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Review

MUSCLE-BONE CROSSTALK: INVOLVEMENT OF MYOKINES IN THE REGULATION OF OSTEOPOROSIS

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Abstract

Osteoporosis (OP) is a systemic skeletal disease, the development of which is co-regulated by multiple tissues throughout the body. As interdependent parts of the locomotor system, muscle and bone are in cross-talk and work together to maintain the dynamic balance of the musculoskeletal system. Previous studies viewed the musculoskeletal system as a mechanical structure and focused on the biomechanical interactions between the two. In recent years, the biochemical crosstalk between bone and skeletal muscle as endocrine organs has been emphasized. In particular, skeletal muscle regulates bone metabolism and OP development by secreting myokines. A comprehensive summary and update of the findings related to the regulation of bone metabolism by myokines in muscle-bone biochemical crosstalk is presented. In this review, we will classify myokines according to their influence on bone formation, bone resorption, and both, in order to gain insights into the pathogenesis of OP and to explore new therapeutic approaches. Furthermore, we also summarize the current myogenic factors or possible myogenic factors with potential research value on bone metabolism, hopefully providing directions for the research related to the musculoskeletal cross-talk and the regulation of bone metabolism by myogenic factors.

Keywords: Osteoporosis, muscle-bone crosstalk, skeletal muscle, bone metabolism, myokines.

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Introduction

Osteoporosis (OP) is a systemic bone metabolism disease that is intimately associated with age. It is characterized by attenuation of bone microstructure, decreased bone mass, increased bone fragility, and elevated fracture risk (Aibar-Almazán *et al.*, 2022). The prevalence of OP and the incidence of osteoporotic fractures are increasing annually as the global population ages (Anam and Insogna, 2021). According to the World Health Organization, OP is already the second prevalent health problem globally after cardiovascular diseases (Aibar-Almazán *et al.*, 2022; Clynes *et al.*, 2020). OP significantly impacts the health of the middle-aged and elderly population and poses a major public health challenge. Its pathogenesis correlates with reduced bone formation by osteoblasts and accelerated bone resorption by osteoclasts, which leads to a dysregulation of bone homeostasis and triggers progressive bone loss (Johnston and Dagar, 2020; Rachner *et al.*, 2011).

As a systemic skeletal disease, the development of OP is co-regulated by multiple systems and tissues, including but not restricted to the endocrine system, locomotor system (Harris *et al.*, 2023; Lin *et al.*, 2023). As essential energy-supplying organs involved in locomotion, there are close interactions and connections between skeletal muscle and bone. The interactions mainly manifest in biomechanical behavior and biochemical crosstalk. Researchers refer to the interaction and connection as muscle-bone crosstalk (Brotto and Bonewald, 2015; Karsenty and Mera, 2018). This review aims to explore the effect of myokines on bone metabolism and its mechanism in the biochemical crosstalk of muscle-bone crosstalk. By revealing the interactions between tissues and organs to regulate the effects on bone remodeling, it can contribute new perspectives and theoretical basis for the research and prevention of OP.

Muscle-Bone Interactions

As crucial interdependent components of the locomotor system, the synergy between muscle and bone functions together to maintain the dynamic equilibrium of the musculoskeletal system (Karsenty and Olson, 2016) (Fig. 1). Once this equilibrium is disrupted, metabolic and functional disorders can occur in both muscle and bone, with sarcope-

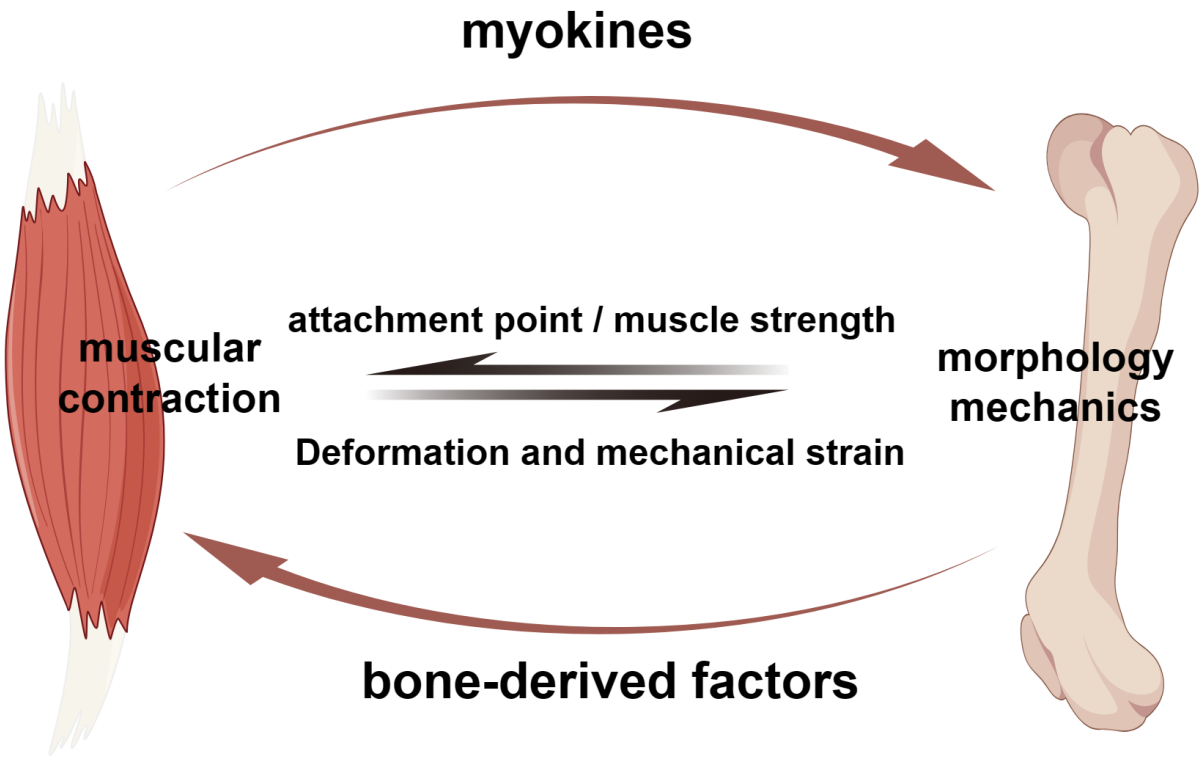

Fig. 1. Biomechanical interactions and biochemical crosstalk exist in bone and muscle cross-talk.

nia and OP being particularly prevalent. The concept of "osteosarcopenia" has been proposed to depict the coexistence of OP and sarcopenia (Hirschfeld *et al.*, 2017). In clinical treatment of OP with the receptor activator for nuclear factor-κB ligand (RANKL) inhibitor denosumab, the muscle strength of upper and lower extremities of patients was enhanced (Rupp *et al.*, 2022). As per research, positive correlation exists between bone density and muscle mass (Lima *et al.*, 2019). When muscle wasting and/or muscle atrophy occurs, the homeostasis of the musculo-skeletal system is disrupted, which leads to bone loss and disruption of the skeletal microstructure (Clynes *et al.*, 2021). Additionally, patients with OP and sarcopenia have a significantly higher risk of fracture than the healthy population. Both are considered to be critical drivers of increased fracture risk (Scott *et al.*, 2019; Teng *et al.*, 2021). Furthermore, fracture healing is strongly positively correlated with the degree and status of muscle tissue coverage. Even when the fracture site is overlaid with periosteum, which is abundant in blood vessels, bone repair is ineffective as compared to the overlaid muscle tissue (Utvåg *et al.*, 1998; Utvåg *et al.*, 1999; Utvåg *et al.*, 2003; Varey and Khan, 2013). To summarize, there exists a crucial and sophisticated regulatory function of muscle on the skeleton, and in-depth investigation of its specific regulatory mechanisms is significant for understanding the pathogenesis of OP and identifying therapeutic targets.

