Integrin αVβ3 as a context-dependent regulator of bone homeostasis: Insights into osteoporosis pathogenesis and therapeutic targeting (Review)

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Abstract. Osteoporosis (OP) is a multifactorial skeletal disorder characterized by progressive bone loss, microarchitectural deterioration and an increased risk of fragility fractures resulting from disrupted bone remodeling. Integrin αVβ3 functions as an important regulator of bone homeostasis by coordinating bone cell-extracellular matrix interactions, mechanotransduction and intracellular signaling across multiple bone cell populations. Through context-dependent actions in osteoclasts, osteoblasts, osteocytes, endothelial cells and immune cells, integrin αVβ3 influences osteoclast adhesion and bone resorption, osteoblast differentiation, angiogenesis, inflammatory responses, and estrogen-associated skeletal remodeling. These diverse functions position integrin αVβ3 at the interface of the multiple signaling pathways involved in maintaining bone-metabolic homeostasis. The present review summarizes current evidence regarding the molecular mechanisms underlying the integrin αVβ3-mediated regulation of bone remodeling, discusses the cell-specific and microenvironment-dependent functions of integrin αVβ3 in OP pathogenesis, and critically evaluates the challenges and future directions for translating integrin αVβ3-targeted strategies into clinical applications against OP.

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1. Introduction

Osteoporosis (OP) is a systemic skeletal disorder resulting from impaired bone remodeling, and is characterized by decreased bone mass, the deterioration of bone microarchitecture and an enhanced risk of fragility fractures (1). This disease arises from an imbalance between osteoclast-mediated bone resorption and osteoblast-driven bone formation, resulting in the progressive development of skeletal fragility and notable morbidity, particularly in older adults (2,3). As population aging continues worldwide, OP remains a notable public health challenge because of its association with increased fracture risk, disability, reduced patient quality of life and increased healthcare burden (4). Despite the availability of antiresorptive and anabolic therapies, numerous patients with OP continue to experience suboptimal therapeutic responses or adverse effects during treatment, underscoring the requirement for improved understanding of the molecular mechanisms governing bone homeostasis (5).

Bone remodeling is coordinated through dynamic interactions among osteoblasts, osteoclasts, osteocytes, endothelial cells, immune cells and the extracellular matrix (ECM) (6). A previous study suggests that ECM-cell communication plays a role in maintaining skeletal integrity, with integrins serving as key mediators that couple extracellular mechanical and biochemical cues to intracellular responses (7). Among members of the integrin family, integrin αVβ3 has emerged as an important regulator of bone homeostasis due to its broad

expression in multiple bone-associated cell types and its ability to integrate signaling pathways involved in cellular adhesion, migration, mechanotransduction, survival and differentiation (8). Through interactions with ECM proteins containing the Arg-Gly-Asp (RGD) motif, integrin αVβ3 has been shown to coordinate multiple biological processes that collectively influence bone remodeling (9).

Accumulating experimental evidence has indicated that integrin αVβ3 participates in several interconnected aspects of skeletal biology. In osteoclasts, integrin αVβ3 has been shown to regulate cytoskeletal organization, adhesion to the bone surface, migration and bone-resorptive activity (10). In osteoblasts and bone marrow mesenchymal stem cells (BMSCs), integrin αVβ3 has been shown to contribute to osteogenic differentiation and mechanosensitive signaling through pathways involving focal adhesion kinase (FAK), PI3K/AKT, MAPK and Wnt-associated signaling (11-13). A study further demonstrated that integrin αVβ3 influences osteocyte-mediated mechanotransduction, angiogenesis within the bone microenvironment, inflammatory signaling and estrogen-associated skeletal adaptation (14). Notably, as discussed in the subsequent sections on osteoblasts, osteoclasts, osteocytes and the estrogen-deficient bone microenvironment, the functions of integrin αVβ3 appear to vary according to cell type and microenvironmental context, suggesting that αVβ3 may function as a multifunctional signaling node rather than as a uniformly beneficial or detrimental regulator of bone homeostasis (15).

Although studies have investigated the individual functions of integrin αVβ3 in specific bone cell populations, current knowledge remains fragmented and, to the best of our knowledge, the interplay among its diverse biological roles has not been comprehensively integrated and critically evaluated in relation to OP pathogenesis (16,17). In particular, the mechanisms by which integrin αVβ3 coordinates communication between pathways for bone remodeling, mechanotransduction, angiogenesis, inflammatory regulation and estrogen signaling remain incompletely elucidated. Furthermore, the context-dependent nature of integrin αVβ3 signaling has important implications for targeted therapy, highlighting the need to carefully evaluate therapeutic strategies that modulate αVβ3 activity (18-23).

The present review systematically summarizes current evidence regarding the molecular mechanisms involved in the integrin αVβ3-mediated regulation of bone homeostasis, with particular emphasis on its roles in osteoblasts, osteoclasts, osteocytes, angiogenesis, inflammation and estrogen-associated skeletal remodeling. The present review also: i) Discusses the context-dependent functions of integrin αVβ3 in OP pathogenesis; ii) critically evaluates the current evidence supporting integrin αVβ3-targeted therapeutic approaches; and iii) highlights the major challenges and future research directions required for the clinical translation of such therapies.

2. Integrin αVβ3 in the cellular regulation of bone remodeling

Bone homeostasis is maintained by the continuous remodeling of bone, in which osteoblast-mediated bone formation and osteoclast-mediated bone resorption are coordinated by osteocytes, ECM cues, vascular signals and immune mediators (24). Disruption of this coupling contributes to progressive bone loss and OP (25). Fig. 1 summarizes the coordinated roles of osteoblasts, osteoclasts and osteocytes, together with the principal signaling mediators that regulate bone formation and resorption. Since integrin αVβ3 is expressed in several skeletal and bone-associated cell populations, a concise overview of the cellular bone-remodeling network is necessary to fully elucidate its functions in a biological context (26,27).

Osteoblasts arise from BMSCs and are responsible for bone mineralization and ECM synthesis. Their differentiation is regulated by osteogenic transcription factors, including runt-related transcription factor 2 (RUNX2) and osterix (OSX), as well as signaling via the bone morphogenetic protein (BMP), Wnt/β-catenin and growth factor signaling pathways (28,29). Osteoblasts also influence osteoclastogenesis through the receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) axis, thereby linking bone formation to resorption (30). Within the context of OP, integrin αVβ3-mediated cell adhesion and mechanotransduction have been shown to modulate osteoblast differentiation and matrix-responsive signaling (31,32).

Osteoclasts are multinucleated cells of hematopoietic origin whose differentiation depends primarily on macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL) signaling. Mature osteoclasts attach to the mineralized bone surface, organize specialized cytoskeletal structures and resorb the bone matrix through acid-mediated mineral dissolution and proteolytic degradation of its organic components (33). Integrin αVβ3 is particularly relevant in osteoclasts because its recognition of RGD-containing ECM proteins supports adhesion, migration and cytoskeletal polarization, thereby facilitating formation of the actin-rich sealing zone required to establish the resorption compartment and enable efficient bone resorption (34,35). These functions provide the strongest mechanistic basis for considering integrin αVβ3 as a therapeutic target in OP-associated bone loss.

Osteocytes are terminally differentiated cells that are derived from the osteoblast cell lineage; these cells are embedded within the mineralized bone matrix and serve as important mechanosensors within the bone tissue. Through their lacuna-canalicular network, these cells regulate both osteoblast and osteoclast activity by modulating sclerostin, dickkopf-1, RANKL, OPG, nitric oxide and ATP signaling (36,37). Integrin αVβ3 has been shown to contribute to osteocyte-mediated mechanotransduction and may therefore influence how mechanical loads are translated into adaptive bone remodeling responses. This role is particularly relevant under estrogen-deficient conditions, in which impaired αVβ3-mediated mechanosensation in osteocytes has been associated with altered focal adhesion organization, an increased RANKL/OPG ratio and reduced cyclooxygenase-2 (COX-2) responses to mechanical stimulation (38).

Bone lining cells, which are osteoblast-lineage cells located on quiescent bone surfaces, including the endosteal surface, also contribute to local bone remodeling through ECM turnover and regulation of the RANKL/OPG axis (39). However, direct evidence defining integrin αVβ3-specific functions in endosteal cells remains limited. Bone lining cells contribute to

