



The Dynamic Osteocyte: Master Signaling Cell Integrating Bone Biology and Systemic Physiology

Dinamik Osteosit: Kemik Biyolojisi ile Sistemik Fizyolojiyi Bütünleştiren Ana Sinyal Hücresi

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Abstract

Osteocytes, long considered passive residents of bone, are now recognized as master regulators of skeletal remodeling and systemic metabolism. This review synthesizes current knowledge on osteocyte signaling, evaluates mechanotransduction mechanisms, and identifies key knowledge gaps to guide future research. A narrative review was conducted using MEDLINE, PubMed, Embase, Cochrane CENTRAL, and Google Scholar for studies published between January 2016 and December 2024. Keywords included "osteocyte signaling," "bone homeostasis," and "mechanotransduction." Included studies encompassed experimental, preclinical, translational, and clinical research. Osteocytes coordinate bone formation and resorption through paracrine and endocrine mediators, including sclerostin, receptor activator of nuclear factor- κ B ligand, wntless-related integration site ligands, and fibroblast growth factor 23. Their extensive lacuno-canalicular network facilitates mechanosensation via fluid shear stress, ion channels (e.g., Piezo1), and cytoskeletal remodeling. Osteocytes also influence mineral metabolism, immune responses, energy homeostasis, and aging. Emerging evidence highlights their heterogeneity and context-dependent signaling, though debates persist regarding primary mechanosensors, signal hierarchy, and spatial regulation of outputs. Osteocytes act as central integrators of mechanical and biochemical cues, orchestrating skeletal and systemic physiology. Advancing *in vivo* models, spatial transcriptomics, and mechanistic studies will deepen understanding of osteocyte signaling, offering promising therapeutic avenues for osteoporosis, metabolic bone disorders, and chronic inflammation.

Keywords: Osteocyte, mechanotransduction, bone remodeling, sclerostin, RANKL, Wnt pathway, FGF23

Öz

Uzun süre kemiğin pasif yerleşik hücreleri olarak kabul edilen osteositlerin, günümüzde iskelet yeniden yapılanmasının ve sistemik metabolizmanın temel düzenleyicileri olduğu anlaşılmıştır. Bu derlemede, osteosit sinyalleşmesine ilişkin güncel bilgilerin sentezlenmesi, mekanotransdüksiyon mekanizmalarının değerlendirilmesi ve gelecekteki araştırmalara yön verecek temel bilgi boşluklarının belirlenmesi amaçlanmıştır. Ocak 2016 ile Aralık 2024 arasında yayımlanan çalışmalar MEDLINE, PubMed, Embase, Cochrane CENTRAL ve Google Scholar veri tabanlarında taranarak anlatsal bir derleme gerçekleştirilmiştir. Aramada "osteosit sinyalleşmesi", "kemik homeostazı" ve "mekanotransdüksiyon" anahtar kelimeleri kullanılmıştır. Deneysel, preklinik, translaşyonel ve klinik araştırmalar derlemeye dahil edilmiştir. Osteositler; sklerostin, nükleer faktör- κ B ligand reseptör aktivatörü, Wntless ile ilişkili entegrasyon bölgesi ligandları ve fibroblast büyüme faktörü 23 dâhil olmak üzere parakrin ve endokrin mediyatörler aracılığıyla kemik oluşumu ve rezorpsiyonunu koordine eder. Osteositlerin geniş laküno-kanaliküler ağı; sıvı kayma gerilimi, iyon kanalları (örneğin, Piezo1) ve hücre iskeletinin yeniden düzenlenmesi yoluyla mekanik uyarıların algılanmasını sağlar. Osteositler ayrıca mineral metabolizmasını, bağışıklık yanıtlarını, enerji homeostazını ve yaşlanmayı da etkiler. Güncel bulgular, osteositlerin heterojenliğini ve bağlama bağlı sinyal özelliklerini ortaya koymakla birlikte, birincil mekanik algılayıcılar, sinyal hiyerarşisi ve hücresel çıktılarının uzamsal düzenlenmesine ilişkin tartışmalar devam etmektedir. Osteositler, mekanik ve biyokimyasal uyarıların bütünleştiren merkezi düzenleyiciler olarak iskelet ve sistemik fizyolojiyi yönlendirir. *In vivo* modellerin, uzamsal transkriptomik yöntemlerin ve mekanistik çalışmaların geliştirilmesi, osteosit sinyalleşmesinin daha iyi anlaşılmasını sağlayarak osteoporoz, metabolik kemik hastalıkları ve kronik enflamasyon için umut verici tedavi olanakları sunabilir.