In the past, it was widely thought that muscle and bone interactions mainly relied on mechanical modulation. Bone furnishes the necessary attachment points for skeletal muscle, and the strength from skeletal muscle contraction acts on the bone. In this process, the skeleton performs a supportive and stabilizing role, while the muscles drive movement by exerting forces on the skeleton and influence the metabolism of the skeleton and changes in bone mass by regulating the loads placed on the skeleton (Xie *et al.*, 2024). As early as 1987, Frost proposed the "mechanoregulation theory", exploring how muscles and bones interact through mechanical signals to regulate bone structure and function (Frost, 1987). Numerous subsequent researches have substantiated this notion. This means that the morphology and mechanical properties of the skeleton have an effect on the force output and movement patterns of the muscles. Correspondingly, the forces generated by muscle contractions act on the bones to regulate their growth and plasticity by affecting their deformation and mechanical strain (Berman *et al.*, 2015; Buck and Stains, 2024; English *et al.*, 2014; Farage-O'Reilly *et al.*, 2024; Frost, 2003). For

instance, in resistance exercise, high-speed contractions are more stimulating to the bones than slow contractions and therefore more favorable to bone growth (Stengel *et al.*, 2005). Moreover, impact activities have also been shown to improve bone density and bone health (Moreira *et al.*, 2014). In summary, there is a formidable biomechanical interaction between muscle and bone in the locomotor system, and this interaction has a profound consequence on their function and activity.

In recent years, with the increasing attention paid to the function of bone and muscle as endocrine organs, the biochemical interaction between the two has gradually become a research focus. Skeletal muscle and bone secrete multiple factors that collaborate and communicate with each other through autocrine, paracrine, and endocrine realizations that collectively maintain the physiological homeostasis of muscle and bone (Karsenty and Olson, 2016). Cytokines and other peptides secreted by muscle fibers are known as myokines (Brotto and Bonewald, 2015). These myokines help regulate muscle mass and energy metabolism in skeletal muscle and influence other tissues, especially in the skeleton. Blood circulation is the predominant pathway by which myokines exert remote interactions. Skeletal muscle and bone, as neighboring organs, can also undergo intercellular and intertissue communication via extracellular vesicles (EVs) and diffusion (Ma *et al.*, 2023; Qin and Dallas, 2019; Takafuji *et al.*, 2020). Whereas molecules with molecular weights less than 40 kDa readily reach neighboring tissues by passive diffusion through the semi-permeable periosteum, factors larger than 40 kDa reach the skeleton to play their functions primarily through blood circulation or EVs transport (Lai *et al.*, 2014). As a conclusion, myokines, playing an essential role in musculoskeletal crosstalk and pivotal in the regulation of skeletal development, growth and function, have become an integral part of research on the development and prevention of OP.

Regulation of Myokine Release

The physiopathological factors that play a major role in the regulation of myokines in muscle-bone interactions are exercise, aging and inflammation. Firstly, in the inflammatory state, inflammation leads to an increased release of cytokines and inflammatory mediators, which directly or indirectly affect the muscle cells and, consequently, the release of myokines (Buchmann *et al.*, 2022). In the inflammatory state, muscle cells produce more inflammation-associated myokines, but this also leads to a decrease in muscle mass and function, affecting normal muscle function and metabolism, which in turn affects myokine synthesis and release (Tu and Li, 2023).

In terms of exercise, moderate exercise increases metabolism throughout the body and promotes the release of myokines. For example, high-intensity exercise increases the metabolic demand of muscle cells and promotes the release of myokines such as Irisin and myostatin from the cells (Iizuka *et al.*, 2014; Pedersen and Febbraio, 2012). Aerobic exercise can increase the metabolic demand of muscles and stimulate skeletal muscles to secrete some myokines with anti-inflammatory effects, which can help reduce systemic chronic inflammation (Petersen and Pedersen, 2005).

During the aging process, muscle mass and function decline with age, and the metabolic capacity of muscle cells decreases, which directly affects the production and release of myokines (Distefano and Goodpaster, 2018). Secondly, during the aging process, there is an increase in systemic inflammation, and there may be a relative increase in inflammation-associated myokines, which can further exacerbate muscle aging and functional decline (Ferrucci *et al.*, 2005). In addition, mitochondrial function decreases in aging, affecting energy production in muscle cells, which in turn affects the secretion of myokines associated with energy metabolism (Grevendonk *et al.*, 2021).

Furthermore, myokine expression and secretion is a complex process involving multiple signalling pathways and regulatory mechanisms. For example, in inflammation-stimulated myokine synthesis and secretion, nuclear factor-kappa-B (NF-κB) plays a key role in this process. Inflammatory factors can activate the NF-κB signalling pathway, thereby stimulating myokine synthesis and secretion (Ren *et al.*, 2022); AMP-activated protein kinase (AMPK) is a key molecule in the regulation of biological energy metabolism. Increased energy expenditure during exercise activates the AMPK signalling pathway, which promotes muscle glucose uptake and fatty acid oxidation, improves muscular endurance and metabolic adaptations, and thus regulates muscular energy metabolism and myokine secretion (Ahsan *et al.*, 2022; Zhou *et al.*, 2022). In addition, mitogen-activated protein kinase (MAPK) signalling pathway and PI3K/Akt signalling pathway may also be involved in the synthesis and secretion of myokines by regulating gene expression and protein translation. In conclusion, the expression and secretion of myokines involves a variety of signalling pathways and regulatory mechanisms, which do not exist in isolation from each other, but rather cross and influence each other to form a complex network, which together regulate the expression and secretion of myokines.

In summary, exercise helps to promote the release of myokines, whereas aging and inflammation tend to lead to a decrease in the release of myokines, which in turn affects muscle-skeletal communication and overall health.

Myokines—Regulator of Dynamic Equilibrium

Myokines are mainly composed of small molecule peptides, growth factors, cytokines, and small molecule organic acids. These myokines play a vital function in bone formation and resorption by regulating the proliferation, differentiation and function of bone-related cells, while af-

fecting the bone microenvironment to maintain bone homeostasis and bone mass balance (Lara-Castillo and Johnson, 2020). Nevertheless, the functions and mechanisms of different myokines in the regulation of bone metabolism vary, and there are two main categories: positive regulation of bone metabolism (Fig. 2) and negative regulation of bone metabolism (Fig. 3). In order to better describe the effects of different myokines on bone metabolism, we categorised them as affecting bone formation, affecting bone resorption and affecting both bone formation and bone resorption, so as to describe the specific function and mechanism of each myokine (Table 1). We will investigate the concrete functions and mechanisms of each myokine in the following section.

Affecting Bone Formation

BDNF

Brain derived neurotrophic factor (BDNF), is a neurotrophic factor expressed primarily by brain cells. Delezie *et al.* (2019) discovered that muscle contraction promotes the secretion of BDNF from skeletal muscle. The ability of BDNF to regulate stem cell differentiation and survival decreases with age and inhibits bone loss in ovariectomy (OVX) mice, so levels of BDNF may have an effect on both aging and postmenopausal osteoporosis (Meng *et al.*, 2023; Xiong *et al.*, 2022). In rat bone tissue, BDNF and its receptor, the tropomyosin-related kinase B (TrkB) mRNA, were highly expressed and jointly involved in the regulation of bone tissue development and remodeling (Yamashiro *et al.*, 2001). Further studies revealed that the binding of BDNF to TrkB receptor could promote the expression of osteoblast differentiation-related transcription factors, such as Runt-related transcription factor 2 (Runx2). In *in vitro* experiments with human marrow mesenchymal stem cells (HMSCs) and *in vivo* experiments with a nude mouse subcutaneous graft model, BDNF treatment promoted osteogenic processes and neurogenesis (Liu *et al.*, 2018). Additionally, skeletal muscle exercise and electrical stimulation increased BDNF release. During fracture healing, BDNF and TrkB are not only involved in angiogenesis and osteogenesis, but also can promote osteogenesis indirectly through neural mechanisms. These studies provide robust evidence for the function of BDNF in promoting bone formation by promoting osteoblast differentiation (Gomarasca *et al.*, 2020; Kilian *et al.*, 2014).

