healing in mice [91]. Another study by Grano et al. further discovered that recombinant irisin administration reduced the expression of inflammatory factors (TNF-α and MIP-1α) but increased the expression of pro-angiogenic factors (VEGF), metalloproteinase (MMP13) and osteogenic factors (BMP2) in fracture mice, indicating that irisin promote fracture healing by inhibiting inflammatory responses and enhancing vessel invasion, bone remodeling, and bone formation [92]. These findings revealed that a decreased serum irisin level was induced by fracture, and irisin administration could promote fracture healing by modulating inflammation, vascularization, bone formation, and bone remodeling. Surprisingly, Li et al. discovered that myogenic irisin can be upregulated by collagen II from squid cartilage (SCII), which effectively promoted endochondral osteogenesis and accelerated fracture healing processes [93]. Above all, irisin, a myokine released by skeletal muscle, effectively promotes fracture healing by regulating multiple biological processes. Thus, irisin is a potential treatment target for better fracture healing as well.

3.2. Osteokines

3.2.1. RANKL

The balance of the OPG/RANKL/RANK axis regulates bone remodeling, which determines its non-negligible roles in regulating fracture healing. In the past few decades, many studies have uncovered the inseparable association between the OPG/RANKL/RANK axis and fracture healing. It was well reported that OPG and RANKL were involved in the healing processes of fracture, with a significantly increased RANKL and OPG in fractured patients, especially in fracture hematoma [94,95]. However, RANKL and OPG ratio after fracture exhibited a controversial change in up-regulation, down-regulation, no significant difference, as well as a fluctuant trend during fracture healing, which could be attributed to the different species, participant features (i.e., the capacity of fracture healing), and fracture healing stages [83,94–98]. Although the change in RANKL and OPG ratio was uncertain, it was demonstrated that the imbalance of RANKL and OPG could result in bone disorders and delayed fracture healing [99,100]. In addition, the inhibition of RANKL has shown attractive effects on promoting fracture healing. Delos et al. and Flick et al. employed RANK-Fc to inhibit RANK signaling and found that RANKL inhibition had no adverse influence on fracture healing and even increase intact bone strength in mice [101,102]. Gerstenfeld and colleagues also demonstrated that RANKL inhibition by Damb enhanced bone strength and stiffness during fracture healing while cartilage removal and fracture callus remodeling was delayed [24]. Besides, Bougioukli et al. systemically administered OPG in combination with locally delivered BMP-2 (an osteoinductive protein that is associated with both bone formation and resorption) to treat fractures in mice and found that the combined OPG and BMP-2 promoted bone healing as compared to BMP-2 alone since OPG potentially inhibited the BMP-2 mediated bone resorption [103].

In general, RANKL/OPG played a critical role in fracture healing by regulating bone resorption and remodeling, and the imbalance of RANKL and OPG impaired fracture healing. Interestingly, although the fibrocartilage and bone remodeling were delayed, RANKL inhibition supported the fracture healing with enhanced strength and stiffness in both impaired and intact bones.

3.2.2. SOST

SOST, a marker of bone turnover, also involves the regulation of fracture healing processes. It was reported that the fractured patients exhibited a significantly and continuously increased SOST concentration in both serum and hematoma compared to the controls [20]. Moreover, the down-regulated SOST expression was crucial to initiate the early healing processes of fragility fracture [104].

Up to now, SOST inhibition has been widely demonstrated to promote various fracture healing processes. Several studies found that SOST

deficiency efficiently promoted bone bridging, intramembranous ossification, and callus maturation by enhancing β-catenin activity, which accelerated fracture healing with increased bone formation and strength in mice [105,106]. Morse et al. confirmed that SOST knockout mice exhibited accelerated fibrocartilage removal and improved bone formation and strength during fracture healing while the bone union was not significantly improved [107]. Similarly, the SOST inhibition mediated by antibodies also showed great potential to accelerate fracture healing. Agholme et al. and Suen et al. treated rats with SOST antibody (SOST-Ab) and found that SOST-Ab treatment significantly accelerated fracture healing, with a notably promoted mineralized callus formation, increased BMD, as well as enhanced neovascularization [108,109]. Besides, the SOST-Ab was found to not only increase bone mass, density, and strength during fracture healing in mice but also to rescue the impaired osteogenesis of diabetic mice by improving osteoblast differentiation and bone mineralization [21,110]. Therefore, SOST inhibition at the early phase of fracture healing was a compelling strategy to accelerate the healing processes of fracture.