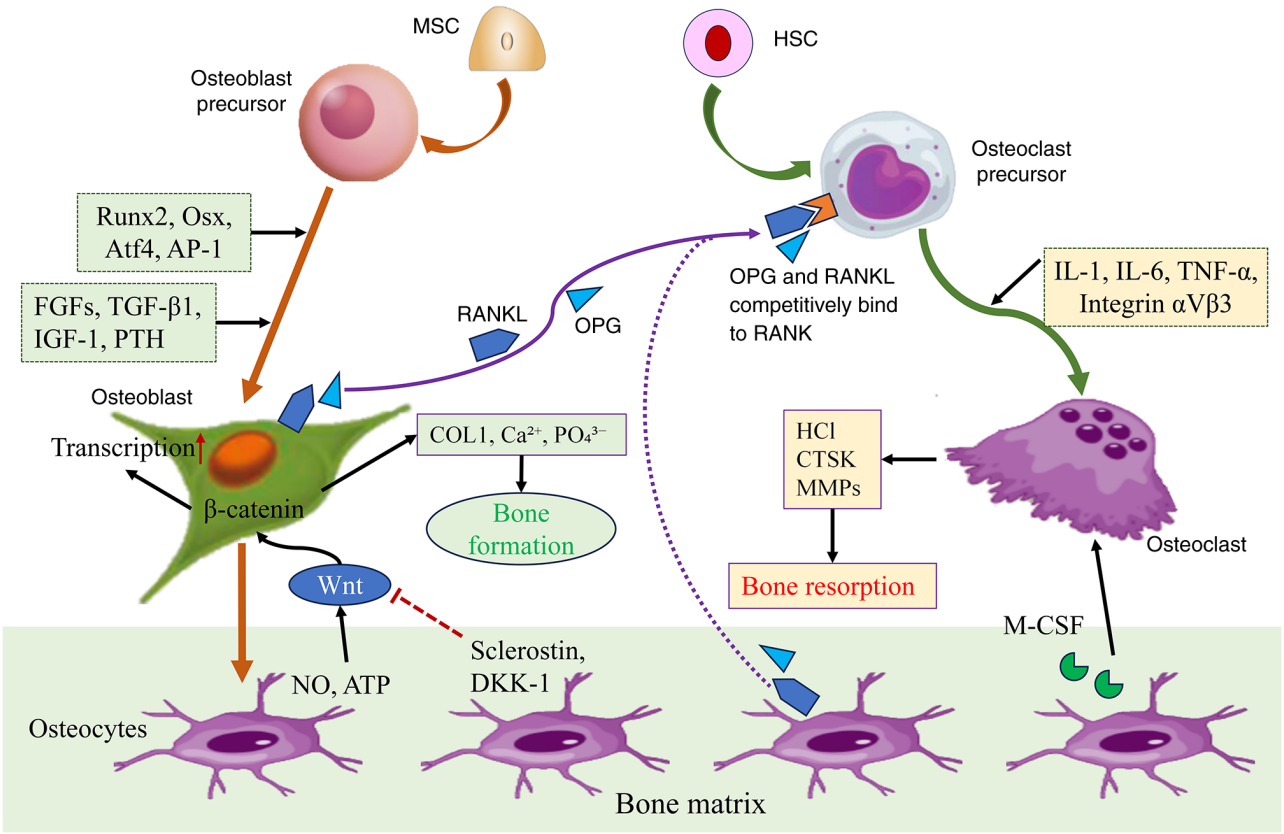

Figure 1. Overview of physiological bone remodeling. The figure summarizes the coordinated interactions among osteoblasts, osteoclasts, osteocytes and their progenitor cells during bone formation and resorption. Major regulatory factors and signaling pathways involved in osteoblast differentiation, osteoclastogenesis and osteocyte-mediated regulation of bone remodeling are shown. Solid arrows indicate activation, differentiation or promotion; blunt-ended lines indicate inhibition; and dashed arrows indicate indirect or paracrine regulation. AP-1, activator protein 1; Atf4, activating transcription factor 4; COL1, type I collagen; CTSK, cathepsin K; DKK-1, Dickkopf-1; FGF, fibroblast growth factor; HCl, hydrochloric acid; HSC, hematopoietic stem cell; IGF-1, insulin-like growth factor-1; M-CSF, macrophage colony-stimulating factor; NO, nitric oxide; OPG, osteoprotegerin; Osx, osterix; PTH, parathyroid hormone; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; Runx2, runt-related transcription factor 2.

the local remodeling microenvironment through interactions with the bone matrix and paracrine regulation of neighboring bone cells. Although αVβ3-specific functions in bone lining cells remain insufficiently characterized and are therefore not discussed further in the present review, these cells are included here to provide the cellular context in which bone remodeling occurs. Bone remodeling depends on coordinated interactions among osteoblasts, osteoclasts, osteocytes and other cells within the local microenvironment. Within this multicellular system, αVβ3 functions in a cell type- and context-dependent manner, contributing to ECM recognition, cytoskeletal organization and mechanotransduction in different skeletal cell populations (40). This framework provides the basis for the more detailed mechanistic discussion of integrin αVβ3 activity in the following sections.

3. Structure, activation mechanisms and biological properties of integrin αVβ3

Integrins are heterodimeric transmembrane receptors that facilitate bidirectional communication between cells and the ECM, thereby regulating cellular adhesion, migration, mechanotransduction, survival and differentiation. In mammals, 18 α and 8 β subunits assemble into 24 distinct integrin heterodimers with different ligand-binding properties. Ligand recognition is determined by the extracellular domains of the αβ heterodimer, whereas the β-subunit cytoplasmic tail has a prominent role in recruiting cytoskeletal and adaptor proteins involved in intracellular signaling (41-43).

Among members of the integrin family, integrin αVβ3 belongs to the RGD-binding subfamily and recognizes ECM proteins containing the RGD motif, including vitronectin, osteopontin (OPN), fibronectin and bone sialoprotein (44). Ligand binding induces conformational activation and receptor clustering, which promotes the assembly of focal adhesion complexes and recruitment of adaptor and signaling proteins, including FAK and Src, thereby enabling integrin αVβ3 to couple extracellular biochemical and mechanical cues to intracellular signaling pathways (45). Consequently, integrin αVβ3 is able to regulate diverse cellular processes, including adhesion, migration, proliferation, survival and mechanotransduction, through signaling networks involving FAK, Src family kinase, the PI3K/AKT signaling pathway, MAPK and Rho GTPases (46-49). These signaling events enable cells to continuously sense and respond to changes in their extracellular microenvironment (50).

Structurally, integrin αVβ3 is a heterodimeric glycoprotein composed of non-covalently associated αV and β3 subunits (Fig. 2A). The αV subunit contains: i) A β-propeller domain; ii) a thigh domain; iii) two calf domains; iv) a transmembrane

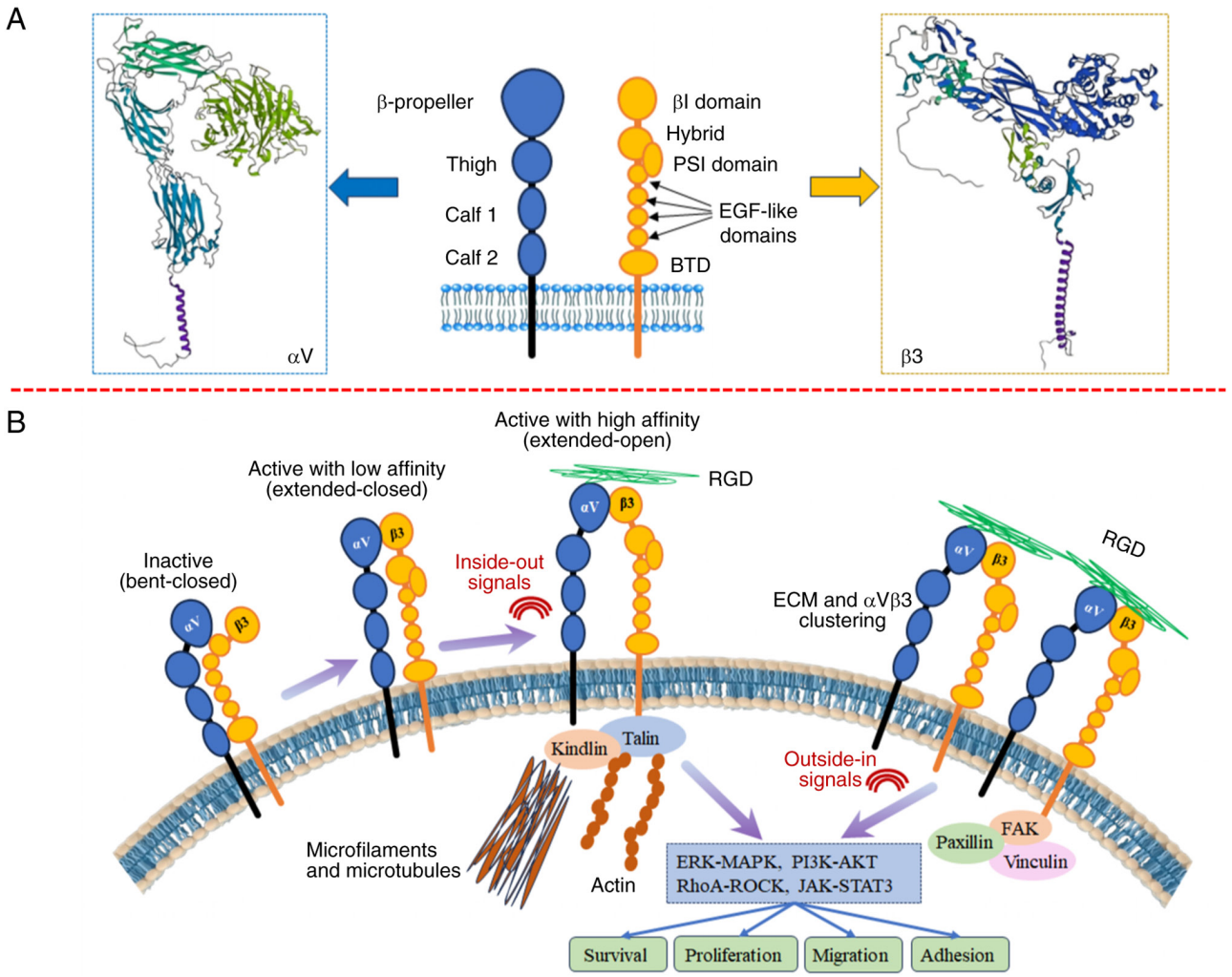

Figure 2. Structural organization, conformational activation and bidirectional signaling of integrin αVβ3. (A) Structural organization of the αV and β3 subunits and their principal extracellular, transmembrane and cytoplasmic domains. (B) Schematic representation of integrin αVβ3 activation from the bent-closed to extended-closed and extended-open conformations and the associated inside-out and outside-in signaling. Talin- and kindlin-mediated inside-out signaling promotes receptor activation, whereas ECM ligand binding and integrin αVβ3 clustering promote focal-adhesion assembly and downstream ERK/MAPK, PI3K/AKT, RhoA/ROCK and JAK/STAT3 signaling. Blue and orange structures represent the αV and β3 subunits, respectively; purple arrows indicate conformational transitions; green strands represent ECM ligands; and red arrows/icons indicate intracellular signaling events. ECM, extracellular matrix; EGF, epidermal growth factor; FAK, focal adhesion kinase; JAK, Janus kinase; PSI, plexin-semaphorin-integrin; BTD, β-tail domain; RGD, Arg-Gly-Asp; RhoA, Ras homolog family member A; ROCK, Rho-associated protein kinase.

helix; and v) a short cytoplasmic tail. On the other hand, the β3 subunit consists of: i) A βI domain; ii) a hybrid domain; iii) a plexin-semaphorin-integrin domain; iv) four epidermal growth factor-like repeats; v) a β-tail domain; vi) a transmembrane helix; and vii) a cytoplasmic tail (51,52). The ligand-binding interface of integrin αVβ3 is formed by the β-propeller domain of the αV subunit together with the βI domain of the β3 subunit. The β3 βI domain contains three divalent metal ion-binding sites: The metal ion-dependent adhesion site (MIDAS), the adjacent to MIDAS and the ligand-associated metal-binding site (also termed the synergistic metal ion-binding site). These sites contribute to ligand binding and its regulation, with the MIDAS metal ion directly coordinating the Asp residue of RGD-containing ligands (53,54).