OGN

Osteoglycine (OGN) is a myokine that is essential in bone tissue and has a significant effect on osteoporosis. *In vivo* experiments have shown that OGN inhibits the differentiation of bone marrow mesenchymal stem cells (BMSCs) to adipocytes and promotes the differentiation of osteoblasts. An effect alters the equilibrium of BMSCs differentiation between osteoblasts and adipocytes, ultimately leading to an increase in bone mass (Chen *et al.*, 2017). Furthermore, OGN enhances bone mineralization by increasing the expression of osteoblast phenotype-related genes such as alkaline phosphatase (ALP), type I collagen, and osteocalcin (OCN). In contrast, OGN decreases the mRNA expression levels of the transcription factors Runx2 and Osterix, which are involved in osteoblast differentiation (Tanaka *et al.*, 2012b). Consequently, OGN is considered to be a myokine capable of inhibiting osteogenic differentiation of early immature osteoblasts but promoting osteoblast differentiation at later stages of differentiation.

SPARC

Osteonectin (ON), also known as secreted protein acidic and rich in cysteine (SPARC), is expressed and secreted by skeletal muscle after exercise (Aoi *et al.*, 2013). According to research, the serum water life of SPARC in osteoporosis patients is significantly decreased (Dalle Carbonare *et al.*, 2009). SPARC contributes to calcium deposition as well as promotes osteoblast proliferation and differentiation, and plays a crucial role in the process of bone formation (Cassuto *et al.*, 2018). The P38 signaling pathway has been widely recognized as a central regulatory mechanism of osteoblast mineralization, and Zhu *et al.* (2020; 2023b) further demonstrated that it is through the P38 signaling pathway that SPARC regulates the mineralization process of the extracellular matrix, and that SPARC has a bi-directional modulatory effect on osteoblast mineralization, i.e., low doses increased osteoblast mineralization, while high doses inhibited osteoblast mineralization. In SPARC knockout mice, the mouse phenotype showed damaged bone formation and increased adipose tissue formation (Delany *et al.*, 2003). Reportedly, c-Fos can be activated in osteoclast precursors and act on osteoclast to promote their proliferation and differentiation (Boyce *et al.*, 2005). However, the effects of c-Fos on adipogenesis have not been previously reported. Some studies have demonstrated that SPARC can act as a decoy counterpart of c-Fos and bind to c-Fos, thereby inhibiting adipose differentiation of BMSCs and promoting cellular differentiation of BMSCs (Hatori *et al.*, 2023). In the pathological process of heterotopic ossification (HO), the silencing of SPARC gene can effectively inhibit HO and could be a potential strategy for the treatment of HO (Wang *et al.*, 2019). In summary, SPARC stimulates the proliferation and differentiation of osteoblasts and thus promotes bone formation and repair.

Affecting Bone Resorption

IL-1 and IL-8

The interleukin (IL) family (interleukins) plays a crucial role in maintaining skeletal homeostasis. Interleukins that negatively regulate bone mainly include IL-1, IL-7, IL-8, IL-11, IL-17, IL-19, IL-23, IL-34, etc. (Chen *et al.*, 2024; Cheng *et al.*, 2017; Dai *et al.*, 2023; Kang and Zhang, 2014; Kim *et al.*, 2017; Moon *et al.*, 2012), while interleukins that positively regulate bone include IL-3, IL-4, IL-10, IL-

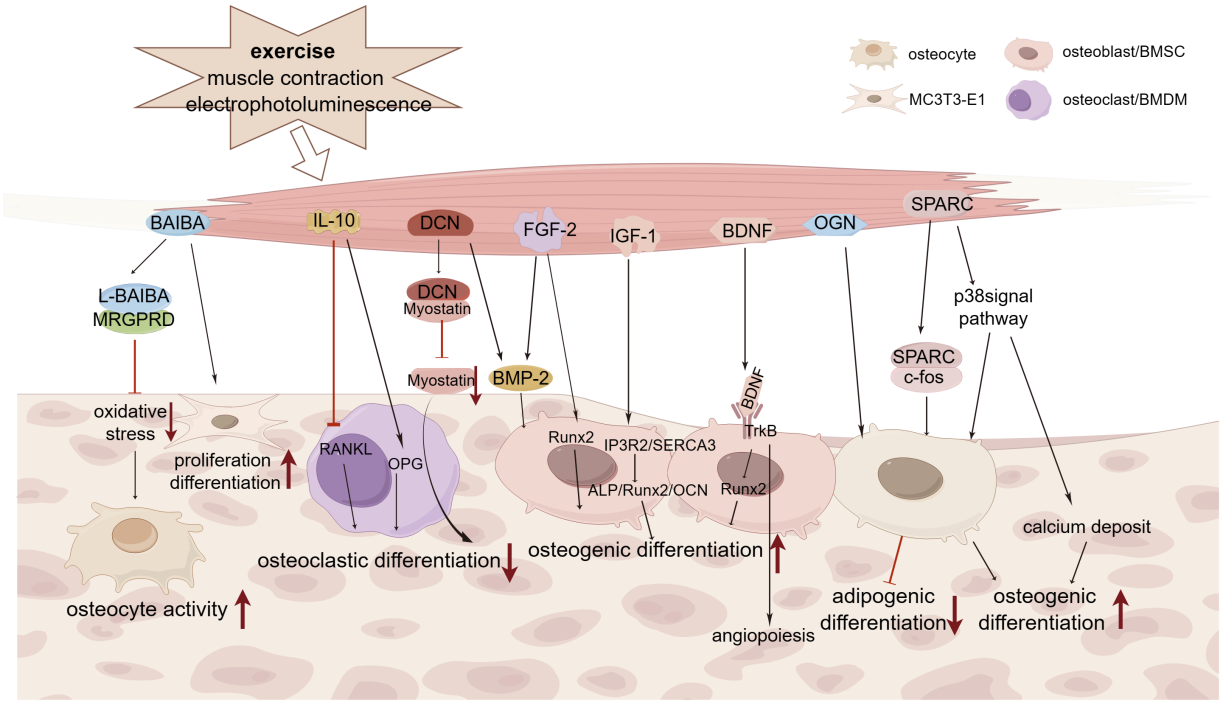

Fig. 2. Mechanisms of negative regulation of bone metabolism by myokines. BAIBA, β-aminoisobutyric acid; MRGPRD, Mas related G protein coupled receptors D; IL, interleukin; RANKL, receptor activator for nuclear factor-κB ligand; OPG, osteoprotegerin; DCN, decorin; FGF-2, fibroblast growth factor-2; BMP-2, bone morphogenetic protein 2; Runx2, Runt-related transcription factor 2; IGF-1, insulin-like growth factor-1; ALP, alkaline phosphatase; OCN, osteocalcin; BDNF, brain derived neurotrophic factor; TrkB, tropomyosin-related kinase B; OGN, osteoglycine; SPARC, secreted protein acidic and rich in cysteine; BMSC, bone marrow mesenchymal stem cell; BMDM, bone marrow-derived macrophages.

12, IL-27, IL-33, etc. (Cheng *et al.*, 2011; Kiyomiya *et al.*, 2015; Lee *et al.*, 2016; Shukla *et al.*, 2017). These cytokines have a significant impact on the process of bone formation and resorption, promoting or inhibiting the homeostatic balance of bone. In particular, IL-1, IL-6, IL-7, IL-8, IL-10, and IL-15 can be secreted by myocytes under different conditions and are categorized as myokines, whose effects on bone will be described in detail in the corresponding module.

IL-1, and IL-8 are all myokines belonging to the interleukin family members that promote osteoclast differentiation and bone resorption. According to research, the expression and secretion level of serum IL-1 in the elderly population and postmenopausal women are significantly increased (Freitas *et al.*, 2024; Malutan *et al.*, 2014). But this may be due in part to the secretion of inflammatory cells, and not entirely to myokines. Moreover, the level of IL-8 is closely related to the occurrence of vertebral osteoporosis (Mundy, 2007; Qiao *et al.*, 2023; Zhu *et al.*, 2023a). IL-1 and IL-8 can be secreted by skeletal muscle stimulated by muscle contraction during exercise workouts (Chiba *et al.*, 2015; Pedersen and Febbraio, 2012), and have been associated with RANKL-induced bone resorption in OP. Both IL-1 and IL-8 indirectly enhance osteoclasts by enhancing RANKL expression differentiation, which are important stimulators for bone resorption (Jules *et al.*, 2012; Kopesky *et al.*, 2014). In addition, research has shown that IL-1 can also directly activate receptor activator for nuclear factor-κB (RANK) signal transduction to regulate osteoclast formation, thereby promoting bone resorption and affecting bone metabolism (Lee *et al.*, 2010). And blocking anti-IL-8 antibodies or using IL-8 receptor inhibitors can inhibit osteoclastogenesis (Kopesky *et al.*, 2014). In summary, IL-1 and IL-8 negatively regulate bone metabolism by facilitating osteoclast differentiation to potentiate bone resorption.