Anahtar kelimeler: Osteosit, mekanotransdüksiyon, kemik yeniden yapılanması, sklerostin, RANKL, Wnt yolağı, FGF23

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Introduction

For decades, bone biology was dominated by the interplay between osteoblasts, which form bone, and osteoclasts, which resorb it. Osteocytes—making up over 90% of all bone cells—were long considered passive, terminally embedded cells with minimal functional significance (1). This perspective has shifted dramatically. Landmark studies over the past two decades have established osteocytes as central regulators of skeletal homeostasis and sophisticated signaling hubs capable of integrating mechanical, biochemical, and endocrine cues (2). Osteocytes influence both local and systemic physiology. Through the secretion of sclerostin, they inhibit osteoblast activity, whereas receptor activator of nuclear factor- κ B ligand (RANKL) production drives osteoclastogenesis, directly coordinating bone remodeling (3). Endocrine roles have also emerged, exemplified by fibroblast growth factor 23 (FGF23) in phosphate homeostasis (4). Furthermore, osteocyte apoptosis is a critical initiator of targeted bone resorption during microdamage repair or glucocorticoid-induced bone loss (5). These findings underscore that understanding osteocyte signaling is not purely academic but central to developing novel diagnostics and therapies for skeletal diseases.

Despite these advances, significant gaps remain. A major controversy concerns the primary mechanosensor within osteocytes: is it the deflection of primary cilia, integrin-based focal adhesion complexes, or fluid shear stress-gated ion channels? The spatial logic of osteocyte signaling is also unclear: how do cortical versus trabecular osteocytes coordinate responses, and how is mechanical load translated into differential formation versus resorption (6)?

This narrative review aims to provide a comprehensive synthesis of osteocyte biology as a signaling cell. Its objectives are to: 1) delineate mechanotransduction and signal transduction mechanisms; 2) critically evaluate osteocyte communication with osteoblasts, osteoclasts, and bone-lining cells; 3) analyze endocrine contributions to mineral metabolism; and 4) identify knowledge gaps and propose actionable future research directions to resolve current controversies.

Materials and Methods

This study was conducted as a narrative review to provide a comprehensive and critical synthesis of contemporary literature on osteocyte signaling. The narrative design enabled integration of mechanistic, preclinical, and clinical evidence while emphasizing areas of a structured search was performed in MEDLINE via Ovid, PubMed, Embase, Cochrane CENTRAL, and Google Scholar. The timeframe was restricted to January 2016 through December 2024 to capture recent advances in osteocyte biology. Search terms included combinations of “osteocyte” with “signaling,” “mechanotransduction,” “communication,” “RANKL,” “sclerostin,” and “FGF23,” linked to “bone remodeling,” “bone metabolism,” or “osteoporosis.” Search strategies were adapted for each database, and additional studies were identified through

manual screening of reference lists.

Eligible studies included *in vitro* and *in vivo* preclinical investigations elucidating osteocyte signaling mechanisms, longitudinal cohort studies and randomized controlled trials evaluating therapeutics targeting osteocyte pathways (such as anti-sclerostin antibodies), and relevant systematic reviews or meta-analyses. Non-English articles, non-peer-reviewed publications, and reports not directly addressing osteocyte signaling or bone physiology were excluded.

Titles and abstracts were screened for relevance, followed by full-text evaluation of selected articles. Data extraction focused on signaling pathways, experimental models, and principal findings, which were synthesized thematically to generate an integrated conceptual framework.

As a narrative review, formal methodological quality assessment and risk-of-bias appraisal were not performed, introducing potential selection bias. The predominance of murine and *in vitro* models may limit direct translational applicability to human physiology. Furthermore, *in vitro* systems may not fully replicate the mechanical and biochemical complexity of the osteocyte lacuno-canalicular network. These limitations are acknowledged in the interpretation of findings.

Molecular and Cellular Mechanisms of Osteocyte Signaling

This section defines the molecular and cellular machinery that enables osteocytes to function as mechanosensory and signaling hubs. Emphasis is placed on structural organization, sensor systems, intracellular transduction pathways, effector outputs, and cell fate decisions. Integration at the tissue and systemic levels is addressed in subsequent sections.

The Lacunar-Canalicular Network: Structural Basis for Communication

Osteocytes reside within lacunae and extend 50-100 dendritic processes through micron-sized canaliculi, forming a dense, interconnected syncytium throughout mineralized bone (7). This lacunar–canalicular network (LCN) serves as a three-dimensional communication system in which interstitial fluid flow generates shear stress that is converted into biochemical signals, establishing osteocytes as widely regarded as dominant mechanosensors of the skeleton (8).

The structural integrity of this network depends on an actin-rich cytoskeleton that stabilizes dendritic projections (9). Gap junctions composed largely of connexin 43 (Cx43) permit direct intercellular communication and rapid signal propagation (10). Cx43 also forms hemichannels that connect osteocytes to the extracellular space and regulate paracrine factor release (11). Osteocyte-specific deletion of Cx43 increases apoptosis, produces empty lacunae in cortical bone, and blunts anabolic responses to mechanical loading (12) (Table 1).