Similar to other integrins, integrin αVβ3 undergoes dynamic conformational transitions among three major states: i) A bent-closed conformation associated with low ligand affinity; ii) an extended-closed conformation that generally retains low ligand affinity; and iii) an extended-open conformation associated with high ligand affinity. These conformational transitions are coupled to bidirectional inside-out and outside-in signaling mechanisms (Fig. 2B) (55). During inside-out signaling, intracellular adaptor proteins, particularly talin and kindlin, bind to the cytoplasmic tail of the β3 subunit, inducing conformational changes that increase ligand-binding affinity (53). Following ligand engagement, outside-in signaling promotes receptor clustering and the assembly of focal adhesion complexes, involving proteins such as FAK, Src, paxillin and vinculin, which activate downstream pathways regulating cytoskeletal organization, gene transcription and other cellular responses to the extracellular environment (56-58).

Within the skeletal system, integrin αVβ3 is expressed in multiple bone-associated cell populations, including osteoclasts, osteoblasts, osteocytes, endothelial cells and several immune cell types. Through interactions with ECM

components, integrin αVβ3 contributes to adhesion and cytoskeletal organization in osteoclasts, differentiation and mechanosensitive signaling in osteoblast-lineage cells, mechanotransduction in osteocytes, angiogenic signaling in endothelial cells and inflammatory signaling in immune and stromal cells (59,60). For example, inhibition of integrin αVβ3 has been shown to attenuate mechanosensitive calcium signaling in osteocytes and to impair mechanically induced COX-2 expression and prostaglandin E2 (PGE2) release. Because COX-2 induction and PGE2 production are established biochemical responses of osteocytes to mechanical stimulation, these findings support the involvement of αVβ3 in coupling mechanical cues to downstream cellular signaling (61). In addition, integrin αVβ3 exhibits functional crosstalk with growth factor receptors, including EGFR and transforming growth factor-β receptor II, thereby coordinating signaling pathways, such as the Ras/MEK/MAPK, PI3K/AKT and RhoA/Rho-associated protein kinase pathways, which influence cell migration, proliferation and survival (62-64).

Collectively, evidence from osteoclast and osteocyte studies indicates that integrin αVβ3 links ECM interactions to intracellular signaling in multiple bone cell populations. Its biological effects are cell type- and context-dependent, reflecting differences in ECM ligand availability, mechanical stimulation and local hormonal or inflammatory conditions. These factors represent components of the local bone microenvironment that can modify αVβ3 expression, activation and downstream signaling. This context dependence may contribute to the diverse functions of αVβ3 in bone remodeling and OP (65,66).

4. Integrin αVβ3 as a context-dependent regulator of bone remodeling

The functional effects of integrin αVβ3 in bone remodeling arise from the coordinated activity of the αVβ3 heterodimer. Although the αV and β3 subunits make distinct structural and signaling contributions, ligand recognition and signal transmission depend on their assembly as a functional receptor. In αVβ3, the extracellular domains of both subunits contribute to ligand binding, whereas the β3 cytoplasmic domain has a prominent role in recruiting intracellular adaptor and signaling proteins. These coordinated properties provide the basis for the cell type-specific effects of αVβ3 subsequently discussed in osteoblast-lineage cells, osteoclasts and osteocytes (67,68). Therefore, elucidating the complimentary roles of these subunits is key to understanding how integrin αVβ3 affects bone remodeling.

The primary function of the αV subunit is to facilitate recognition of the ECM via interactions with RGD-containing ligands, such as fibronectin, vitronectin, OPN and bone sialoprotein (44). Such interactions play important roles in mediating cell adhesion and transducing extracellular signals that regulate osteogenic differentiation and skeletal organization. Experimental evidence has shown that αV subunit-mediated signaling is involved in osteogenic differentiation by stimulating the activation of various signaling cascades, such as the BMP2/SMAD and ERK/STAT pathways, which induce the differentiation of BMSCs into osteoblasts (69,70). In addition to its involvement in bone development, the αV subunit, as part of the αVβ3 heterodimer, contributes to osteoclast attachment and migration through recognition of RGD-containing matrix ligands, including OPN and vitronectin. These interactions facilitate osteoclast adhesion and cytoskeletal organization required for subsequent bone resorption (71). The implication of these findings is that the αV subunit of integrin acts as an interface for bone cells in relation to the ECM during bone resorption and formation (72).

On the other hand, signaling within cells is mediated by the β3 integrin subunit after receptor-ligand binding. In osteoclasts, the interaction of the β3 subunit with molecules such as talin-1 and kindlin-3 is important for the activation of integrins and the formation of focal adhesions, which are necessary for cytoskeletal reorganization and cellular attachment to the bone matrix (73). β3 subunit-mediated intracellular signaling is characterized by the recruitment and activation of Src family kinases and focal adhesion-associated proteins, which interact with downstream signaling networks, including JNK and NF-κB pathways, to regulate osteoclast function (74). Further evidence indicates that β3-integrin signaling interacts with the microRNA-17 (miR-17)/osteoclastic protein-tyrosine phosphatase (PTP-oc)/ephrin type-A receptor 4 (EphA4) regulatory axis during osteoclast activation. In this axis, miR-17 negatively regulates PTP-oc expression, whereas PTP-oc activates Src signaling by dephosphorylating the inhibitory Tyr527 residue and suppresses the inhibitory signaling of EphA4. These interconnected mechanisms modulate β3-integrin signaling, cytoskeletal organization and osteoclast activity (34,75). Although these signal transduction pathways have been predominantly studied in osteoclasts, they have also been shown to serve roles in osteoclast-osteoblast communication during coupled bone remodeling (76,77).

Collectively, the biological functions of the αV and β3 subunits are best understood in the context of the functional αVβ3 heterodimer rather than as independent activities. Both subunits contribute to the extracellular ligand-binding interface, whereas the β3 cytoplasmic domain has a prominent role in recruiting adaptor and signaling proteins that transmit ligand-dependent signals to the cell interior (78). Skeletal and microenvironmental cell populations further indicate that the functional consequences of αVβ3 signaling vary according to cellular context. These include regulation of osteogenic and mechanosensitive responses in osteoblast-lineage cells and osteocytes, adhesion and cytoskeletal organization in osteoclasts, angiogenic signaling in endothelial cells and inflammatory responses in immune and stromal cells. Such effects may also be influenced by local factors, including ECM ligand availability, mechanical stimulation, hormonal status and inflammatory conditions. Thus, αVβ3 is more appropriately considered a context-dependent regulator of bone remodeling than a receptor that exerts a uniform biological effect across skeletal cell populations (79-81).

Although there are differences in the structure and signaling properties of the αV and β3 integrin subunits, their functional roles are merged through the binding of the integrin αVβ3 dimeric complex. It is therefore necessary to consider that the biological activities regulated by integrin αVβ3 that are described in the following sections, such as the differentiation of osteoblasts, osteoclast function, angiogenesis and

bone microenvironmental signaling, represent the combined activity of both subunits of integrin αVβ3 (82).

Integrin αVβ3 regulates osteoblast function and bone formation. Bone formation is a well-coordinated process comprising the proliferation, differentiation, matrix secretion and mechanoresponsiveness of osteoblast-lineage cells (83). A growing body of work has indicated that the integrin αVβ3 receptor serves a notable role in various steps of osteoblast biology by integrating mechanical and biochemical information from the ECM into intracellular signals that regulate osteogenesis (84-86). Rather than acting as an independent osteogenic stimulus, integrin αVβ3 appears to function as a signaling mediator that coordinates cell adhesion, cytoskeletal organization, mechanotransduction and growth factor signaling. These processes can influence osteogenic differentiation and bone formation by regulating downstream pathways such as FAK/MAPK and PI3K/AKT and osteogenic transcriptional programs, including RUNX2-dependent responses (87).

The process of osteogenic differentiation necessitates the formation of stable associations between osteoblasts or BMSCs and the ECM (88). Integrin αVβ3 recognizes RGD-containing ECM ligands, including fibronectin, vitronectin and OPN, and contributes to the assembly of focal adhesion complexes that physically couple the ECM to the actin cytoskeleton. These complexes recruit adaptor and signaling proteins, including talin, vinculin and FAK, thereby enabling extracellular adhesive and mechanical cues to regulate cytoskeletal organization and downstream osteogenic signaling. In experimental models, αVβ3-dependent focal adhesion formation and FAK activation have been associated with the regulation of osteogenic markers, including RUNX2 and alkaline phosphatase (ALP) (44). The binding of ligands to integrin αVβ3 also induces the recruitment of proteins associated with focal adhesions, such as FAK, Src-family tyrosine kinases, paxillin, talin and vinculin, leading to the activation of downstream signaling pathways that regulate cell survival and differentiation (89). Therefore, the aforementioned events regulating integrin αVβ3-mediated adhesion provide the molecular foundations on which the osteogenic signaling cascade takes place.

Regarding pathways downstream of integrin αVβ3, activation of the FAK/PI3K/AKT pathway has been established as one of the key signaling processes by which the integrin αVβ3-ECM interaction triggers the osteogenic differentiation of osteoblasts. Previous studies have indicated that integrin αVβ3 activation leads to FAK phosphorylation, which in turn induces PI3K/AKT signaling and the expression of osteogenic transcription factors, such as Runx2 and Osx (15,23). These transcription factors regulate the expression of osteoblast-associated genes, including ALP, osteocalcin, OPN and type I collagen. Osteogenic differentiation indicates that the contribution of these signaling responses to osteogenesis varies according to cell type, differentiation stage and the nature of the mechanical stimulus applied to the extracellular environment (90,91).