IL-7

IL-7 is a myokine secreted by skeletal muscle cells with as yet undefined secretion conditions (Pedersen and Febbraio, 2012). IL-7 is highly expressed in OVX mice and is negatively associated with bone mass (Weitzmann *et al.*, 2002). It has been demonstrated that IL-7 promotes osteoclast differentiation by enhancing osteoclast cytokine production by T cells (Weitzmann *et al.*, 2000). Nevertheless, research on the application of IL-7Rα target antibody to collagen-induced arthritis (CIA) mice found that blocking the IL-7/IL-7R pathway reduced osteoclast formation by

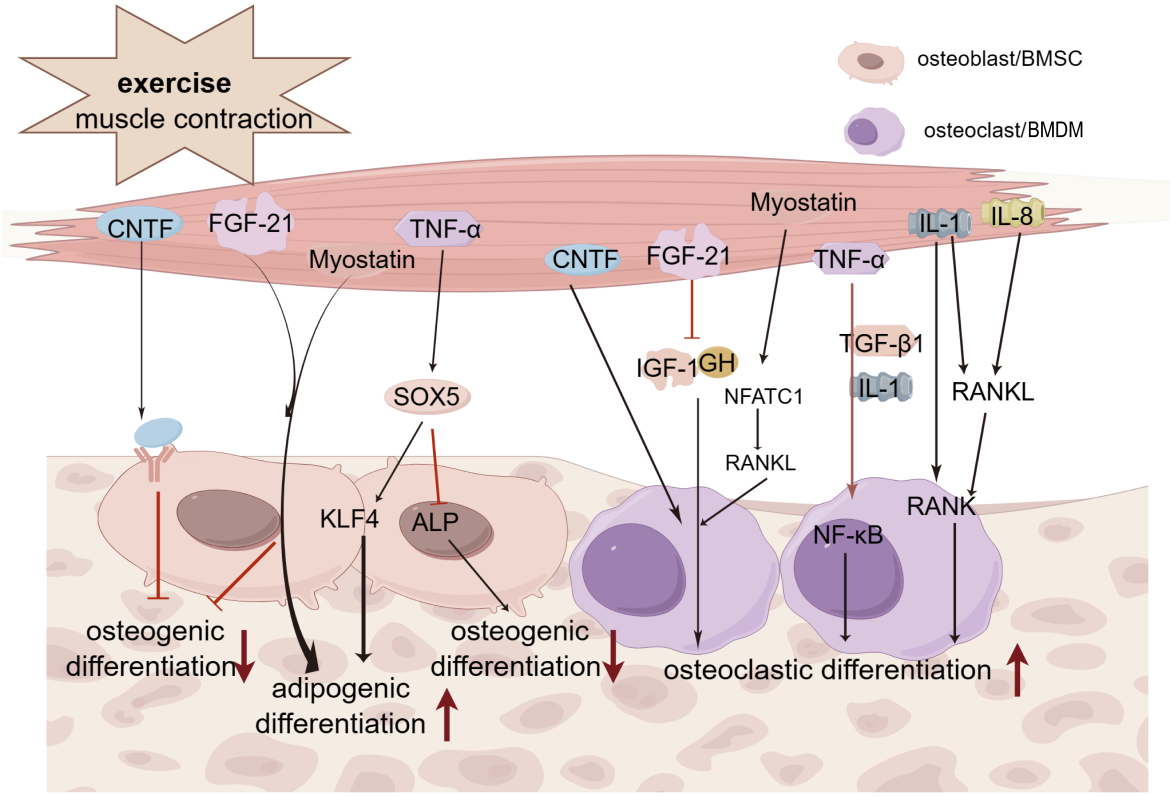

Fig. 3. Mechanisms of positive regulation of bone metabolism by myokines. CNTF, ciliary neurotrophic factor; FGF-21, fibroblast growth factor-21; TNF-α, tumor necrosis factor-α; GH, growth hormone; NFATC1, nuclear factor of activated T cells; TGF-β, transforming growth factor beta; NF-κB, nuclear factor-kappa-B; RANK, receptor activator for nuclear factor-κB; SOX5, SRY-box transcription factor 5; KLF4, Kruppel-like factor 4.

changing the RANKL/RANK/osteoprotegerin (OPG) ratio. To explore the function and mechanism of this pathway in depth, the results showed that IL-7 can also potentially restrain osteoclast formation directly through the signal transducer and activator of transcription 5 (STAT5) signaling pathway (Xu *et al.*, 2021). In summary, IL-7 has a bidirectional regulatory effect on osteoclasts. The underlying reasons for this discrepancy could be that the bidirectional regulatory effect of IL-7/IL-7R signaling on osteoclast differentiation is equilibrated in the context of normal bone immunity, but is disrupted in diseases such as rheumatoid arthritis (Xu *et al.*, 2021).

Affecting Both Bone Formation and Resorption

BAIBA and GABA

β-aminoisobutyric acid (BAIBA) is a novel amino acid that was first discovered in urine (Crumpler *et al.*, 1951). It is secreted by PGC-1α-expressing skeletal muscle cells, and its secretion is positively correlated with the amount of exercise. According to research, in women with osteoporosis, the serum concentration of BAIBA is decreased and the risk of fracture is increased (Wang *et al.*, 2020b). BAIBA exists in two enantiomers, D-BAIBA and L-BAIBA. L-BAIBA originates from muscle contraction and binds to Mas related G protein coupled receptors D (MRGPRD), thereby inhibiting oxidative stress-induced cell death, which in turn maintains osteoblast activity and prevents bone loss (Hamrick and McGee-Lawrence, 2018; Kitase *et al.*, 2018). Notably, the expression level of MRGPRD was higher in osteoblasts of young mice and significantly lower in older mice. Thus, the response of osteoblasts to BAIBA diminishes with age, which may contribute to the development of bone loss. Furthermore, BAIBA was demonstrated to stimulate the proliferation and differentiation of MC3T3-E1 cells (Zhu *et al.*, 2018). γ-aminobutyric acid (GABA), a myokine similar to BAIBA, was observed to be significantly increased in plasma and skeletal muscle levels after exercise. GABA may act as a PGC1q-mediated myokine role and plays an influential aspect in the release of growth hormone in the adaptive response to exercise (Roberts *et al.*, 2017). It has been pointed out that both aminobutyric acid is positively correlated with bone mineral density (BMD) and negatively correlated with the risk of osteoporosis, and can be used as a biomarker for the diagnosis of osteoporosis (Wang *et al.*, 2020b). In summary, BAIBA and GABA promote bone formation by regulating osteoblast activity and osteoclast differentiation.

Table 1. Categorization of myokines regulating bone metabolism and their mechanisms of action.