Cx43 interacts with integrins at dendritic attachment sites, suggesting an integrated mechanotransduction complex (13). Super-resolution imaging demonstrates colocalization of β 3 integrin with pannexin 1, purinergic receptor P2X7, and

calcium voltage-gated channel subunit α_1H (CaV3.2) along dendritic processes—structures absent from the cell body (14). Mechanical stimulation of dendrites triggers directional calcium influx through integrin $\alpha_5\beta_3$ (integrin-dependent mechanisms (9), supporting the view that dendritic processes function as specialized mechanosensory domains.

Molecular Mechanosensors: Primary Cilia, Integrins, and Ion Channels

Osteocytes transduce fluid shear stress through multiple mechanosensitive systems operating in parallel, including primary cilia, integrin-based adhesions, ion channels, and select G protein-coupled receptors. The primary cilium, a microtubule-based projection from the cell body, deflects under fluid flow and activates signaling pathways involving polycystin-1 (PC1) (15).

Integrins anchor osteocytes to the canalicular matrix. Integrin β_1 is enriched at the cell body, whereas integrin β_3 localizes predominantly to dendritic puncta (14), reflecting spatial specialization. Among mechanosensitive ion channels, PIEZO1 mediates mechanically induced calcium entry in osteocytes (16). Pharmacological activation of PIEZO1 reproduces load-induced calcium responses and suppresses sclerostin expression, whereas knockdown attenuates fluid flow-induced signaling (17). Conditional Piezo1 deletion leads to marked reductions

in cancellous bone mass and cortical thickness, with severely impaired anabolic responses to mechanical loading (18).

Transient receptor potential vanilloid 4 (TRPV4) localizes to discrete sites along osteocyte processes in proximity to $\alpha_5\beta_3$ integrin attachments (14). The balance between depolarizing cation influx and hyperpolarizing potassium efflux likely determines activation thresholds (19). Certain G protein-coupled receptors also act as direct mechanosensors; fluid shear stress induces conformational changes in the parathyroid hormone type 1 receptor (PTH1R) independent of ligand binding (20) (Table 1).

Together, these pathways indicate a distributed and context-dependent mechanosensory apparatus rather than a single dominant sensor.

Intracellular Signal Transduction: From Membrane to Nucleus

Mechanical stimulation rapidly activates second messenger systems. Nitric oxide (NO) production increases within minutes via endothelial NO synthase activation and is required for subsequent prostaglandin E_2 synthesis and sclerostin downregulation (21).

Mechanical cues further regulate nuclear responses through yes-associated protein/transcriptional coactivator with PDZ-binding motif (TAZ), which shuttle between cytoplasm and nucleus.

Table 1. Major osteocyte-derived signaling molecules and actions

Molecule	Primary action	Target cells	Key references	Physiological context	Disease relevance
Sclerostin	Inhibits Wnt/ β -catenin signaling	Osteoblasts	(3,22)	Mechanical unloading, aging	Osteoporosis (target of romosozumab)
RANKL	Promotes osteoclast differentiation	Osteoclast precursors	(1,39,40)	Targeted remodeling, microdamage	Osteoporosis, inflammatory bone loss
FGF23	Regulates phosphate homeostasis	Kidney (proximal tubule)	(4,28,29)	Phosphate/vitamin D balance	CKD-MBD, hypophosphatemic rickets
PGE ₂	Promotes bone formation	Osteoblasts	(21)	Mechanical loading response	Mechanotransduction
Wnt ligands	Promotes bone formation, cell survival	Osteoblasts	(22,70)	Coupling, anabolic windows	Bone formation
OPG	Decoy receptor for RANKL	Osteoclast precursors	(39)	RANKL buffering	Osteoprotection
DKK1	Wnt antagonist	Osteoblasts	(35)	Formation inhibition	Diabetes, myeloma
EVs	Interorgan communication, miRNA transfer	Multiple distant tissues	(26,27)	Systemic signaling	Alzheimer's, osteoarthritis
NO	Vasodilation, signaling mediator	Endothelium, osteoblasts	(21)	Acute load response	Mechanotransduction
TGF- β	Coupling factor	Osteoblasts	(47)	Matrix release signals	Remodeling balance
PTHrP	Local calcium regulation	Osteocytes, osteoblasts	(20,43)	Perilacunar remodeling	Lactation, calcium demand

RANKL: Receptor activator of nuclear factor- κ B ligand, FGF23: Fibroblast growth factor 23, PGE₂: Prostaglandin E₂, OPG: Osteoprotegerin, DKK1: Dickkopf-related protein 1, EVs: Extracellular vesicles, NO: Nitric oxide, TGF- β : Transforming growth factor-beta, PTHrP: Parathyroid hormone-related protein, CKD-MBD: Chronic kidney disease-mineral bone disorder

Osteocyte-specific deletion leads to low bone mass, impaired mechanical properties, disorganized collagen architecture, and reduced mechanoresponsiveness (23). The LINC complex couples the actin cytoskeleton to the nuclear lamina, enabling direct transmission of force to the nucleus (24).