Further evidence has suggested that rather than employing a signaling mechanism based on a one-dimensional pathway, integrin αVβ3 interacts with several osteogenic signaling pathways. Integrin αVβ3-associated signaling can modulate MAPK pathways, including ERK and JNK, although the resulting effects on osteogenic differentiation depend on the cellular and experimental context. In addition, αVβ3 participates in crosstalk with BMP-2 signaling; β3-integrin-dependent adhesion and cytoskeletal organization can facilitate BMP-2-induced SMAD signaling, thereby contributing to osteoblast differentiation (92,93). Taken together, these results indicate that integrin αVβ3 is a signaling coordinator that facilitates the integration of upstream ECM-based signals with conventional osteogenesis-related signaling pathways, such as the BMP and Wnt/β-catenin pathways (94,95).

Another important physiological mechanism that regulates bone formation, in which integrin αVβ3 serves an important role, is mechanical stimulation. In order to maintain bone homeostasis, it is necessary to effectively convert mechanical loads into biochemical responses, since osteoblasts are continuously subjected to tensile strain, fluid shear stress and matrix deformation. As a mechanosensitive receptor, integrin αVβ3 is involved in this process by connecting extracellular mechanical signals to intracellular signaling responses via focal adhesions complexes (96,97). Experimental evidence indicates that fluid shear stress activates integrin αVβ3 in osteocytes, particularly at dendritic processes, leading to PI3K/AKT signaling and subsequent opening of connexin-43 hemichannels. These hemichannels facilitate the release of signaling molecules such as PGE2, thereby contributing to osteocyte-mediated communication with neighboring bone cells and the anabolic response to mechanical loading. Additionally, cyclic tensile stress stimulates cytoskeletal reorganization and the maturation of focal adhesions via integrin αVβ3-dependent FAK activation and yes-associated protein nuclear translocation, thus promoting early osteogenesis (98). In conditions where gravity has been altered, integrin αVβ3-mediated PI3K signaling also controls the activity of the osteogenic transcription factor Runx2, implying that mechanical insensitivity due to defects in mechanotransduction could be a reason for the bone loss observed in cases of mechanical unloading or in microgravity environments (99). Taken together, these observations suggest that integrin αVβ3 represents an important mechanotransducer that acts as a bridge between physical stimuli and genes that control bone development. However, the role of integrin αVβ3 in bone mechanobiology appears to depend on the characteristics of the mechanical stimulus, including its type, magnitude, frequency and duration, as well as the responding cell type and differentiation state (92). These variables can influence the extent and nature of αVβ3-mediated mechanotransduction and its downstream effects on osteogenic responses.

Emerging research has indicated an even wider scope of action for integrin αVβ3 outside of mature osteoblasts. In a recent study (100), osteocyte-specific deletion of the β3 integrin subunit resulted in impaired osteoblast-mediated bone formation, reduced osteogenic capacity of BMSCs, and decreased bone mass in load-bearing long bones. These changes were accompanied by impaired biomechanical properties, including reductions in maximum load-bearing capacity, maximum displacement, stiffness and bone hardness, indicating compromised bone mechanical strength and material properties. This suggests that osteocyte-dependent integrin αVβ3-mediated signaling has a notable effect on osteoblast activity via intercellular communication during bone remodeling. Similarly,

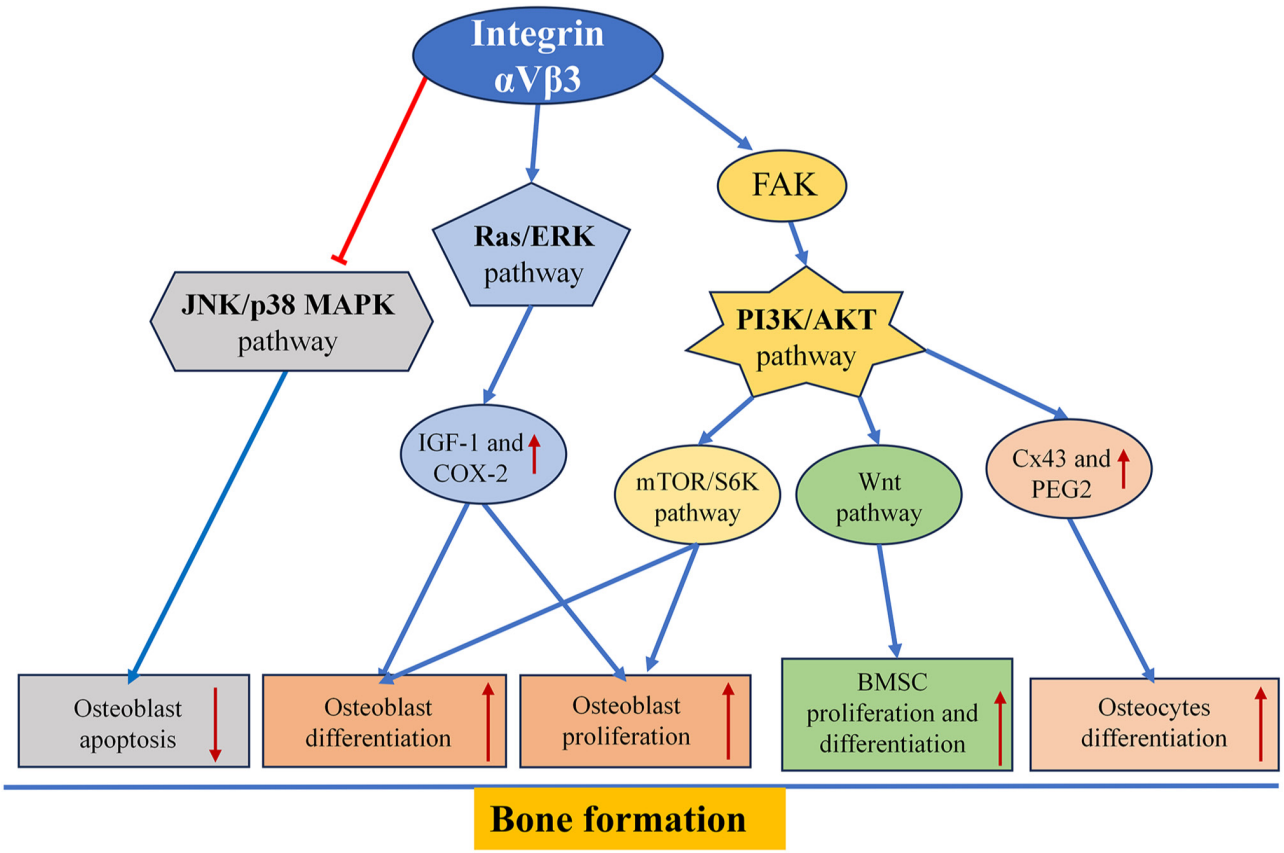

Figure 3. Proposed integrin αVβ3-associated signaling network in osteogenic regulation. The diagram summarizes major signaling pathways associated with integrin αVβ3 regulation of osteoblast/BMSC survival, proliferation and differentiation, together with osteocyte mechanotransduction and adaptive bone responses. Integrin αVβ3-associated pathways include FAK/PI3K/AKT, Ras/ERK, mTOR/S6K, Wnt/β-catenin and context-dependent JNK/p38 MAPK signaling. Mechanotransduction-associated responses include regulation of Cx43, COX-2 and PGE2. Solid blue arrows indicate activation or positive regulation; red blunt-ended lines indicate inhibition; and upward- and downward-facing arrows indicate increased and decreased expression or activity, respectively. BMSC, bone marrow mesenchymal stem cell; COX-2, cyclooxygenase-2; Cx43, connexin-43; FAK, focal adhesion kinase; IGF-1, insulin-like growth factor-1; PGE2, prostaglandin E2; S6K, ribosomal protein S6 kinase.

a study by Mas-Moruno *et al* (101) revealed that elevated integrin αVβ3 levels were associated with increased osteoblast proliferation and differentiation, whereas the pharmacological inhibition of integrin αVβ3 led to decreased levels of ALP, Runx2 and nuclear yes-associated protein.

Despite consistent results indicating the involvement of integrin αVβ3 in osteogenic regulation, the detailed molecular mechanisms involved in integrin αVβ3-mediated regulation remain ambiguous; this is especially true in the context of osteocyte-to-osteoblast regulatory signals. Collectively, these findings indicate that integrin αVβ3 contributes to the coupling of ECM adhesion and mechanical cues with intracellular pathways that regulate osteogenic differentiation and bone formation. This mechanistic relationship may be relevant to bone tissue engineering, as biomaterial properties and RGD-containing ligands can be designed to modulate integrin-mediated adhesion, focal adhesion signaling and osteogenic responses. Thus, αVβ3 represents a potential interface through which biomaterial-based strategies could influence bone regeneration; however, their therapeutic applicability to OP requires further validation in disease-relevant models. The signaling pathways responsible for osteogenesis that are mediated by integrin αVβ3 are shown in Fig. 3.

Integrin αVβ3 regulates osteoclast function and bone resorption. Bone resorption is an important part of the process of bone remodeling, and facilitates bone turnover by replacing old or damaged bone tissue without disturbing the mineral balance of the body. The process of bone resorption is controlled by osteoclasts, which are large multinucleated cells belonging to the monocyte/macrophage cell lineage. The differentiation and function of osteoclasts are precisely regulated by external ECM molecules and cytokines (102,103). Among the adhesion molecules expressed by osteoclasts, integrin αVβ3 is a major receptor mediating interactions with ECM proteins within the bone matrix. Through these interactions, αVβ3 contributes to cytoskeletal reorganization, mechanotransduction, osteoclast motility, polarization and bone resorption. Integrin αVβ3 can therefore also be considered to be a signaling molecule, rather than a simple adhesion molecule (104,105).