Interestingly, Alzahrani et al. compared the efficiency of SOST knockout and SOST-Ab injection on fracture healing in mice and found that SOST antibody injection had similar therapeutic outcomes to SOST knockout but achieved complete fracture healing at an earlier stage [111]. Moreover, SOST-Ab treatment by subcutaneous injections was reported to not only promote impaired metaphyseal bone healing but increase bone formation in untraumatized bone [109], suggesting its great potential for improving bone mass and strength in the whole body after systemic administration. Thus, SOST inhibition by antibody seemed to be a safer and more effective strategy to promote fracture healing. However, the safety and effectiveness of SOST antibodies for fracture healing should be further validated in fracture patients.

In summary, myokines (myostatin and irisin) and osteokines (RANKL and SOST) are differentially expressed in response to fracture or musculoskeletal injuries, and the interventions for these biochemical factors could regulate multiple biological healing processes, accelerating fracture healing (Fig. 3).

4. Potential intervention targets based on muscle-bone crosstalk for osteosarcopenia-related fracture

Up to now, no pharmacological agents have been approved by Food and Drug Administration for osteosarcopenia, and only physical activity, especially resistance exercise, was well recognized as an effective treatment. However, in fractured patients, increased bed rest time and reduced physical activity are inevitable, which means that resistance exercise and functional recovery cannot be effectively obtained in the short term. Thus, new treatments are urgent to be developed for fracture patients with osteosarcopenia. With a further understanding of muscle-bone crosstalk, developing technology or drug to regulate muscle-bone crosstalk is promising.

Among various myokines, myostatin emerges as the most promising molecular target. Clinical trials have reported that myostatin inhibition by its antibody LY2495655 and bimagrumab or soluble receptor ACE-031 can increase muscle mass and physical performance in sarcopenic patients [112,113]. Studies also demonstrated that increased myostatin levels in sarcopenic status hinder fracture healing [11], while myostatin inhibition promoted fracture healing and skeletal muscle regeneration simultaneously [86]. Besides, other myostatin inhibitors, such as follistatin were also reported to promote skeletal muscle and bone regeneration [86,114,115]. Surprisingly, the myostatin could also be regulated by some physical approaches, especially LMHFV, which was found to increase skeletal muscle mass and strength, promote callus formation, and accelerate fracture healing via myostatin suppression in sarcopenic mice [11,116]. These findings highlighted the great potential of myostatin inhibition through physical or chemical approaches in the future osteosarcopenia-related fracture treatment. However, no studies have evaluated the role of myostatin inhibition in both skeletal and muscle regeneration among fracture patients, and more clinical trials should be conducted to confirm its positive treatment effects. Irisin is another possible molecular target to improve skeletal muscle and bone metabolism, as well as accelerate fracture healing simultaneously. Irisin was well-accepted to improve the mass and function of skeletal muscle and bone [30,59]. Patients with osteoporotic fractures (e.g., vertebral and hip fractures) showed decreased serum irisin levels [82,117,118], and irisin administration are demonstrated to accelerate the healing processes of