Mechanotransduction is closely linked to metabolic state. Osteocytes reside in a relatively hypoxic microenvironment and rely largely on glycolytic metabolism (25). Their secretome includes soluble mediators and extracellular vesicles (EVs) capable of traversing the LCN and entering systemic circulation. EVs from young mice improve cognitive function in Alzheimer's disease models and mediate bone–cartilage communication in osteoarthritis (26). In addition, osteolineage cells can transfer functional mitochondria to myeloid cells through tunneling nanotubes and EVs, revealing an additional mechanism of intercellular coordination (27) (Table 1).

Effector Outputs: Sclerostin, RANKL, and Other Signaling Molecules

Sclerostin, encoded by *SOST* gene and secreted primarily by mature osteocytes, inhibits bone formation by antagonizing Wnt/ β -catenin signaling. Mechanical loading suppresses sclerostin expression, permitting anabolic activity (22). Brief axial loading induces localized and transient loss of sclerostin in osteocytes located within high-strain regions (3).

Osteocytes are the principal source of RANKL, the cytokine essential for osteoclast differentiation. Osteocyte-specific RANKL deletion results in severe osteopetrosis, failed tooth eruption, and absence of cancellous osteoclasts (39). Following fatigue-induced microdamage, surviving osteocytes surrounding apoptotic cells upregulate RANKL and related mediators to recruit osteoclasts precisely to damaged sites (40).

Osteocytes produce additional signaling molecules that modulate bone remodeling, including Wnt ligands that promote formation and osteoprotegerin (OPG) that buffers RANKL activity. The balance between these effectors determines net remodeling outcomes (Table 1).

Cell Fate Decisions: Apoptosis and Senescence as Signaling Events

Osteocyte apoptosis initiates bone loss in settings such as disuse, microdamage, glucocorticoid excess, sex steroid deficiency, and aging (3). Mechanical stimulation promotes survival through integrin-, steroid receptor coactivator/sarcoma kinase (Src)-, focal adhesion kinase (FAK)-, and extracellular signal-regulated kinase (ERK)-dependent pathways (30). Sex steroids preserve osteocyte viability via rapid activation of inducible phosphoinositide 3-kinase and Src/Shc/ERK signaling through non-genotropic mechanisms (31). Bisphosphonates enhance survival through ERK activation and Cx43-dependent signaling independent of gap junction formation (5). In contrast, glucocorticoid-induced apoptosis involves proline-rich tyrosine kinase 2 (PYK2) activation and disruption of FAK-mediated survival signaling (32).

The penumbra model clarifies targeted remodeling: apoptotic osteocytes mark the site of damage, while adjacent viable cells

upregulate RANKL to execute localized resorption (23,39). This spatial organization ensures that resorption is confined to damaged bone while preserving healthy tissue.

Cellular senescence represents a distinct fate characterized by irreversible cell cycle arrest and acquisition of a senescence-associated secretory phenotype (SASP) composed of inflammatory cytokines, proteases, and growth factors (33,49). Pharmacologic elimination of senescent cells or suppression of their secretory activity prevents age-related bone loss and attenuates radiation-induced skeletal damage in mice (28,49). Unlike apoptosis, which provides a spatially targeted signal for remodeling, senescence exerts broader, chronic effects on the bone microenvironment through sustained SASP factor release.

Osteocytes as Systemic Regulators

While the preceding section focused on the molecular machinery within individual osteocytes, osteocyte functions extend far beyond the bone microenvironment. This section examines how osteocyte-derived signals reach distant organs and contribute to whole-body physiology and disease.

Endocrine Functions: FGF23 and Mineral Metabolism

Osteocytes function as endocrine regulators beyond the bone microenvironment. They produce FGF23, a hormone controlling phosphate balance and vitamin D metabolism (29). Excess FGF23 causes hereditary hypophosphatemic rickets and tumor-induced osteomalacia, whereas deficiency results in hyperphosphatemia and ectopic calcifications (30). In chronic kidney disease, sustained FGF23 elevation contributes to mineral bone disorder and increased cardiovascular mortality (35,36) (Table 1).

Interorgan Communication: Extracellular Vesicles and Beyond

Osteocyte-derived sclerostin also influences systemic metabolism, affecting adipose tissue and glucose homeostasis (31). Osteocytic peroxisome proliferator-activated receptor gamma (PPAR γ) signaling regulates sclerostin expression and mediates bone deterioration associated with diabetes (32).