Myokins	Effect on bone resorption	Effect on bone formation	Ref
Affecting bone formation			
BDNF	Not determined	BDNF and TrkB combine to promote osteoblast formation	Liu *et al.*, 2018 Gomarasca *et al.*, 2020
OGN	Not determined	Increased bone mineralization and increased osteoblast formation	Chen *et al.*, 2017 Tanaka *et al.*, 2012b
SPARC	Not determined	Increased bone mineralization and increased osteoblast formation	Cassuto *et al.*, 2018 Zhu *et al.*, 2020
Affecting bone resorption			
IL-1	Promote osteoclast formation, and increase bone resorption	Not determined	Jules *et al.*, 2012 Lee *et al.*, 2010
IL-7	Promote osteoclast differentiation. Inhibits osteoclast formation through STAT5 signaling pathway	Not determined	Weitzmann *et al.*, 2000 Weitzmann *et al.*, 2002 Xu *et al.*, 2021
IL-8	Enhanced osteoclast generation induced by RANKL	Not determined	Kopesky *et al.*, 2014
Affecting both bone formation and resorption			
BAIBA	Prevent bone loss	BAIBA stimulated the proliferation and differentiation of MC3T3-E1 cells	Kitase *et al.*, 2018 Zhu *et al.*, 2018 Hamrick and McGee-Lawrence, 2018
CNTF	Stimulates osteoclast formation	Inhibit osteoblast differentiation and inhibit bone formation	Johnson *et al.*, 2014 Yong *et al.*, 2022
DCN	Prevent bone loss	Promotes calcium deposition and improves bone formation	Kanzleiter *et al.*, 2014 Han *et al.*, 2015
FGF-2	Disruption of the FGF-2 gene leads to decreased bone mass	FGF-2 regulates the expression of transcription factors Runx2 and Osterix to promote the differentiation of osteoblasts.	Kodama *et al.*, 2009 Montero *et al.*, 2000
FGF-21	FGF-21 may promote bone resorption by inhibiting IGF-1 and GH.	Stimulate BMSC lipogenic differentiation to inhibit osteogenic differentiation	Zhang *et al.*, 2012 Wei *et al.*, 2012 Wu *et al.*, 2012
GABA	Prevent bone loss	Promote bone formation	Wang *et al.*, 2020b
IGF-1	Not determined	Binding with IGF-1R in the periosteal promotes osteoblast differentiation.	Kirk *et al.*, 2020 Tahimic *et al.*, 2013 Tresguerres *et al.*, 2022
IL-6	Promote osteoclast formation and inhibited RANK pathway to inhibit osteoclast differentiation	Inhibit osteoblast differentiation, and activation of JAK/STAT3 pathway promoted osteoblast differentiation	Feng *et al.*, 2022 Yoshitake *et al.*, 2008 Kaneshiro *et al.*, 2014
IL-10	Prevent bone loss	Promote bone formation	Sapra *et al.*, 2021 Wang *et al.*, 2020a

Table 1. Continued.

Myokins	Effect on bone resorption	Effect on bone formation	Ref
IL-15	Stimulate osteoclast production. Activation of NK cells stimulated osteoclast apoptosis	IL-15 overexpression up-regulates bone mineral content.	Okabe *et al.*, 2017 Takeda *et al.*, 2014 Quinn *et al.*, 2009
Irisin	Promote proliferation and differentiation of BMDM	Up-regulated expression of OPN and sclerostin enhances osteoblast differentiation	Colaianni *et al.*, 2014 Estell *et al.*, 2020
LIF	Promote osteoclast differentiation	Promote BMSCs osteoblast differentiation	Weivoda *et al.*, 2020 Liang *et al.*, 2021
Myostatin	Activation of NFATC1 pathway accelerates osteoclast formation induced by RANKL.	Inhibit osteoblast generation	Deng *et al.*, 2017 Dankbar *et al.*, 2015 Mitra *et al.*, 2023
METRNL	Inhibit bone resorption. Inhibiting the effect of inflammatory markers on bone resorption	In MG63 cells, METRNL overexpression resulted in reduced mineralized nodules and inhibited OPG and OPN mRNA expression.	Jung *et al.*, 2018 Gong *et al.*, 2016
PGE2	Promote osteoclast differentiation and inhibit osteoclast activity	Promote BMSC differentiation and increase bone formation	Arikawa *et al.*, 2004 Kobayashi *et al.*, 2005 Chen *et al.*, 2019
TNF-α	TNF-α can induce osteoclast formation independently of RANKL signaling.	Inhibit osteogenic differentiation of BMSCs	Kobayashi *et al.*, 2000 Xu *et al.*, 2018

BDNF, brain derived neurotrophic factor; TrkB, tropomyosin-related kinase B; OGN, osteoglycine; SPARC, secreted protein acidic and rich in cysteine; IL, interleukin; RANKL, receptor activator for nuclear factor-κB ligand; BAIBA, β-aminoisobutyric acid; CNTF, ciliary neurotrophic factor; DCN, decorin; FGF-2, fibroblast growth factor-2; Runx2, Runt-related transcription factor 2; FGF-21, fibroblast growth factor-21; GH, growth hormone; GABA, γ-aminobutyric acid; IGF-1, insulin-like growth factor-1; RANK, receptor activator for nuclear factor-κB; OPN, osteopontin; LIF, leukemia inhibitory factor; BMSCs, bone marrow mesenchymal stem cells; NFATC1, nuclear factor of activated T cells; METRNL, meteorin-like; OPG, osteoprotegerin; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor-α; STAT5, signal transducer and activator of transcription 5; BMDM, bone marrow-derived macrophages; JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; NK, natural killer.

CNTF

Ciliary neurotrophic factor (CNTF), a polypeptide hormone-like protein encoded by specific genes, is categorized in the family of IL-6 cytokines secreted by skeletal muscle (Sims, 2016). Furthermore, *in vitro* experiments have indicated that binding of CNTF to its soluble receptor inhibits osteoblast gene expression and has an inhibitory effect on osteoblast differentiation, and that in myotube-conditioned medium, CNTF can stimulate osteoclast formation in combination with other myofactors (Johnson *et al.*, 2014). Besides, studies in dental osteoblasts identified significant attenuation of mineralized nodule formation, impaired OPG release, and significant down-regulation of mRNA levels of Runx2, OCN, bone morphogenetic protein 7 (BMP-7), and bone sialoprotein (BSP) after stimulation with exogenous CNTF, so CNTF was hypothesized to be a potent inhibitor of osteoprogenitivity (Johnson *et al.*, 2014; Yong *et al.*, 2022). However, it was surprisingly found that in female mice, CNTF inhibited bone mineralization and hindered trabecular bone formation, whereas in male mice, CNTF promoted bone cortical formation, but the specific mechanism was not known (McGregor *et al.*, 2010). To sum up, CNTF can inhibit osteoblast differentiation and bone formation on the periosteum, and it is regarded as a negative regulator of bone metabolism.

DCN

Decorin (DCN) is a small molecule proteoglycan and a myokine regulated by exercise. Research has shown that DCN can promote fracture healing, and the degree of DCN glycosylation is reduced in mice with senile-induced bone dysplasia (Chan *et al.*, 2018; Han *et al.*, 2015). The expression of DCN in skeletal muscle increases after prolonged training, while at the same time there is a corresponding decrease in muscle and circulating levels of myostatin (Hittel *et al.*, 2010; Saremi *et al.*, 2010). Reasons for this change can be attributed to the function of DCN in antagonizing myostatin, which directly binds to myostatin and inhibits its activity, thus undermining the negative regulatory effects of myostatin on muscle and bone (Kanzleiter *et al.*, 2014). Be-

sides, DCN possesses capability to promote calcium deposition and bone matrix formation. DCN cooperates synergistically with bone morphogenetic protein 2 (BMP-2) to improve bone formation and promote bone healing (Han *et al.*, 2015). DCN-modified collagen hydrogel has been shown to act as a delivery vehicle for BMP-2, effectively delivering BMP-2 and microvascular fragments together to the site of bone injury (Ruehle *et al.*, 2019). To summarize, DCN promotes bone formation and bone repair by inhibiting myostatin and synergizing with BMP-2.

IGF-1 and FGF-2

Pedersen and Febbraio (2012) investigators found that insulin-like growth factor-1 (IGF-1) and fibroblast growth factor-2 (FGF-2) are key growth factors produced and secreted by skeletal muscle, which have a significant contribution to skeletal development. These two growth factors are predominantly distributed on muscle fibers adjacent to the periosteum, and their corresponding receptors, i.e., IGF-1R and FGFR2, are also expressed on the periosteum. Therefore, these two myokines are competent to act directly on the periosteum by means of paracrine secretion (Hamrick *et al.*, 2010; Hamrick, 2012).