Initially, osteoclast-mediated resorption of bone involves the firm attachment of mature osteoclasts to the mineralized surface of the bone. Integrin αVβ3 helps to achieve this step by recognizing RGD motifs present in various ECM proteins, such as OPN, vitronectin and bone sialoprotein, which are abundant in the bone matrix (73,106,107). Ligand binding enhances integrin αVβ3 clustering and the assembly of adhesion complexes, thereby promoting osteoclast attachment,

migration and polarization. These processes are essential for organizing the actin-rich sealing zone and ruffled border, which establish an isolated resorption compartment where acid and proteolytic enzymes are released to dissolve the mineral phase and degrade the organic bone matrix (108). Adhesion events also lead to intracellular signal transduction mediated by adaptor proteins, such as talin, kindlin-3, FAK, paxillin and Src family kinases, linking the recognition of ECM proteins to cytoskeletal rearrangement (109,110).

Cytoskeletal rearrangement is essential for osteoclast resorptive function because dynamic actin remodeling organizes individual podosomes into higher-order structures, including podosome clusters, rings and belts. On mineralized bone surfaces, these actin-rich adhesion structures reorganize into the sealing zone, which anchors the osteoclast to bone and isolates the resorption lacuna from the surrounding extracellular environment. Thus, the formation and remodeling of podosome rings represent intermediate stages in the cytoskeletal organization required to establish and maintain the functional sealing zone during bone resorption (111). Based on experimental research, the role of integrin αVβ3 signaling in the formation of podosome rings has been shown to be mediated by FAK, Src, proline-rich tyrosine kinase 2 (Pyk2), phospholipase C, p130Cas and other proteins found in focal adhesions (106,112). This signaling promotes formation of the ruffled border, facilitates osteoclast anchorage to the mineralized bone surface, and enables polarized secretion of hydrochloric acid and proteolytic enzymes, including cathepsin K and MMPs, which collectively mediate demineralization and degradation of the bone matrix (33). Thus, integrin αVβ3 not only mediates osteoclast adhesion, but is also important for organizing the architecture required for bone resorption.

In addition to being involved in the activity of fully developed osteoclasts, integrin αVβ3 is also responsible for the development and maturation of osteoclasts. Osteoclast formation is predominantly regulated by the RANKL-mediated activation of NF-κB, MAPK and nuclear factor of activated T cells 1 (NFATc1) (113,114). According to the available evidence, integrin αVβ3 signaling acts in coordination with established osteoclastogenic pathways rather than functioning independently, with signaling crosstalk contributing to osteoclast differentiation and resorptive function. Activation of integrin αVβ3 promotes Src-dependent signaling and the formation of signaling complexes involving immunoreceptor tyrosine-based activation motif-containing adaptor proteins, including DNAX-activating protein of 12 and Fc receptor γ. These complexes recruit downstream signaling molecules such as Syk and interact with osteoclast regulatory pathways that influence cytoskeletal organization and signaling through MAPKs and NFATc1 (44,115,116). This coordinated signaling contributes to the expression of osteoclast-associated genes, including tartrate-resistant acid phosphatase, cathepsin K and MMP-9, which are associated with osteoclast differentiation and bone-resorptive function (117). Thus, rather than acting as an independent driver of osteoclastogenesis, integrin αVβ3 cooperates with RANKL/RANK-dependent signaling and is particularly important for the cytoskeletal organization, polarization and resorptive function of mature osteoclasts.

Further research has highlighted additional crosstalk between integrin αVβ3 and M-CSF signaling in the osteoclastogenic process (118,119). Interactions between M-CSF and M-CSF receptor (c-FMS) increase the survival and proliferation of osteoclast precursor cells and affect integrin activation. Experimental evidence has shown that signaling via c-FMS elevates the ligand-binding capacity of integrin αVβ3 and induces Rac-dependent cytoskeletal reorganization (120). By contrast, the levels of M-CSF in integrin β3-deficient mice have been shown to be increased, thus indicating that the M-CSF/c-FMS interaction represents a compensatory mechanism against reduced osteoclast differentiation and supporting the presence of feedback loops between the c-FMS pathway and the integrin αVβ3 pathway. These findings highlight the importance of signaling crosstalk in osteoclast biology, whereby integrin αVβ3 cooperates with other receptor-mediated pathways to coordinate osteoclast differentiation, cytoskeletal organization and resorptive function (121).

Integrin αVβ3 activity is also modulated by the microenvironment within the bone. Acidification of this environment during bone resorption facilitates the activation of NFATc1, leading to higher expression levels of integrin αVβ3 and increased migration of osteoclasts via the Pyk2/Src signaling pathway (122). Furthermore, OPN has not only been shown to act as an adhesion protein but also to represent an important signaling molecule that stimulates the process of podosome assembly. The binding of OPN to the receptor integrin αVβ3 leads to the activation of the Src/FAK pathway, as well as the lowering of intracellular calcium levels by activating plasma membrane Ca^{2+}-ATPases (123). These findings illustrate how ECM composition and local biochemical conditions dynamically regulate integrin αVβ3-dependent osteoclast activity.

Research has also indicated the involvement of integrin αVβ3 in communication between osteoclasts and the bone microenvironment. Inflammatory cytokines and immune mediators have been shown to increase the activation of osteoclasts via integrin αVβ3-dependent mechanisms, whereas reciprocal communications between osteoclasts and cells derived from the osteoblast lineage have been shown to serve a notable role in bone remodeling processes (10,124). Although this topic is considered in more detail in the following sections, it should be noted that integrin αVβ3 operates in a larger regulatory system outside of osteogenic cells, involving ECM molecules, inflammatory agents and biomechanical factors.

Since the expression levels of integrin αVβ3 are elevated in mature osteoclasts, pharmacological targeting of integrin αVβ3 has received notable attention as a potential therapeutic approach to decrease bone resorption (125,126). Targeting integrin αVβ3 or its associated downstream signaling components, including Pyk2 and Src, has been shown to impair osteoclast adhesion, migration and cytoskeletal organization, thereby reducing bone-resorptive activity (108). Furthermore, modulation of αVβ3-associated signaling may influence osteoclast formation in inflammatory bone microenvironments through effects on Th17-associated inflammatory responses. Reduced Th17 activity can attenuate osteoclastogenesis by decreasing IL-17-mediated induction of RANKL in osteoclast-supporting cells and by limiting other pro-osteoclastogenic inflammatory signals. Thus, any effect of αVβ3 modulation on the Th17 response could indirectly influence RANKL-dependent osteoclast formation (127).

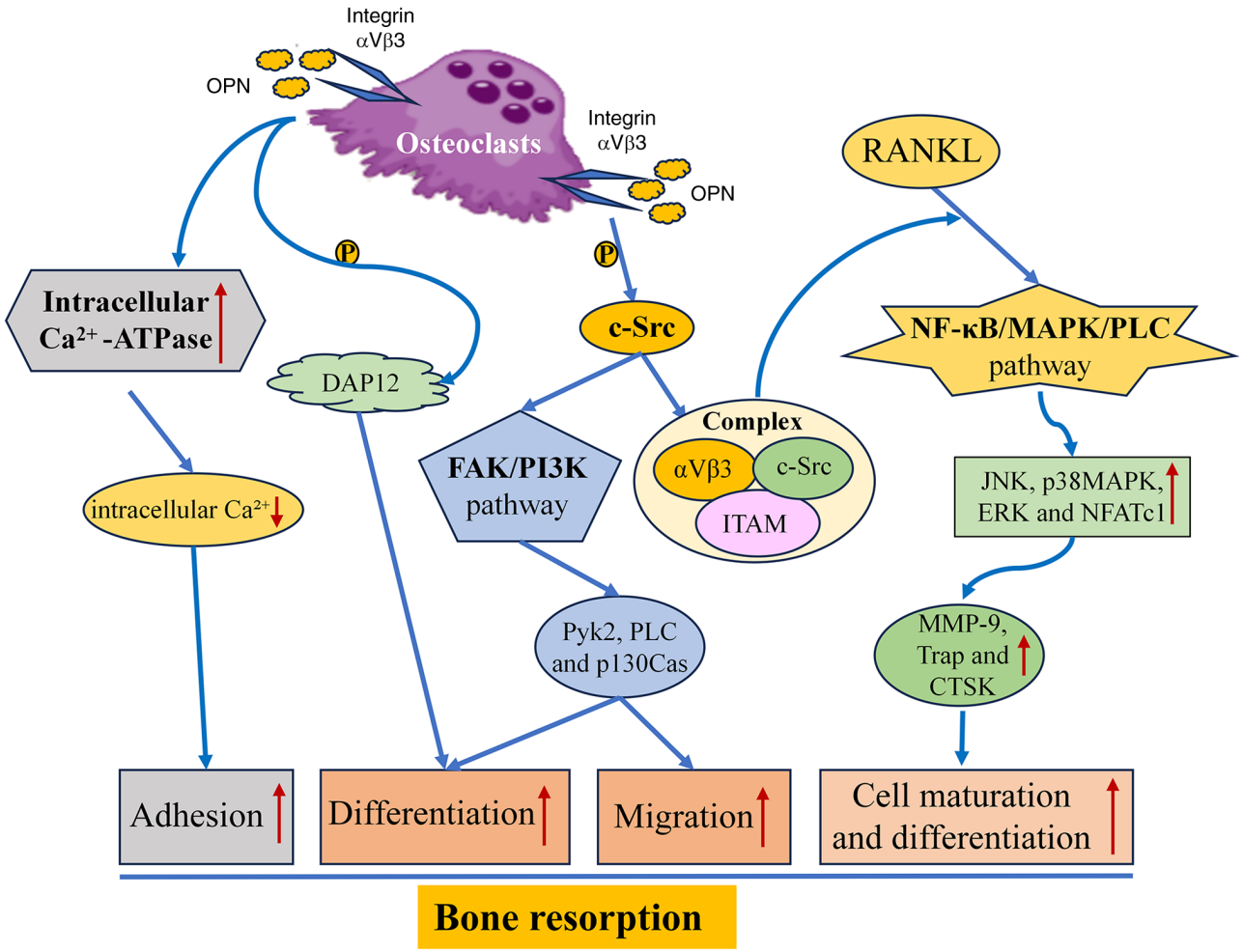

Figure 4. Integrin αVβ3-associated signaling in osteoclast function and bone resorption. The schematic summarizes integrin αVβ3-mediated signaling involved in osteoclast adhesion, migration, cytoskeletal organization, differentiation and bone resorption. Ligand-dependent integrin αVβ3 activation engages c-Src, FAK/PI3K and DAP12/ITAM-associated signaling and downstream mediators, including Pyk2, PLC and p130Cas. Crosstalk with RANKL-dependent signaling promotes activation of NF-κB, MAPK and NFATc1 and the expression of osteoclast-associated genes, including MMP-9, TRAP and CTSK. Solid arrows indicate activation or signaling progression; upward- and downward-facing arrows indicate increased and decreased activity or expression, respectively. c-Src, cellular Src tyrosine kinase; CTSK, cathepsin K; DAP12, DNAX-activating protein of 12 kDa; FAK, focal adhesion kinase; ITAM, immunoreceptor tyrosine-based activation motif; NFATc1, nuclear factor of activated T cells 1; OPN, osteopontin; P, phosphate group; PLC, phospholipase C; Pyk2, protein tyrosine kinase 2; RANKL, receptor activator of NF-κB ligand; TRAP, tartrate-resistant acid phosphatase.