Bone–muscle crosstalk is bidirectional: conditioned media from osteocyte-like cells accelerates myogenesis, while exercise-induced muscle factors protect osteocytes from apoptosis (33). Circulating osteocyte-derived EVs further extend this influence to distant organs, including the brain, where EVs from young mice enhance cognitive function in Alzheimer's disease models (26). These findings position osteocytes as nodes in a broader interorgan communication network.

Osteocyte Signaling in Disease States

Dysregulation of osteocyte signaling pathways contributes directly to skeletal and systemic disease states, illustrating the physiological importance of the mechanisms described above.

Osteoporosis and Estrogen Deficiency: Estrogen deficiency increases sclerostin expression, epigenetic alterations reduce osteogenic activity, FGF23 rises, and RANKL expression escalates, collectively favoring bone resorption over formation (29) (Table

1). Romosozumab, a monoclonal antibody targeting sclerostin, represents the first therapy to directly exploit osteocyte biology and has proven effective in treating postmenopausal osteoporosis (34,51).

Chronic Kidney Disease–Mineral Bone Disorder (CKD-MBD): CKD-MBD illustrates the systemic consequences of dysregulated osteocyte signaling, as phosphate retention drives sustained FGF23 secretion that becomes maladaptive, contributing to cardiovascular mortality (34,36).

Diabetes and Skeletal Fragility: In diabetes, hyperglycemia and advanced glycation end-products impair osteocyte function and increase sclerostin and Dickkopf-related protein 1 expression, contributing to skeletal fragility (35). Osteocytic PPAR γ signaling mediates some of these effects (32).

Local Inflammation: Periodontal Disease: Periodontal disease provides another example: bacterial infection activates the toll-like receptor/myeloid differentiation primary response 88 pathway in alveolar osteocytes, leading to RANKL upregulation and localized bone resorption (36) (Table 2).

Having established the molecular toolkit osteocytes use to sense and transmit signals (section 3) and their systemic reach (section 4), we now examine how these individual pathways are orchestrated at the tissue level to coordinate bone remodeling—the process by which the skeleton maintains its integrity and adapts to physiological demands.

Osteocyte Coordination of Bone Remodeling

The molecular mechanisms detailed in section 3 operate within individual osteocytes, but skeletal homeostasis requires the coordinated activity of thousands of these cells across the bone matrix. This section examines how osteocyte networks integrate local and systemic signals to produce coherent remodeling responses that align skeletal adaptation with physiological demands.

The Remodeling Cycle: Osteocytes as Conductors

Bone remodeling replaces old or damaged bone through tightly coupled osteoclast-mediated resorption followed by osteoblast-driven formation. Osteocytes direct this sequence with spatial and temporal precision (37). In cortical bone, remodeling proceeds within basic multicellular units (BMUs); on cancellous surfaces, it occurs in coordinated cellular packets. The LCN provides the structural framework that allows osteocytes to target remodeling to specific regions of need (38).

Spatial Organization of Targeted Remodeling

As detailed in section 3.5, osteocyte apoptosis provides a spatially precise signal for remodeling initiation. The “penumbra” model clarifies this process: apoptotic osteocytes mark the site of damage, while adjacent viable cells upregulate RANKL and chemotactic factors that recruit osteoclasts selectively to compromised matrix (5,40,44). Resorption is thus confined to damaged bone and followed by coupled formation to restore structure (46).

This spatial precision depends on the LCN architecture described in section 3.1, which enables rapid communication between apoptotic cells and their neighbors while limiting signal diffusion to healthy regions.

Mechanical Integration at the Tissue Level

Building on the mechanotransduction pathways detailed in sections 3.2–3.3, mechanical loading suppresses resorption and stimulates formation through osteocyte-dependent mechanisms at the tissue level. Osteocytes discriminate between loading and unloading, dynamic and static forces, and differences in strain magnitude (41). Brief loading episodes suppress sclerostin for hours, creating transient anabolic windows, whereas sustained unloading increases sclerostin and RANKL expression, driving disuse-associated bone loss (34).

In vivo imaging studies reveal that osteocyte calcium responses encode strain magnitude by increasing the proportion of activated cells rather than signal amplitude, supporting a binary recruitment model (59). This population-level response transforms individual cell mechanosensitivity into graded tissue-level adaptation.

The multiscale integration of osteocyte signaling—from molecular sensors to systemic effects—is illustrated in Figure 1, which serves as a roadmap for the sections that follow.

Hormonal Integration: Parathyroid Hormone, Estrogen, and Glucocorticoids

Osteocytes integrate endocrine signals with mechanical input to fine-tune remodeling. Parathyroid hormone (PTH) exerts context-dependent effects: intermittent exposure is anabolic, while sustained elevation is catabolic (42). These effects are mediated through PTH1R signaling in osteocytes, which regulates both sclerostin and RANKL expression. Intermittent PTH suppresses sclerostin and promotes formation, whereas continuous PTH increases RANKL and enhances resorption (43).