In vivo experiments have confirmed that muscle-secreted IGF-1 contributes to bone growth and development by acting directly on bone via paracrine secretion (Locatelli and Bianchi, 2014). Extensive studies have proven that IGF-1 can promote osteogenic differentiation of BMSCs (Kirk *et al.*, 2020; Tahimic *et al.*, 2013; Tresguerres *et al.*, 2022). Wu *et al.* (2020) demonstrated that IGF-1 intervention in BMSCs significantly increased the levels of cellular osteogenic markers alkaline phosphatase (ALP), Runt-related transcription factor 2 (Runx2), and osteocalcin (OCN). Additionally, intracellular calcium signals inositol 1,4,5-trisphosphate receptor type 2 (IP3R2) and sarco/endoplasmic reticulum calcium ATPase 3 (SERCA3) were also significantly elevated, confirming that IGF-1 can induce osteogenic differentiation of BMSCs by upregulating calcium signaling, and hypothesizing that this may be mediated through the Akt signaling pathway (Wu *et al.*, 2020). Furthermore, most IGF-binding proteins (IGFBPs) expressed in skeletal muscle, such as insulin like growth factor binding protein 2 (IGFBP2) and insulin like growth factor binding protein 5 (IGFBP5), can bind to IGF-1 to regulate IGF-1 activity. Among them, there is a negative correlation between serum levels of IGFBP2 and bone mineral density (Lebrasseur *et al.*, 2012), whereas the binding of IGFBP5 to IGF-1 enhances IGF-1-mediated osteoanabolism, but the exact mechanism needs to be further explored.

Similar to IGF-1, fibroblast growth factor-2 (FGF-2) is capable of promoting bone growth and restoration by promoting osteoblast formation (Coffin *et al.*, 2018). Kodama *et al.* (2009) demonstrated that FGF-2/FGF2R signaling regulates bone anabolism by activating the Runx2 and BMP-2 pathways to promote osteoblast proliferation and differentiation, thereby enhancing bone regeneration. From a research on FGF-2 knockout mice, researchers revealed that the bone trabecular structure of knockout mice gradually deteriorated with age, and the bone volume and rate of bone formation were also significantly diminished (Montero *et al.*, 2000). Altogether, these findings suggest that IGF-1 and FGF-2 secreted by skeletal muscle promote bone growth and repair by facilitating osteogenesis.

FGF-21

Fibroblast growth factor-21 (FGF-21), as a member of the FGF family, is composed of myokines that mainly regulate glucose and lipid metabolism (Sun *et al.*, 2021). Recent research revealed that FGF-21 can negatively regulate bone metabolism by promoting bone resorption and inhibiting bone formation. Experimental data showed that bone mass was lower in FGF-21 high expression mice and elevated in FGF-21 knockout mice. Simultaneously, FGF-21 gene high-expressing mice had decreased IGF-1 levels and reduced growth hormone (GH) sensitivity, suggesting that FGF-21 may promote bone resorption by inhibiting IGF-1 and GH (Wei *et al.*, 2012; Wu *et al.*, 2012; Zhang *et al.*, 2012). Further, FGF-21 stimulated BMSC lipogenic differentiation and inhibited osteogenic differentiation, further inhibiting bone formation. Yet, in studies related to bone metabolism in alveolar bone, FGF-21 can promote alveolar bone formation through the hepatocyte growth factor (HGF)-mediated PI13/Akt signaling pathway (Yang *et al.*, 2019). Conclusively, FGF-21 as such negatively regulates bone metabolism and OP.

IL-10

Interleukin-10 (IL-10) is a cytokine principally secreted by T cells, monocytes and macrophages with anti-inflammatory and immunomodulatory effects. Meanwhile, IL-10 can be induced by exercise to release myokines from skeletal muscles. IL-10 has a promotive effect on bone health and metabolism (Garneau *et al.*, 2020). Research has shown that IL-10 levels in patients with osteoporosis are significantly lower than levels in healthy individuals (Kotrych *et al.*, 2016; Tu *et al.*, 2021). Much more, in patients with low BMD as well as vertebral compression fractures, their levels of IL-10 and osteoprotegerin (OPG) were significantly diminished, whereas levels of tumor necrosis factor-α (TNF-α), IL-6, and RANKL were significantly elevated (Azizieh *et al.*, 2017; Ma *et al.*, 2021). In *in vitro* experiments, the expression level of IL-10 was significantly decreased in OVX mice, and IL-10-deficient mice had elevated levels of RANKL and OPG, increased bone resorption, and diminished bone formation, whereas IL-10 overexpression inhibited the development of OP in OVX mice (Dresner-Pollak *et al.*, 2004; Sapra *et al.*, 2021; Wang *et al.*, 2020a). In terms of regulatory mechanisms, the current research demonstrated that IL-10 can effectively in-

hibit osteoclastogenesis and promote osteoblast differentiation, while the detailed molecular mechanisms and pathways need to be further investigated.

IL-6 and IL-15

IL-6 and IL-15 are vital pro-inflammatory factors that can be secreted by skeletal muscle and are widely expressed in a variety of cells including macrophages and fibroblasts (Pedersen *et al.*, 2007). According to research, in postmenopausal osteoporosis, the serum level of IL-6 is significantly increased, which may not be entirely due to myokines, but also the secretion of inflammatory cells (Abildgaard *et al.*, 2020). Levels of IL-15 were also increased in OVX mice (Cline-Smith *et al.*, 2020; Fischer and Haffner-Luntzer, 2022). In physiological processes such as muscle contraction, short-term bed rest and aging, the level of IL-6 produced by muscle cells rises and is released into the systemic circulatory system (Drummond *et al.*, 2013; Lavin *et al.*, 2020; Steensberg *et al.*, 2000). Existing studies have illustrated that IL-6 not only directly induces osteoclast differentiation, but also indirectly promotes osteoclast formation by regulating RANKL expression in osteoblasts and stromal cells (Feng *et al.*, 2022). Meanwhile, IL-6 inhibits the differentiation of bone marrow-derived macrophages (BMDM) cells into osteoclasts by suppressing the RANK signaling pathway in them (Yoshitake *et al.*, 2008). Notably, IL-6 has a bidirectional regulatory effect on osteoblast differentiation. It can both inhibit osteoblast differentiation by activating the SHP2/MEK2/ERK and SHP2/PI3K/Akt2 pathways and promote osteoblast differentiation by activating the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathway (Kaneshiro *et al.*, 2014). Thus, IL-6 has a stimulatory effect on both bone formation and bone resorption.

IL-15 acts as a stimulator of TNF-α and can potentiate the negative regulatory effects of TNF-α on bone. Meanwhile, IL-15 synergizes with RANKL to induce osteoclastogenesis, thereby promoting bone resorption (Okabe *et al.*, 2017). Nevertheless, IL-15 also activates natural killer (NK) cells in a dose-dependent manner, which then stimulates osteoclast apoptosis and exerts an inhibitory effect on bone resorption (Takeda *et al.*, 2014). Interestingly, when skeletal muscle secreted plenty of IL-15 resulting in elevated circulating levels of IL-15, mice had diminished body fat mass and increased bone mineral content (Quinn *et al.*, 2009).

In summary, IL-6 and IL-15 play complicated roles in bone metabolism, and how to regulate one of their specific roles to achieve the maintenance of bone homeostasis is of crucial research value.

Irisin

Irisin is a muscle factor derived from the cleavage product of fibronectin type III domain-containing protein 5 (FNDC5), which is produced and released into the circulatory system during muscle contraction (Colaianni *et al.*, 2020). Numerous previous studies have shown that Irisin exerts a positive influence on both muscle and bone formation (Kim *et al.*, 2018; Waseem *et al.*, 2022). Bone tissue is the main target organ of Irisin, which promotes bone formation by increasing osteoblast activity. Treatment with low doses of exogenous Irisin has been reported to improve cortical bone volume and strength (Colaianni *et al.*, 2017). Moreover, Irisin is able to enhance osteoblast differentiation by acting on osteoblasts and upregulating the expression of osteopontin (OPN) and sclerostin (Colaianni *et al.*, 2014). Research has also indicated that with aging and insufficient exercise, Irisin levels in the body decrease accordingly (Arias-Loste *et al.*, 2014; Huh *et al.*, 2012). This phenomenon is particularly evident in patients with osteoporosis, whose serum Irisin levels are generally below the normal range. Hence, serum Irisin levels can be used as one of the important indicators for predicting osteoporosis (Badr Roomi *et al.*, 2021). In addition, low serum Irisin levels may lead to accelerated bone loss, further exacerbating the risk of osteoporosis. In FNDC5 knockout mice, the level of RANKL mRNA in bone was significantly reduced and the number of femoral trabeculae was significantly higher in mice than in wild-type mice. This suggests that Irisin has a critical role in skeletal development and remodeling (Kim *et al.*, 2018). Nonetheless, the updated study indicated that Estell *et al.* (2020) confirmed that Irisin could directly act on osteoclast progenitor cells and promote their proliferation and differentiation. It further confirms that Irisin stimulates bone remodeling while also promoting bone resorption. In summary, serum Irisin level can serve as guidance for the prediction of osteoporosis, and the equilibrium remodeling process of Irisin in skeletal muscle plays a pivotal role in the maintenance of skeletal homeostasis.