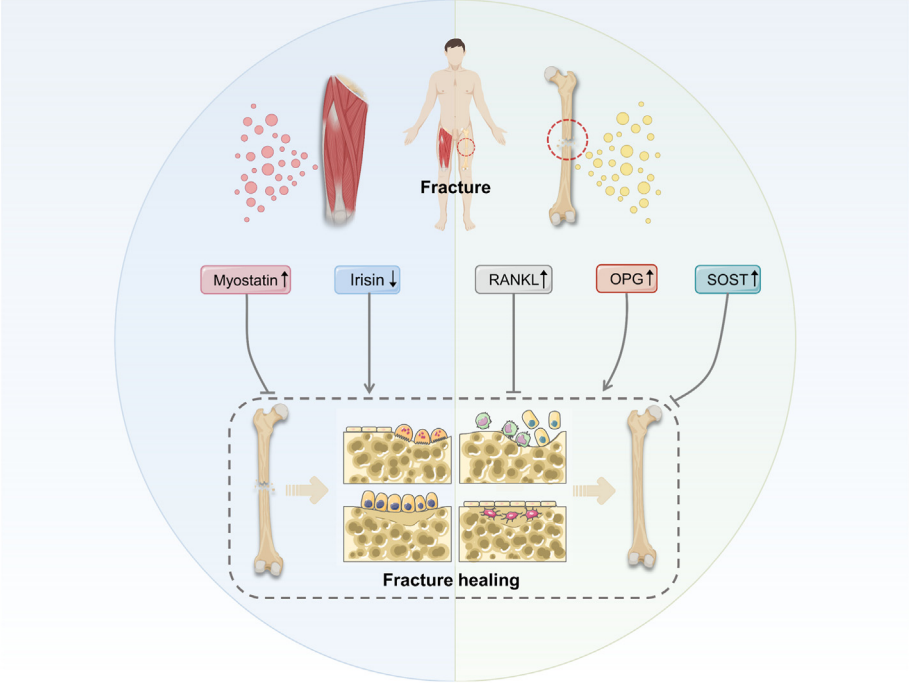

Figure 3. Myokines and osteokines differentially respond to fracture and regulate fracture healing.

fracture [91,92]. The level of irisin can be increased by some diet supplementation, such as SCII [93]. However, no clinical trials to investigate the effects of irisin on fracture patients with osteosarcopenia, and thereby the feasibility of irisin as a treatment target should be further determined.

The interventions targeting several osteokines (SOST and RANKL) also present potential to treat osteosarcopenia-related fractures. The increased SOST expression after fracture was found to delay fracture healing and decrease the mass and strength of skeletal muscle and bone. SOST deficiency or inhibition has shown to increase BMD in osteoporotic patients [74], improve muscle mass and function in diabetic or older mice [77,78], and promote fracture healing in rats and mice via regulating various healing processes [105–111], thereby showing the potential for osteosarcopenia-related fracture treatment. Compared to SOST deletion, SOST inhibition in the early phase of fracture healing is a more attractive strategy due to its higher safety and earlier fracture healing [111]. However, the compelling effects of SOST inhibition on muscle recovery and fracture healing were only observed on small animals, further studies on large animals or humans are necessary to validate them. Compare to SOST, RANKL shows a higher translational potential in osteosarcopenia-realted fracture since it has been served as a molecular

Table 1
Other potential targets for osteosarcopenia-related fracture via muscle-bone crosstalk.

Myokines/ Ostekines	Potential effects on osteosarcopenia-related fracture		
	Skeletal muscle	Bone	Fracture healing
IGF-1	Promote muscle regeneration [124]	Promote bone formation [125]	Accelerate fracture healing [119,126,127]
FGF-2	Stimulate muscle growth and inhibit muscle atrophy [128,129]	Stimulate bone formation [18]	Promote fracture healing [120,121,130]
Decorin	Promote skeletal muscle regeneration and repair [131]	Promote bone formation [132]	Involve in fracture healing [132]
BAIBA	Prevent muscle function loss [133]	Prevent osteocyte apoptosis and bone loss [133]	Not determined
BNDF	Regulate satellite cell function and muscle regeneration [134]	Promote the osteogenesis of BMSCs [135]	Stimulate VEGF secretion from osteoblasts during fracture healing [136]
METRNK	Improve muscle regeneration in aging [137]	Promote osteoblast differentiation [138]	Involve in fracture healing [138]
IL-6	Regulate muscle wasting and renewal [139]	Modulate bone formation and resorption [140]	Dual roles in fracture healing [141,142]
OCN	Maintain muscle mass [143]	Enhance bone mineralization and strength [144]	Not determined
PEG2	Improve muscle regeneration and function [145]	Induce bone formation and remodeling [146, 147]	Accelerate fracture healing [148]
Wnt3a	Promote myogenesis of stem cells [149]	Promote osteoblastogenesis and bone formation [150,151]	Involve in fracture healing [152]