Estrogen preserves bone mass partly by maintaining osteocyte viability (section 3.5) and restraining RANKL expression (39). In contrast, glucocorticoids induce osteocyte apoptosis, elevate sclerostin and RANKL, and suppress perilacunar remodeling, contributing to glucocorticoid-induced osteoporosis (44).

Perilacunar Remodeling: A Specialized Osteocyte Function

Beyond directing surface remodeling, osteocytes remodel the matrix immediately surrounding their lacunae—a process termed perilacunar remodeling or osteocytic osteolysis (45). This involves expression of matrix-degrading enzymes such as cathepsin K, MMP13, and MMP14 and is regulated by PTH, PTHrP, and mechanical unloading (43). During lactation, osteocytic osteolysis mobilizes calcium for milk production; unloading similarly expands the lacunar–canalicular system through local resorption (45). This mechanism enables rapid mineral mobilization independent of classical BMU activity.

Coupling Formation to Resorption

The net skeletal outcome depends on coupling between resorption and formation. Osteocytes influence this balance through both matrix-derived and cell-derived signals. Growth factors released from resorbed bone matrix—including TGF-β, insulin-like growth factor-1, and bone morphogenetic proteins—promote osteoblast recruitment and differentiation (47). Osteocytes further contribute by producing canonical coupling factors such as Wnts and cardiotrophin-1, supporting osteoblast activity at remodeling sites (48).

Age-Related Remodeling Dysregulation

Aging disrupts osteocyte-mediated coordination through two distinct but related cell fates introduced in section 3.5: apoptosis and senescence. Apoptosis provides targeted signals for focal remodeling, but excessive apoptosis with age depletes the osteocyte network. Simultaneously, the accumulation of senescent osteocytes creates broader dysfunction through SASP factors that favor resorption and suppress formation (33,49). This, combined with structural deterioration of the LCN and increased empty lacunae, shifts the remodeling balance toward net bone loss with age (50).

Future Directions: Toward an Integrated Osteocyte Biology

Osteocyte research is transitioning from descriptive cell biology toward integrated systems-level investigation. Having examined

molecular mechanisms (section 3), systemic regulation (section 4), and tissue-level remodeling (section 5), this final section considers how emerging technologies and conceptual frameworks can unify these layers into a coherent model of skeletal and systemic regulation. New technologies now permit interrogation of osteocytes at molecular resolution while preserving their anatomical context. The central challenge is to connect gene programs, mechanotransduction, metabolism, and endocrine signaling into a coherent physiological framework that explains skeletal adaptation and systemic disease.

Technological Frontiers

Transcriptomic Mapping: Single-Cell and Spatial Approaches

Comprehensive transcriptomic profiling has revealed more than 1,000 genes differentially expressed in osteocytes compared with other bone cells, the majority with unknown skeletal function. Importantly, human homologs of several of these genes are linked to monogenic skeletal disorders and complex traits, highlighting the translational relevance of osteocyte-specific gene networks (54). Single-cell RNA sequencing is beginning to resolve osteocyte heterogeneity across maturation states and disease contexts (55). Early osteocytes near bone surfaces express higher levels of osteocalcin, RANKL, and PTHrP, whereas deeply embedded

Table 2. Osteocyte signaling alterations in bone diseases				
Disease state	Key osteocyte changes	Molecular mediators	Key references	Therapeutic implications
Postmenopausal osteoporosis	↑ Sclerostin, ↑ RANKL, ↑ apoptosis	Estrogen deficiency, ↑ RANKL/OPG ratio	(1,29,33)	Anti-sclerostin antibodies (romosozumab)
CKD-MBD	↑ FGF23 (maladaptive), ↓ Klotho	Phosphate retention, ↑ FGF23	(4,28,36)	FGF23 blockade (investigational)
Type 2 diabetes	↑ Sclerostin, ↑ DKK1, ↓ viability	Hyperglycemia, AGEs, PPARγ signaling	(31,32,35)	PPARγ modulation, anti-sclerostin
Glucocorticoid-induced	↑ Apoptosis, ↑ RANKL, ↓ Cx43	PYK2 activation, ↓ survival signaling	(5,44,55)	PYK2 inhibition (preclinical)
Aging	Senescence, SASP network deterioration	p16/p21, JAK-STAT, ↓ autophagy	(48,49,52)	Senolytics (dasatinib+quercetin), senomorphics
Periodontal disease	↑ RANKL, TLR/ MYD88 activation	Bacterial LPS, local inflammation	(35)	Local anti-RANKL strategies
Disuse/osteoporosis	↑ Sclerostin, ↑ RANKL, ↑ apoptosis	Mechanical unloading, ↓ NO/PGE ₂	(3,21,41)	Mechanical loading mimetics
Cancer-associated	↑ Sclerostin, ↑ RANKL/OPG ratio	Tumor-derived factors, microenvironment	(22,46)	Anti-sclerostin, bone-targeted agents
Osteogenesis imperfecta	Altered LCN, abnormal signaling	Collagen mutations, secondary effects	(7,8)	Unclear—needs investigation
Lactation	↑ Perilacunar remodeling	↑ PTHrP, ↑ calcium demand	(43,45)	Targets for calcium mobilization