LIF

Leukemia inhibitory factor (LIF) is a multifunctional cytokine that is produced and released by skeletal muscle cells (Broholm and Pedersen, 2010). Exercise and increased mechanical loading effectively promote LIF expression (Du *et al.*, 2020). It has been shown that LIF is a coupling factor between osteoblasts and osteoclasts, regulating bone remodeling and energy metabolism (Weivoda *et al.*, 2020). The mechanism is that LIF is able to promote osteoclast differentiation through the STAT3 pathway, but it was found that LIF also promotes osteoblast differentiation through the same signaling pathway, i.e., the STAT3 signaling pathway (Weivoda *et al.*, 2020). Recent studies have also found that LIF can promote osteoblast differentiation in hypoxia-treated BMSCs *in vitro*, which in consequence enhances bone repair (Liang *et al.*, 2021). However, the specific mechanisms and effects of LIF in the regulation of bone metabolism are still controversial and uncertain, and further in-depth studies and research are still indispensable.

Myostatin

Myostatin, also named growth differentiation factor-8 (GDF-8), is a member of the transforming growth factor beta (TGF-β) superfamily. Myostatin has been in the spotlight as the first myokine to be discovered since it was first reported in 1997 (McPherron *et al.*, 1997). Myostatin plays a role as a negative regulator in skeletal muscle, with inhibitory effects on muscle cell proliferation and differentiation (Allen *et al.*, 2008; Kirk *et al.*, 2020). *In vivo* experiments have suggested that systemic deletion of myostatin significantly increases bone mineral density (BMD) (Omosule *et al.*, 2021). Concurrently, myostatin promotes the lipogenic differentiation of BMSC, which in turn inhibits their osteogenic differentiation (Deng *et al.*, 2017; Mitra *et al.*, 2023). In addition, myostatin accelerated receptor activator for nuclear factor-κB ligand (RANKL)-induced osteoclast formation through activation of the nuclear factor of activated T cells (NFATC1) signaling pathway (Dankbar *et al.*, 2015). Activin receptor type IIB fusion protein (ActRIIB-Fc) binds to myostatin and inhibits its inhibitory effect on skeletal muscle, making it a potent inhibitor of myostatin. Bialek *et al.* (2014) demonstrated by *in vivo* experiments that mice treated with ActRIIB-Fc significantly increased muscle mass and bone mass. Taken together, these observations demonstrate that myostatin negatively regulates bone homeostasis by inhibiting BMSC osteogenic differentiation to diminish bone formation and promoting osteoclast formation to increase bone resorption.

Meteorin-Like

Meteorin-like (METRNL), a newly discovered myokine, is synthesized and secreted by skeletal muscle during exercise. METRNL has significant metabolic functions and is able to inhibit the inflammatory response in adipose tissue and induce adipose browning through AMPK- or PPARδ-dependent signaling mechanisms in skeletal muscle (Jung *et al.*, 2018; Lee *et al.*, 2020). Moreover, METRNL reduces the levels of inflammatory markers such as IL-6 and TNF-α, which in turn inhibits the effects of these inflammatory markers on bone resorption (Jung *et al.*, 2018). Nevertheless, METRNL seems to exhibit a significant inhibitory effect on the differentiation process of osteoblasts as well. In human osteogenic sarcoma MG63 cells, overexpression of METRNL leads to a decrease in mineralized nodule formation. Furthermore, METRNL significantly suppresses the mRNA expression levels of osteoprotegerin (OPG) and osteopontin (OPN), which increases osteoclast activity and affects the process of bone resorption (Gong *et al.*, 2016). In summary, METRNL inhibits the process of bone resorption by inflammatory factors and can under certain conditions inhibit bone formation.

PGE2

Prostaglandin E2 (PGE2) is an important inflammatory mediator that can be released by myocytes in skeletal muscle in response to exercise or other stimuli (Liu *et al.*, 2016). PGE2, as an important regulator of bone metabolism, promotes increased bone mass and regenerative bone repair (Zhang *et al.*, 2002). It has been found that PGE2 can mediate sensory nerves to control bone homeostasis and promote regeneration, and knockdown of the prostaglandin E2 receptor 4 (EP4) gene in sensory nerves significantly reduced bone mass in mice (Chen *et al.*, 2019). For one, incremental increase in PGE2 skeletal levels significantly promotes BMSC osteogenic differentiation and promotes bone formation. For another, PGE2 can synergize with RANKL to promote osteoclast differentiation through EP2 and EP4 receptors (Arikawa *et al.*, 2004; Kobayashi *et al.*, 2005). Nonetheless, it has been indicated that PGE2 seems to inhibit the resorptive activity of mature osteoclast via EP4 receptor and adenylate cyclase lineage (Mano *et al.*, 2000). In conclusion, PGE2 can promote osteoclastogenesis and inhibit osteoclast differentiation to positively regulate bone metabolism. The effect of PGE2 on osteoclast activity remains controversial and requires more in-depth and comprehensive research.

TNF-α

TNF-α, a pro-inflammatory cytokine secreted by skeletal muscle regulated by long-term exercise training, has been shown to have a significant bone resorption-inducing effect (Lavin *et al.*, 2020). According to research, in postmenopausal women with osteoporosis, the lack of estrogen will change the expression of estrogen target genes, and thus increase the secretion of TNF-α (Cheng *et al.*, 2022). TNF-α is capable of inducing osteoclast differentiation and promoting bone resorption independently of the RANKL/OPG system by activating the NF-κB signaling pathway (Kobayashi *et al.*, 2000). However, since TNF-α induces the production of multiple inhibitory proteins, its ability to induce osteoclast formation alone becomes limited. Interestingly, IL-1 and TGFβ1 can enhance the induction of osteoclast differentiation by TNF-α (Yao *et al.*, 2022). On the other hand, TNF-α can up-regulate the expression of SRY-box transcription factor 5 (SOX5) during the osteogenic differentiation of BMSCs, and then inhibit the osteogenic differentiation of BMSCs by up-regulating the Kruppel-like factor 4 (KLF4) signaling pathway and inhibiting the expression of osteogenic markers such as ALP (Xu *et al.*, 2018). In conclusion, TNF-α negatively regulates bone metabolism by promoting osteoclast differentiation and inhibiting osteogenic differentiation of BMSC.

Other Factors

Beyond the relatively well-studied myofactors mentioned above, numerous myofactors have been mentioned in myoskeletal-related studies. However, the secretion con-

ditions or functions of these myokines in the intermuscular bone communication remain to be elucidated, and represent prospective directions for further studies on the regulation of OP by musculoskeletal communication in the future.