However, these findings should be interpreted with caution because integrin αVβ3 is not restricted to osteoclasts and is also expressed in other cell populations within the bone microenvironment, including osteoblast-lineage cells, osteocytes, endothelial cells and certain immune cells. Consequently, therapeutic strategies targeting αVβ3 should consider its cell type- and context-dependent functions, and approaches that preferentially modulate osteoclast-associated αVβ3 signaling may help limit unintended effects on other αVβ3-expressing cells (128-130). The molecular mechanisms of osteoclast-mediated bone resorption that are regulated by integrin αVβ3 are illustrated in Fig. 4.

The available evidence supports an important role for integrin αVβ3 in osteoclast function by coupling bone-matrix adhesion to intracellular signaling that regulates cytoskeletal organization, polarization and resorptive activity. Rather than acting as a single dominant regulator of bone resorption, αVβ3 functions in coordination with other osteoclast regulatory systems, including RANKL/RANK and M-CSF/c-FMS signaling. Crosstalk among these pathways enables ECM engagement and cytokine-derived signals to converge on cytoskeletal regulatory mechanisms required for effective bone resorption. Consequently, the functional contribution of αVβ3 depends on the broader signaling context of the osteoclast rather than on αVβ3 activity alone (131-133). Future research utilizing cell-specific genetic systems, intravital microscopy and transcriptomic analysis will prove useful in elucidating the specific role of integrin αVβ3 in osteoclast-mediated bone resorption and will guide future development of effective treatments for OP.

Integrin αVβ3 regulates bone angiogenesis. The process of bone remodeling is tightly linked to angiogenesis, since newly developed blood vessels are required to deliver oxygen, nutrients, osteoprogenitor cells and other molecules that regulate bone remodeling and growth to the site of remodeling. Integrin αVβ3 has been demonstrated to mediate the processes involved in this angiogenic response by regulating endothelial

cell migration, adhesion, survival, and interactions between osteogenic and endothelial cells (96,134).

However, integrin αVβ3 is not an angiogenic growth factor *per se*; rather, it functions as an adhesion and signaling receptor that integrates ECM-derived signals with growth factor receptor signaling in endothelial cells. αVβ3 expression is relatively low in quiescent endothelium but is increased in activated endothelial cells during angiogenesis. Within bone, angiogenesis is an integral component of processes such as bone formation, fracture repair and remodeling, where newly formed vessels support tissue regeneration and osteogenic activity. Experimental studies have shown that pharmacological blockade of αVβ3 can inhibit neovascularization in several angiogenesis models, with comparatively limited effects on established vessels (118,123). These findings support a role for αVβ3 in endothelial activation, migration and survival during vascular remodeling (115,116,118,123). However, genetic and pharmacological studies have produced context-dependent findings; therefore, αVβ3 should be regarded as a modulator of angiogenic signaling rather than as an indispensable regulator of vascular development or maintenance (22,106,121,135).

From a molecular perspective, interactions between integrin αVβ3 and VEGFR2 take place with notable frequency. This signaling interface helps to coordinate the reactions of endothelial cells to angiogenic stimuli. When integrin αVβ3 is activated, FAK and Src family kinases are recruited, which results in the phosphorylation of VEGFR2 and subsequent activation of the PI3K/AKT and MAPK pathways. This in turn contributes to endothelial cell migration, proliferation and survival, and also leads to new blood vessel network formation (136-138). It is thus evident that integrin αVβ3 and VEGFR2 work cooperatively to support bone angiogenesis.

ECM remodeling may facilitate αVβ3-dependent endothelial responses during angiogenesis by modifying the accessibility of integrin-binding sites within the local matrix. Proteolytic remodeling can expose RGD-containing binding sites and alter the availability of αVβ3 ligands, thereby supporting endothelial cell adhesion and migration. In addition, αVβ3 recognizes ECM proteins such as OPN and vitronectin, interactions that can promote endothelial adhesion and migratory signaling. MMP-2 further contributes to pericellular ECM degradation and remodeling, thereby facilitating endothelial invasion through the surrounding matrix (139,140).

It has been demonstrated that integrin αVβ3-mediated regulation of angiogenesis is also affected by interactions between osteogenic cells and immune cells. Specifically, alternatively activated M2 macrophages have been shown to stimulate angiogenesis via integrin αVβ3-related pathways (141). Angiogenesis and osteogenesis are closely coupled during bone development, remodeling and repair, as illustrated by specialized bone vasculature, particularly type H vessels, which are spatially associated with osteoprogenitor cells and participate in reciprocal signaling between endothelial and osteogenic cell populations (29,96). Within this broader framework of angiogenic-osteogenic coupling, the aforementioned findings suggest that αVβ3 may contribute to communication between endothelial cells and bone-associated cells by integrating ECM-dependent adhesion with angiogenic signaling. However, the specific contribution of αVβ3 to this intercellular crosstalk remains less well defined than its established role in endothelial adhesion and angiogenic signaling.

Integrin αVβ3 regulates the bone microenvironment. Bone remodeling takes place in a notably dynamic microenvironment, in which immunological signaling, hormonal control, ECM structure and mechanical forces combine to regulate the homeostasis of the skeleton. A number of studies have shown that integrin αVβ3 serves a notable role in the regulatory mechanisms involved in interactions among bone cells, immune cells, endothelial cells and the ECM. Thus, αVβ3 may influence bone remodeling not only through its direct effects on bone-resorbing and bone-forming cells, but also through its actions in other components of the local bone microenvironment, including endothelial and immune cells (142,143). Collectively, current evidence indicates that αVβ3 participates in bone remodeling through cell type- and context-dependent mechanisms operating across the local bone microenvironment. In osteoclasts, αVβ3-mediated matrix adhesion is coupled to cytoskeletal organization and resorptive function; in osteocytes, αVβ3 contributes to mechanotransduction and mechanically induced biochemical responses; and in endothelial cells, αVβ3 participates in adhesion and signaling associated with angiogenesis. αVβ3-dependent responses may also be modified by inflammatory and hormonal conditions, including estrogen deficiency. These interconnected processes illustrate how αVβ3 signaling can link matrix-derived, mechanical, vascular and microenvironmental cues to cellular responses relevant to bone remodeling (Fig. 5).

Osteoimmune regulation. Inflammation has been widely acknowledged as a notable cause of bone loss and OP. In inflammatory bone microenvironments, integrin αVβ3 is expressed by several cell populations, including osteoclasts, activated macrophages, angiogenic endothelial cells and certain stromal cells, where it contributes to cell-ECM interactions, migration and inflammatory or resorptive signaling (125,131). Through these cell type-specific functions, αVβ3 may contribute to crosstalk between inflammatory responses, angiogenesis and osteoclast-mediated bone resorption (144,145). Experimental evidence indicates that pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-17, promote osteoclastogenesis primarily by enhancing RANKL/RANK-dependent signaling and by modifying the inflammatory microenvironment. These cytokine-driven mechanisms can converge with αVβ3-associated signaling during osteoclast differentiation and activation; however, αVβ3 should not be considered the principal mediator of their osteoclastogenic effects. In inflammatory stromal cells, particularly synovial fibroblasts, increased production of RANKL and MMPs contributes to osteoclast formation and tissue destruction. Furthermore, Th17 cells promote osteoclastogenesis through IL-17 production and RANKL-associated mechanisms, while OPN-integrin interactions may modulate Th17-cell adhesion and inflammatory responses (145-147).

Role of macrophages in αVβ3-regulated inflammatory signaling. Macrophages have also been shown to serve a role in integrin αVβ3-regulated inflammatory signaling pathways. In human monocyte-derived macrophages, ligation of integrin