CKD-MBD: Chronic kidney disease–mineral bone disorder, AGEs: Advanced glycation end-products, PPARγ: Peroxisome proliferator-activated receptor gamma, Cx43: Connexin 43, SASP: Senescence-associated secretory phenotype, TLR: Toll-like receptor, MYD88: Myeloid differentiation primary response 88, LPS: Lipopolysaccharide, NO: Nitric oxide, PGE₂: Prostaglandin E₂, LCN: Lacunar-canalicular network, PTHrP: Parathyroid hormone-related protein

cells preferentially express sclerostin (56). Serial collagenase/ethylenediaminetetraacetic acid digestion combined with fluorescence-activated cell sorting has enabled isolation of viable osteocytes suitable for transcriptomic analysis, overcoming long-

standing technical barriers imposed by the mineralized matrix (57). Integration of single-cell sequencing with spatial transcriptomics and computational modeling is further refining maps of osteocyte diversity and lacunar–canalicular organization (58).

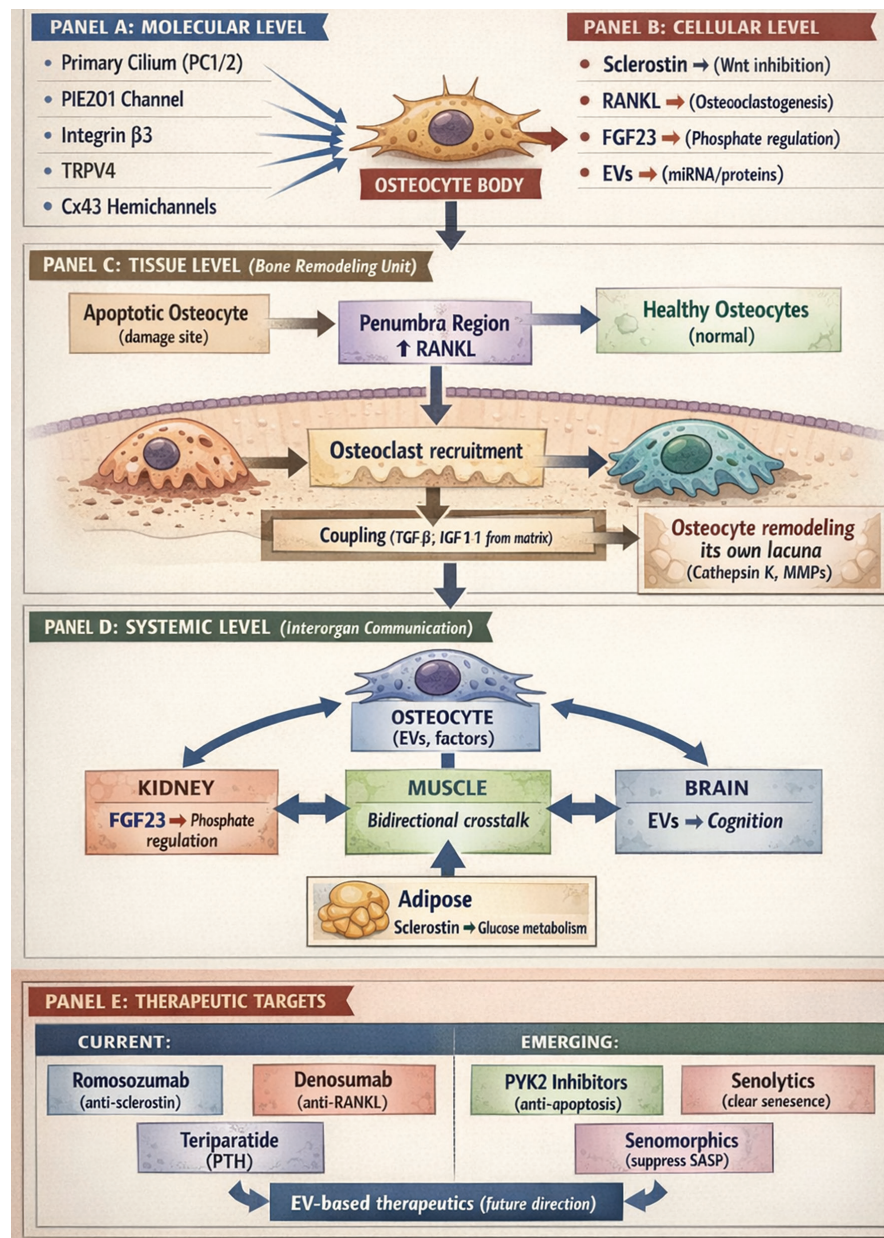


Figure 1. The osteocyte as a multiscale signaling Hub

Osteocytes integrate mechanical and biochemical signals across multiple organizational levels. Panel A depicts molecular mechanosensors including the primary cilium, PIEZO1 ion channels, integrin $\beta 3$ attachments, TRPV4 channels, and connexin 43 hemichannels. Panel B shows cellular effector outputs: sclerostin (inhibiting Wnt signaling), RANKL (promoting osteoclastogenesis), FGF23 (regulating phosphate metabolism), and extracellular vesicles (EVs) carrying bioactive cargo. Panel C illustrates tissue-level coordination of bone remodeling: apoptotic osteocytes mark damage sites, adjacent cells in the “penumbra” upregulate RANKL to recruit osteoclasts, and coupling factors from resorbed matrix recruit osteoblasts for formation. The inset shows perilacunar remodeling, where osteocytes locally degrade and replace surrounding matrix. Panel D depicts systemic interorgan communication via FGF23 (kidney), EVs (brain), and sclerostin (adipose, muscle). Panel E summarizes current and emerging therapeutic strategies targeting osteocyte pathways. Together, these scales illustrate the osteocyte’s role as the central integrator of skeletal and systemic physiology

Cx43: Connexin 43, RANKL: Receptor activator of nuclear factor- κB ligand, FGF23: Fibroblast growth factor 23, MMPs: Matrix metalloproteinases, PTH: Parathyroid hormone, SASP: Senescence-associated secretory phenotype

Epigenetic regulation remains poorly defined. Deoxyribonucleic acid methylation, histone modifications, and chromatin accessibility likely shape osteocyte differentiation and functional plasticity, yet systematic profiling is limited (55). Clarifying these mechanisms will be essential for understanding age-related transcriptional drift and disease susceptibility.

Advanced Imaging: Visualizing Osteocytes in Action