Abbreviations: IGF-1, insulin-like growth factor-1; FGF-2, fibroblast growth factor-2; BAIBA, beta-aminoisobutyric Acid; BNDF, brain-derived neurotrophic factor; METRNL, meteorin-like; IL-6, interleukin-6; OCN, osteocalcin; PGE2, prostaglandin E2.

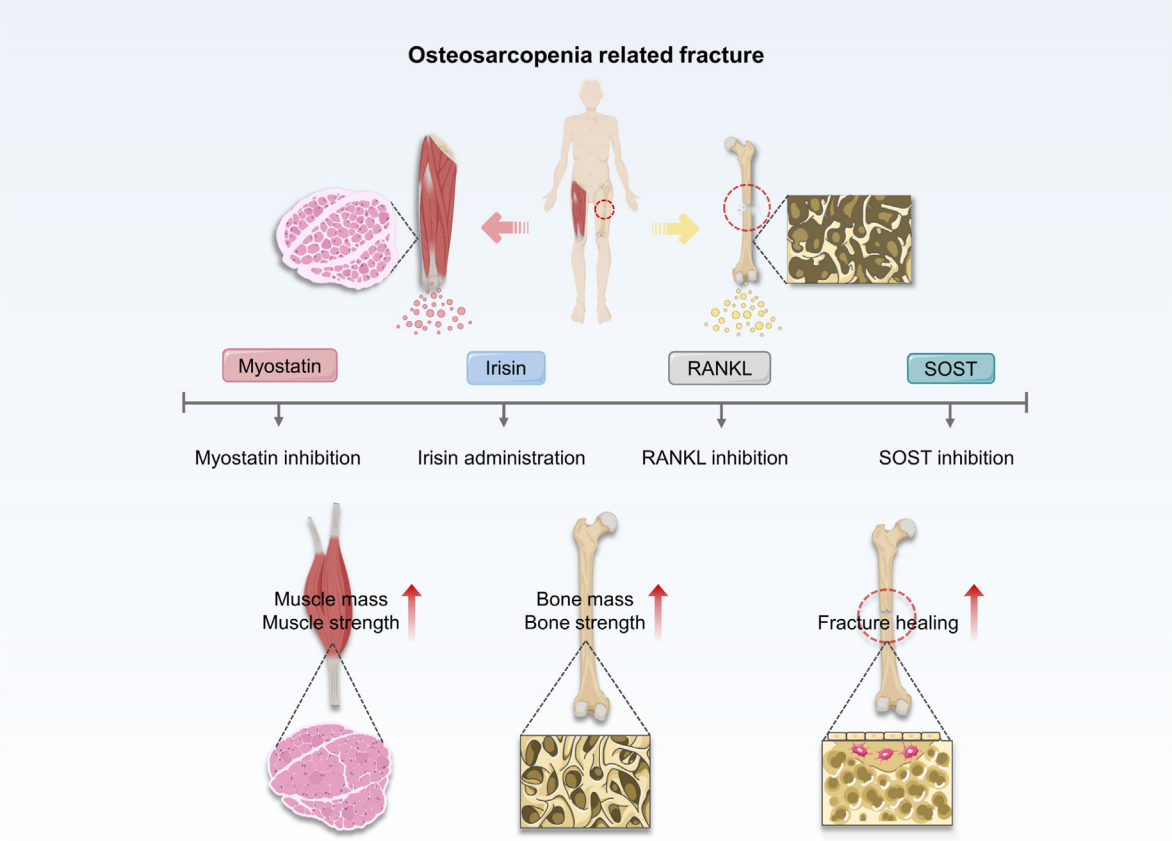

Figure 4. Potential myokine/osteokine targets for the treatment of osteosarcopenia-related fractures.