FAM5C may be a bone anabolic factor produced by muscle cells, and its overexpression promotes BMSC osteogenic differentiation (Tanaka *et al.*, 2012c). Insulin like growth factor binding protein 5 (IGFBP5) can be secreted by C2C12 cells and plays a role in bone formation and bone metabolism (Hamrick *et al.*, 2010). In transmembrane protein 119 (Tmem119) overexpressing C2C12 cells, osteogenic differentiation markers and mineralization are increased, and Tmem119 was demonstrated to promote the differentiation of myoblasts into osteoblasts (Tanaka *et al.*, 2012a). RANKL can be expressed by a variety of cell types, with RANKL produced by osteoblasts and precursors being essential for osteoclastogenesis, and it has been demonstrated that muscle cells can also express RANKL and OPG and can play a regulatory role in bone resorption (Juffer *et al.*, 2014; Xiong *et al.*, 2011). Semaphorins (signaling hormones) can be secreted during muscle development, of which Sema4D inhibits bone formation, Sema3D increases bone formation, and a lack of Sema3D lead to an increase in osteoclasts and a decrease in bone mass (Fard and Tamagnone, 2021; Hayashi *et al.*, 2012; Negishi-Koga *et al.*, 2011). Platelet-derived growth factor-B (PDGF-B) can be secreted by muscle cells and enhances muscle cell proliferation, and it has now been demonstrated that PDGF-BB is implicated in the coupling of angiogenesis and osteogenesis (Cecerska-Heryć *et al.*, 2022; Hamaguchi *et al.*, 2023; Peng *et al.*, 2020). The above myokines are proven to be secreted by skeletal muscle, but the secretion conditions and their regulatory functions and mechanisms on bone metabolism need to be further investigated.

Osteopontin is a muscle growth inhibitor-binding protein that can attenuate osteoclast formation to promote bone mass by inhibiting muscle growth inhibitor in bone (Kawao *et al.*, 2018; Saitoh *et al.*, 2020). Matrix metalloproteinase-2 (MMP-2) enhances osteoblast activity and is a potential target for promoting bone formation (Feng *et al.*, 2016), and its related MMP-3 and MMP-9 have also been shown to be involved in regulating OP (Zheng *et al.*, 2018). TNF-β is a factor identified in the identification of muscle tissue secreted proteins, and targeting TGF-β can be an effective treatment for osteogenesis imperfecta (Song *et al.*, 2022; Tauer *et al.*, 2019). Connective tissue growth factor (CTGF) is a multifunctional protein identified in the proteomic identification of mouse skeletal muscle secretome proteins, present in the secretory proteins of skeletal myoblasts, and CTGF overexpression may imbalance cartilage homeostasis (Omoto *et al.*, 2004; Yang *et al.*, 2022). Bone morphogenetic protein-1 (BMP-1), identified in immunohistochemical analyses of skeletal muscle type I and IIa fibers, promotes differentiation of BMSCs into osteoblasts *in vitro* and facilitates bone formation and bone homeostasis (Su *et al.*, 2020). Cathepsin K plays an important role in the process of bone resorption, and Cathepsin K inhibitors can be used as potential therapies for the treatment of OP (Drake *et al.*, 2017; Zou *et al.*, 2022). The above factors have been shown to exist in the regulation of bone metabolism and to be associated with skeletal muscle, but whether, under what conditions, and how they are secreted by muscle tissue has not been elucidated. More importantly, whether it is factors of skeletal muscle origin that take on a major regulatory role is also critical to consider.

Applications and Limitations of Muscle-Bone Crosstalk

Exercise can stimulate muscle secretion of myogenic factors, which in turn regulate osteoblasts, osteoclasts and osteoclasts, promoting bone production and inhibiting bone resorption. At the same time, the factors secreted by bones can also act on muscle tissues to improve muscle mass and alleviate muscle loss (Gries *et al.*, 2022). Therefore, in patients with sarcopenia and osteoporosis, appropriate exercise can help improve muscle and bone health. A deeper understanding of the mechanisms of muscle-bone interactions can help to investigate the pathogenesis of diseases such as sarcopenia, osteoporosis and osteosarcopenia. These studies can provide new ideas and targets for early diagnosis and intervention.

However, there are some limitations to the study and application of muscle-bone interactions. For example, muscle-bone interactions may vary between individuals, making it difficult to generalise the effects of interventions and treatments to a wide range of populations; muscle-bone interactions involve a variety of secretory factors, signalling pathways, and regulatory mechanisms that are incompletely understood, leaving many unknowns to be explored. The identification of effective therapeutic targets and the development of appropriate treatments remain challenging.

Future Directions for Exploration of Myokine-Regulated OPs

With the gradual deepening of the research, the functions and mechanisms of myokines in regulating bone metabolism and OP in the context of muscle-bone crosstalk will be elucidated in a more in-depth and comprehensive manner. In particular, the myokines involved in bone metabolism that are not yet understood need further investigation. While revealing the mechanisms of myokines in regulating bone metabolism, researchers also put emphasis on the practical application of these factors in bone diseases such as OP. For one thing, understanding the secretion conditions and influencing factors of myokines can help researchers intervene from the source to realize the prevention and treatment of OP; for another, specific myokines with definite bone metabolism regulation can be targeted to develop corresponding OP medicines or therapeutic strategies, e.g., stimulating the secretion of Irisin, myostatin in-

hibitor and follicle inhibitor through exercise. Besides, myokines existence in the regulation of physiopathological states such as muscle atrophy and muscle regeneration through processes such as autocrine secretion. Combined with clinical data, this suggests that treatments targeting only sarcopenia or OP may not be sufficient for effective fracture prevention. Hence, targeting both tissues simultaneously is a potential new direction for treating OP and preventing osteoporotic fractures in the future. The co-regulation of bone and skeletal muscle by biological rhythms, neural networks, fat metabolism, diet and nutrition, and exercise activity are also considerations that need to be taken into account in the research and treatment of musculoskeletal disorders.

Conclusions

The research of myokines in the muscle-bone "crosstalk" has a broad application prospect. Through in-depth research of the regulatory role and mechanism of these factors, we hope to provide a comprehensive and updated theoretical basis and practical guidance for the research and treatment of OP. Meanwhile, it may also provide new perspectives and strategies for the prevention and treatment of other musculoskeletal and skeletal diseases.

List of Abbreviations

OP, osteoporosis; RANKL, receptor activator for nuclear factor-κB ligand; RANK, receptor activator for nuclear factor-κB; BMD, bone mineral density; EVs, extracellular vesicles; BAIBA, β-aminoisobutyric acid; MRGPRD, Mas related G protein coupled receptors D; GABA, γ-aminobutyric acid; BDNF, brain derived neurotrophic factor; TrkB, tropomyosin-related kinase B; HMSCs, human marrow mesenchymal stem cells; DCN, decorin; BMP-2, bone morphogenetic protein 2; IGF-1, insulin-like growth factor-1; IGFBPs, insulin-like growth factor binding proteins; FGF-2, fibroblast growth factor-2; IL, interleukin; OPG, osteoprotegerin; TNF-α, tumor necrosis factor-α; OGN, osteoglycine; BMSCs, bone marrow mesenchymal stem cells; ALP, alkaline phosphatase; PGE2, prostaglandin E2; EP4, prostaglandin E2 receptor 4; ON, osteonectin; SPARC, secreted protein acidic and rich in cysteine; HO, heterotopic ossification; CNTF, ciliary neurotrophic factor; FGF-21, fibroblast growth factor-21; GH, growth hormone; HGF, hepatocyte growth factor; OVX, ovariectomy; GDF-8, growth differentiation factor-8; TGF-β, transforming growth factor beta; NFATC1, nuclear factor of activated T cells; ActRIIB-Fc, activin receptor type IIB fusion protein; FNDC5, fibronectin type III domain-containing protein 5; OPN, osteopontin; LIF, leukemia inhibitory factor; METRNL, meteorin-like; MMP-2, matrix metalloproteinase-2; IGFBP5, insulin like growth factor binding protein 5; Tmem119, transmembrane protein 119; PDGF-B, platelet-derived growth factor-B; CTGF, connective tissue growth factor; BMP-1, bone morphogenetic protein-1; IGFBP2, insulin like growth factor binding protein 2; Runx2, Runt-related transcription factor 2; OCN, osteocalcin; NF-κB, nuclear factor-kappa-B; AMPK, AMP-activated protein kinase; BMDM, bone marrow-derived macrophages; STAT5, signal transducer and activator of transcription 5; JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; NK, natural killer; SOX5, SRY-box transcription factor 5; KLF4, Kruppel-like factor 4.

Availability of Data and Materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

GZM contributed to the design of this work. GZM contributed to the interpretation of data. GZM and YNC analyzed the data. GZM and YNC drafted the work. QHZ and YNC revised critically for important intellectual content. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study is a review article and is only a collation of ideas from other articles and is not ethical.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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