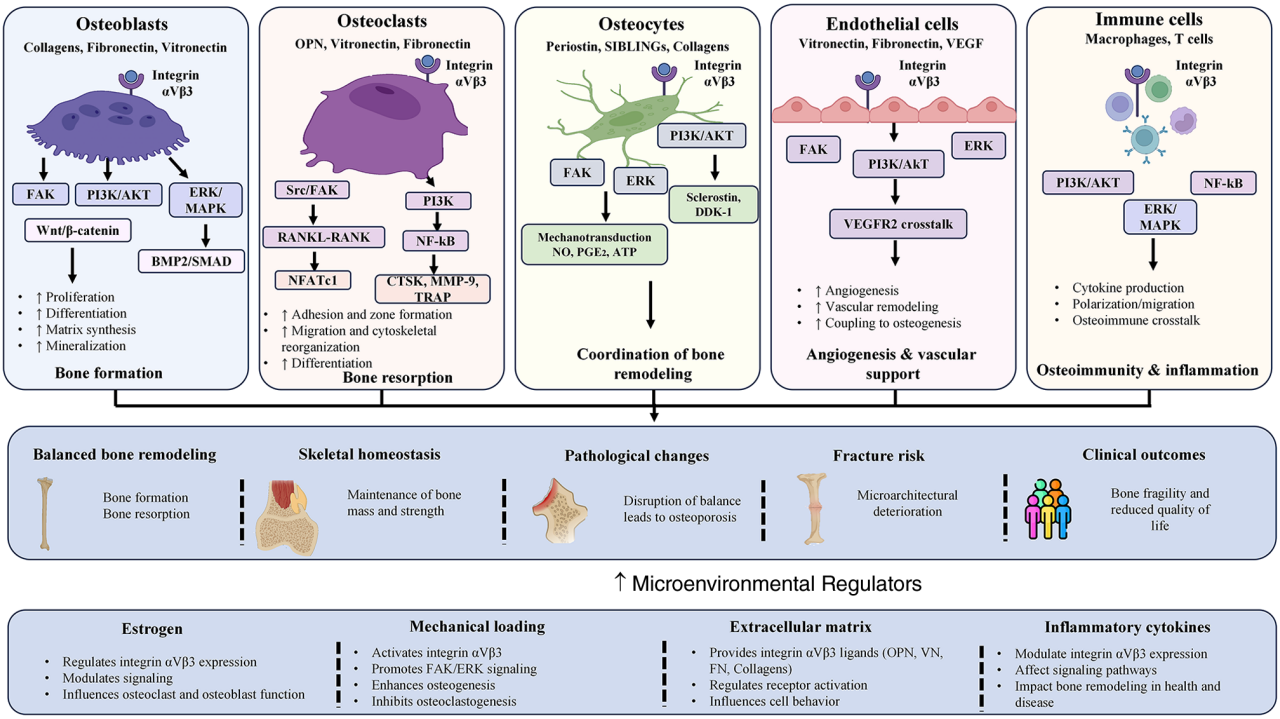

Figure 5. Context-dependent functions and therapeutic modulation of integrin αVβ3 in bone remodeling and osteoporosis. The schematic summarizes the cell type-specific functions of integrin αVβ3 in osteoblasts, osteoclasts, osteocytes, endothelial cells and immune cells and their contributions to bone formation, bone resorption, mechanotransduction, angiogenesis and inflammatory regulation. The figure also illustrates microenvironmental factors that modulate integrin αVβ3 signaling and potential strategies for selectively targeting αVβ3-associated pathological bone remodeling. Colored panels represent the different bone and bone-associated cell populations. AKT, protein kinase B; BMP, bone morphogenetic protein; CTSK, cathepsin K; DKK-1, Dickkopf-1; FAK, focal adhesion kinase; FN, fibronectin; NF-κB, nuclear factor-κB; NFATc1, nuclear factor of activated T cells 1; NO, nitric oxide; OPG, osteoprotegerin; OPN, osteopontin; PGE2, prostaglandin E2; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; SIBLINGs, small integrin-binding ligand N-linked glycoproteins; TRAP, tartrate-resistant acid phosphatase; VN, vitronectin.

αVβ3 has been shown to activate PI3K/Akt-dependent NF-κB signaling and to enhance NF-κB responses to pro-inflammatory stimuli, including lipopolysaccharide and TNF-α. This response is accompanied by increased expression of NF-κB-dependent pro-inflammatory mediators, indicating that αVβ3 signaling can modulate macrophage inflammatory activation (131). Neutrophils may also contribute to inflammation-associated bone remodeling by accumulating at inflammatory sites and releasing pro-inflammatory mediators, reactive oxygen species and neutrophil extracellular traps, which can enhance osteoclastogenic signaling and thereby favor bone resorption. Integrins, including αVβ3 in specific contexts, may contribute to neutrophil adhesion and migration; however, the direct contribution of neutrophil αVβ3 to inflammatory bone loss remains less well established than its role in osteoclasts. Evidence from rheumatoid arthritis further supports the involvement of αVβ3 in inflammatory bone resorption, where increased αVβ3 expression has been reported in osteoclasts and activated macrophages within affected joints (148). In osteoclasts, αVβ3-dependent signaling promotes migration, cytoskeletal organization and resorptive activity, whereas αVβ3-associated macrophage responses may contribute to the inflammatory environment that supports osteoclast activation and local bone erosion (149). Despite the different pathological natures of rheumatoid arthritis and OP, these findings support the potential impact of integrin αVβ3-mediated immune responses on bone remodeling.

Estrogen-dependent regulation of integrin αVβ3. Estrogen deficiency is a notable factor in the development of OP after menopause, and its influence on bone turnover has been related to its impact on osteoblasts, osteoclasts, osteocytes and immune cells (150,151). Recent research has supported the involvement of integrin αVβ3 in the estrogen-dependent regulation of bone homeostasis (152). Experimental studies using ovariectomy (OVX) models have demonstrated apparently divergent effects of β3 integrin signaling. Global β3 integrin deficiency protects mice against OVX-induced bone loss, consistent with the requirement for functional β3 integrin in osteoclast-mediated bone resorption. These apparently contrasting findings likely reflect the cell type-specific functions of αVβ3. In osteoclasts, αVβ3 supports cytoskeletal organization and bone-resorptive activity, whereas in osteocytes it contributes to mechanosensation and the signaling required for adaptive bone formation. Conversely, estrogen deficiency has been associated with reduced αVβ3 expression or localization in osteocytes and impaired skeletal adaptation to mechanical loading, characterized by defective osteocyte mechanotransduction and attenuated mechanically induced osteogenic responses (153,154). For example, genetic ablation of the integrin β3 subunit has predominantly been shown to hamper osteoclast adhesion, organization of the cytoskeleton and resorption activities, and hence diminish the rate of bone loss induced by ovariectomy (155). On the other hand, estrogen deficiency has been demonstrated to impact the mechanotransduction process in osteocytes,

where decreased levels of integrin αVβ3 disrupt focal adhesions, reduce actomyosin contraction and affect downstream signaling mechanisms required for bone homeostasis (139). In osteocytes, estrogen withdrawal reduces αVβ3 localization at mechanosensitive focal adhesions and is accompanied by increased RANKL expression and decreased OPG expression, resulting in an elevated RANKL/OPG ratio. This shift enhances osteocyte-derived paracrine signals that favor RANKL-dependent differentiation and activation of osteoclast precursors; it does not imply that reduced αVβ3 expression within osteoclasts directly promotes their differentiation. Estrogen withdrawal also impairs the mechanically induced COX-2 response in osteocytes, an effect similarly observed following αVβ3 antagonism. Because COX-2 induction is part of the osteocyte response to fluid shear stress and contributes to prostaglandin-mediated signaling involved in adaptive bone remodeling, loss of this response indicates impaired mechanotransduction and a reduced capacity to translate mechanical loading into appropriate remodeling signals (95,96). Thus, the consequences of reduced αVβ3 function are cell type-dependent: Impaired αVβ3 function in osteocytes can alter mechanosensation and osteoclastogenic paracrine signaling, whereas β3 deficiency in osteoclasts compromises the adhesion and cytoskeletal organization required for efficient bone resorption (156,157). Therefore, the effects of integrin β3 deficiency on bone homeostasis are notably different from those arising from estrogen deficiency.

The apparently divergent skeletal outcomes observed across β3-integrin deficiency and estrogen-deficiency models may reflect differences in the cell populations affected and in the mechanisms by which αVβ3 signaling is altered. Global or lineage-specific deletion of β3 integrin may influence several αVβ3-dependent cellular functions, whereas estrogen deficiency can alter αVβ3 localization and mechanotransduction in osteocytes together with broader hormonal effects on the bone microenvironment. Notably, osteocyte-specific β3 integrin deletion has been shown to reduce bone mass and impair mechanically induced bone formation, supporting a direct role for osteocyte β3 integrin in skeletal mechanotransduction. Further studies integrating cell type-specific conditional genetic models with spatial and single-cell approaches may help distinguish the contributions of αVβ3 signaling in osteocytes, osteoclasts and other bone-associated cells and clarify how estrogen deficiency modifies these cell-specific mechanisms.

5. Therapeutic potential and translational challenges of targeting integrin αVβ3 in OP

Increasing numbers of scientific studies have supported the importance of integrin αVβ3 as an effective therapeutic target for OP because of the role of this integrin in several aspects of bone remodeling (158,159). Although traditional antiresorptive agents work on the basis of targeting osteoclasts, the modulation of integrin αVβ3 activity can have a notable impact on multiple signaling pathways associated with the maintenance of bone homeostasis. At the same time, the wide distribution of integrin αVβ3 in different types of tissue and its various roles in these tissues pose certain challenges for developing novel treatments for OP.

Evidence supporting integrin αVβ3 as a potential therapeutic target in OP is derived predominantly from preclinical studies using cellular and animal models. Pharmacological inhibition of αVβ3 has been shown to impair osteoclast adhesion and cytoskeletal organization, including disruption of actin-ring and sealing-zone formation, thereby reducing bone-resorptive activity (64,69,160). For example, HSA-ARLDDL, a highly selective αVβ3 antagonist, inhibited RANKL-induced osteoclast formation and attenuated cancellous bone loss in the tibia and femur of ovariectomized mice, while having no detectable effect on osteoblast differentiation or calcium deposition under the experimental conditions examined (69). In addition to direct αVβ3 antagonism, experimental inhibition of αVβ3-associated intracellular signaling components, particularly Pyk2 and Src, has been associated with disruption of osteoclast cytoskeletal organization, migration and resorptive function (64,161). Collectively, these preclinical findings identify αVβ3 and its associated signaling machinery as potential antiresorptive targets in conditions characterized by excessive osteoclast activity; however, their therapeutic efficacy, selectivity and safety in human OP remain to be established (1,162). Taken together, these studies provide evidence that the involvement of integrin αVβ3 in pathological bone resorption could be targeted for the treatment of conditions with excess osteoclastic activity.