target for osteoporosis treatment in clinical. The inhibition of RANKL was also reported to improve skeletal muscle mass, strength, and function [67,69]. Inspiringly, Damb, a RANKL antagonist for osteoporosis treatment, was also demonstrated to effectively increase muscle mass, strength, and function [90], as well as improved bone strength and stiffness during fracture healing [24]. Thus, Damb is a promising drug to treat osteosarcopenia-related fractures, which should be further confirmed by randomized controlled trials.

Several myokines and osteokines also show the potential to serve as molecular targets for osteosarcopenia-related fracture treatment (Table 1). Their positive roles in regulating bone metabolism, muscle metabolism, or fracture healing suggest their capacity to intervene osteosarpenia-related fractures. Among these factors, IGF-1 and FGF-2 were well-accepted to promote skeletal muscle and bone formation [26]. The local delivery of these two factors was also been demonstrated to accelerate fracture healing in humans or large animals [119–121]. However, both these factors were expressed in various tissues and played significant roles in their development and homeostasis. The approaches of systemic intervention targeting muscle and bone should be further explored to minimize side reactions.

Above all, with a deeper understanding of the muscle-bone crosstalk, we have noticed the critical roles of myokines and osteokines in the incidence, development, and treatment of osteosarcopenia and fracture. Myostatin, irisin, SOST, and RANKL are potential molecular targets to treat osteosacopenia and osteosarcopenia-related fractures (Fig. 4). More clinical trials based on targeting myokines or osteokines are underway, and their effectiveness and safety to treat fracture patients with osteosarcopenia will be answered. Since these patients suffer from a combination of local fracture and systemic skeletal muscle and bone loss, the efficacy of these interventions should be evaluated with the status of facture, bone, and skeletal muscle considered. The time to bone union after fracture can be accessed with X-ray radiography, and the muscle and bone mass can be accurately determined by dual-energy X-ray absorptiometry (the preferred technique for sarcopenia and osteoporosis diagnosis) [3,120]. Additionally, the functional recovery of facture patients with osteosarcopenia, as indicated by skeletal muscle and bone strength, should be evaluated using several physical commonly-used assessments like grip strength, gait speed, short physical performance battery, and 400 m walk test [3,122,123]. These important outcomes should be considered in future clinical trials to prove the feasibility of regulating muscle-bone crosstalk for osteosarcopenia-related fracture treatment.

5. Conclusion

The muscle-bone crosstalk via biochemical signals regulates skeletal muscle and bone metabolism, probably participating in the development of musculoskeletal diseases. In this review, we discussed the possible role of myokines (irisin and myostatin) and osteokines (RANKL and SOST) in the development and treatment of osteosarcopenia, as well as fracture healing. Importantly, due to the compelling effects on improving the mass, strength, and functions of skeletal muscle and bone, as well as accelerating fracture healing, myostatin, irisin, RANKL, and SOST show great potential to serve as molecular targets for osteosarcopenia-related fracture treatment.

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CRediT authorship contribution statement

Renwang Sheng: Conceptualization, Investigation, Writing – original draft. **Mumin Cao:** Investigation, Writing – original draft. **Mingyuan Song:** Investigation, Writing – review & editing. **Mingyue Wang:** Visualization. **Yuanwei Zhang:** Methodology, Investigation. **Liu Shi:** Investigation. **Tian Xie:** Investigation. **Yingjuan Li:** Supervision. **Jinyu Wang:** Conceptualization, Writing – review & editing, Funding acquisition. **Yunfeng Rui:** Conceptualization, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare no competing financial interest.

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