Several approaches have since been employed to study the pharmacology of integrin αVβ3 signaling. Dual blockade of c-FMS and integrin αVβ3 has been shown to provide improved suppression of osteoclast differentiation compared with their individual blockade in preclinical models (141). This suggests that targeting multiple signal transduction pathways may be more effective therapeutically than targeting individual osteogenic pathways. Additionally, studies have shown promising results regarding the use of natural inhibitors. For example, tablysin-15 has been shown to block osteoclast differentiation predominantly through the inhibition of integrin αVβ3-induced activation of the FAK pathway, whereas cilengitide has been shown to prevent integrin αVβ3-dependent cell adhesion and bone resorption in osteoclasts (139,163). These results support the therapeutic efficacy of integrin αVβ3-targeting therapy to mitigate osteoclastic activity; however, additional research is required to establish the efficacy and safety of such therapies (160).

Clinical data for therapies targeting integrin αVβ3 remain relatively sparse. In a study by Murphy *et al* (140), administration of L-000845704, an inhibitor of integrin αVβ3, markedly decreased the levels of biochemical indicators of bone resorption and increased bone mineral density in postmenopausal women. Although these findings suggest potential therapeutic relevance, clinical evidence supporting integrin αVβ-targeted therapies remains limited. Adequately powered randomized controlled trials with longer follow-up periods are therefore required to determine their efficacy in reducing fracture risk and to establish their long-term safety. Therefore, integrin αVβ3-based approaches should be considered as investigational, rather than clinically proven therapies for OP.

Notably, the use of integrin αVβ3 as a target for OP therapy poses certain biological problems. Although targeting osteoclast-associated αVβ3 signaling may provide an approach to suppress excessive bone resorption, αVβ3 is not restricted to

osteoclasts and is also expressed in osteoblast-lineage cells, osteocytes, endothelial cells, macrophages and other immune cell populations. Consequently, systemic αVβ3 inhibition may affect αVβ3-dependent functions in non-osteoclast cells, highlighting the importance of cell-selective targeting when developing αVβ3-directed therapies for bone disorders. Thus, systematic blockage may also affect various physiological processes outside of bone resorption. For example, as the role of integrin αVβ3 is important in endothelial cell function and angiogenesis, long-term inhibition may negatively affect vascular remodeling and tissue repair (160). Furthermore, since integrin αVβ3 is present in platelets and immune cells, there remains a potential risk that integrin αVβ3 inhibition may negatively affect immune function and wound healing, although this issue has not been extensively investigated in clinical trials for OP (93).

The challenges with targeting integrin αVβ3 also include the context-dependent nature of its activity. Experimental data have shown that the inhibition of integrin αVβ3 signaling leads to reduced osteoclast-mediated bone resorption (64,69). However, in the case of estrogen deficiency, study has shown that reduced integrin αVβ3 expression in osteocytes is associated with impaired mechanotransduction and notable bone loss (139). Despite their contradictory nature, these two observations may be explained by the fact that integrin αVβ3 serves different roles in distinct cells in the skeletal system (155). The skeletal effects of altered integrin β3/αVβ3 signaling appear to depend on the cell type and experimental context. In osteocytes, β3 integrin deletion impairs mechanotransduction and mechanically induced bone formation, whereas estrogen withdrawal alters αVβ3 localization at focal adhesions, disrupts mechanosensitive signaling and modifies the RANKL/OPG ratio (164,165). Additional factors that may contribute to differences among experimental findings include the cell population targeted, the use of global vs. cell type-specific genetic deletion, developmental or compensatory responses to gene deletion, the duration and severity of estrogen deficiency and differences between genetic, pharmacological and hormonal models. These variables should therefore be considered when interpreting apparently divergent effects of αVβ3/β3-integrin perturbation on bone homeostasis. Collectively, these observations support a cell type- and context-dependent role for integrin αVβ3 in skeletal homeostasis rather than a uniformly beneficial or detrimental effect on bone remodeling. Accordingly, therapeutic development should consider the distinct functions of αVβ3 across bone-associated cell populations rather than relying solely on systemic receptor blockade. Preclinical studies have demonstrated that selective αVβ3 antagonism can suppress osteoclast-mediated bone resorption and attenuate ovariectomy-induced bone loss (153,166). Future strategies aimed at improving therapeutic selectivity may include preferential targeting of osteoclast-associated αVβ3 signaling or selective modulation of downstream signaling components while preserving αVβ3-dependent functions in other skeletal cells. However, these more selective approaches remain largely investigational and require further experimental and clinical validation. Furthermore, advancements in the fields of spatial transcriptomics, single-cell multi-omics and conditional genetics will be important for elucidating the roles of integrin αVβ3 on a cell-specific level and identifying patients who would benefit the most from integrin αVβ3-targeted therapy.

6. Summary and perspectives

Bone remodeling is a highly coordinated process that depends on continuous communication among osteoblasts, osteoclasts, osteocytes, endothelial cells, immune cells and the ECM. Throughout the present review, integrin αVβ3 has been highlighted as an important molecular interface linking ECM interactions with intracellular signaling pathways that collectively regulate skeletal homeostasis. Rather than functioning solely as an adhesion receptor, integrin αVβ3 integrates biochemical and mechanical signals to influence osteoblast differentiation, osteoclast activation, osteocyte-mediated mechanotransduction, angiogenesis and immune-skeletal interactions. These diverse biological functions position integrin αVβ3 as an important regulator of bone remodeling and contribute to its involvement in the pathogenesis of OP.

One of the most notable takeaways from previous research regarding the activity of integrin αVβ3 is that the biological effects of integrin αVβ3 are context-dependent. Experimental studies have indicated that integrin αVβ3 contributes to osteogenic differentiation through the coordinated regulation of focal adhesion signaling, cytoskeletal organization and mechanotransduction, while simultaneously facilitating osteoclast adhesion, migration and bone-resorptive activity through interactions with ECM ligands and RANKL-associated signaling pathways. In addition, integrin αVβ3 has been shown to participate in angiogenesis and osteoimmune communication by integrating endothelial, inflammatory and ECM-derived signals within the bone microenvironment. Notably, studies have indicated that the function of integrin αVβ3 differs among osteoblasts, osteoclasts, osteocytes, endothelial cells and immune cells, emphasizing that the biological activity of integrin αVβ3 should be interpreted with regards to its specific cellular and microenvironmental context, rather than considered as uniformly beneficial or detrimental in bone homeostasis.

Current evidence has also indicated that integrin αVβ3-targeting may offer potential as a novel treatment strategy for diseases associated with increased bone resorption. In one preclinical study, selective inhibition of integrin αVβ3 with HSA-ARLDDL suppressed RANKL-induced osteoclastogenesis and attenuated ovariectomy-induced cancellous bone loss, supporting the potential of αVβ3 as an antiresorptive therapeutic target in OP (69). However, clinical data supporting the efficacy and long-term safety of αVβ3-targeted therapies for OP remain limited, and the expression of αVβ3 across multiple cell types raises additional concerns regarding therapeutic specificity and potential off-target effects. As such, the effects of treatment on physiological angiogenesis, wound healing, immunomodulation and platelets need to be considered in the development of any novel drug that targets the integrin αVβ3 receptor. Thus, the selective modulation of integrin αVβ3 probably represents a more promising therapeutic option for the treatment of skeletal disorders than treatments involving all-out integrin αVβ3 blockade.

Although substantial progress has been made in understanding integrin αVβ3 signaling in bone, several

important questions remain unresolved. First, the molecular mechanisms underlying the cell type-specific functions of αVβ3 require further clarification, particularly how αVβ3-dependent responses in osteoblasts, osteoclasts, osteocytes, endothelial cells and immune cells collectively influence intercellular communication during physiological and pathological bone remodeling. Second, the apparently divergent skeletal outcomes observed in β3-integrin genetic-deficiency and estrogen-deficiency models highlight the need to distinguish the effects of cell type-specific loss of β3/αVβ3 function from the broader effects of estrogen deficiency on osteoclast activity, osteocyte mechanotransduction and RANKL/OPG-mediated remodeling. Finally, although interactions between αVβ3 and signaling pathways including Wnt/β-catenin, BMP, PI3K/AKT, MAPK and RANKL/RANK have been described, their relative contributions, temporal coordination and cell type-specific integration during bone remodeling remain incompletely understood. Defining these context-dependent signaling relationships will be important for determining when and in which cellular compartments αVβ3 represents an appropriate therapeutic target. Therefore, future research should focus on the application of sophisticated experimental techniques that can elucidate the complex spatiotemporal nature of the integrin αVβ3 signaling pathway in bone remodeling. Techniques such as conditional cell-specific knockout studies, lineage tracing, spatial omics, single cell multi-omics and intravital imaging may contribute to an improved understanding of the processes involved in integrin αVβ3 signaling in the bone microenvironment. Simultaneously, the generation of selective drug delivery systems, allosteric modulators and combinatorial therapies may help to enhance the therapeutic potential of integrin αVβ3-targeting while maintaining the physiological role of integrin αVβ3 outside of skeletal tissues.

In conclusion, current evidence indicates that integrin αVβ3 contributes to bone remodeling by coupling interactions with ECM ligands to intracellular signaling that regulates cell adhesion, cytoskeletal organization, mechanotransduction and other cell type-specific responses in bone-associated cells. Its functional consequences vary among osteoclasts, osteoblast-lineage cells, osteocytes, endothelial cells and immune cells and depend on the local signaling and microenvironmental context. Although substantial progress has been made in defining these functions, important questions remain regarding the molecular determinants of cell type-specific αVβ3 signaling, its integration with other bone-remodeling pathways and the consequences of selectively modulating this receptor in different skeletal cell populations. Addressing these knowledge gaps will improve understanding of αVβ3-dependent mechanisms in OP and help determine whether cell-selective or pathway-specific modulation of αVβ3 can be translated into safe and effective therapeutic strategies for OP and other disorders characterized by abnormal bone remodeling.

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Availability of data and materials

Not applicable.

Authors' contributions

CC contributed to conceptualization, development of the review methodology, literature investigation and interpretation, preparation of figures and visualization, and drafting of the manuscript. XH contributed to literature investigation and evaluation, development of the review methodology, preparation of figures and visualization, and drafting of the manuscript. SW, YD, QZ, GC and ZC contributed to literature identification and evaluation, synthesis and interpretation of the evidence and critical revision of the manuscript for important intellectual content. JJ and JG contributed to conceptualization, supervision, project administration, funding acquisition and critical review and editing of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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