Advances in multiphoton microscopy, tissue clearing, and reporter systems now permit high-resolution imaging of osteocytes within intact bone (55). A major step forward has been the development of *in vivo* loading devices compatible with real-time imaging. Using such systems, osteocyte calcium responses were shown to encode strain magnitude by increasing the proportion of activated cells rather than signal amplitude, supporting a binary recruitment model (59). These approaches bridge *in vitro* mechanotransduction studies and whole-bone physiology, allowing direct observation of network behavior under defined strain conditions.

Technical hurdles remain. Osteocyte isolation still requires careful validation to preserve native transcriptional states (60). Imaging fragile structures such as the primary cilium within mineralized tissue remains challenging, and improved fixation and imaging protocols are needed to determine its orientation and functional relevance *in vivo* (61).

Organ-on-Chip and Ex Vivo Models

Organ-on-a-chip platforms and live imaging strategies further enable analysis of osteocyte–osteoblast–osteoclast interactions under mechanical load (47). Future refinements may clarify the temporal sequence of cellular recruitment during remodeling and how aging or pharmacologic interventions shift activation thresholds.

Fundamental Unresolved Questions

The Mechanosensation Hierarchy: Despite substantial progress, fundamental integrative questions remain. At the cellular level, whether osteocytes function as the dominant mechanosensors *in vivo* or operate in concert with other osteolineage cells remains unsettled (62). The relative contributions of fluid shear, matrix deformation, and substrate strain—and how distinct sensors integrate these cues—are incompletely understood (63). The molecular basis of primary cilium–mediated sensing, including potential activation of PC1/2 or TRPV4 channels, requires confirmation under physiological loading conditions (15). Advances in cell type–specific genetic tools should clarify these mechanisms (62).

Metabolic Regulation of Osteocyte Function: Osteocytes rely on tightly regulated glucose and amino acid metabolism to sustain survival within a hypoxic niche (55). Inhibition of glucose transporter 1 reduces RANKL and osteocalcin expression, linking cellular energetics to remodeling capacity (64). Disruption of von Hippel–Lindau protein enhances hypoxia-inducible factor-1 α signaling and increases bone mass, underscoring coupling between oxygen sensing and skeletal homeostasis (65). Taurine production has emerged as a modulator of sclerostin and Wnt

signaling (66). Age-associated energy deficits and circadian disruption further compromise osteocyte function (67). Defining how metabolic decline drives skeletal fragility remains a priority.

The Senescence-Apoptosis Continuum: The temporal relationship between osteocyte senescence and apoptosis is unclear (55,49). Transcriptomic data from aged bone reveal upregulation of innate immune and inflammatory pathways, including Janus kinase/signal transducer and activator of transcription signaling (68). Whether these changes initiate senescence or arise secondarily remains unresolved. Autocrine feedback loops may modulate osteocyte responsiveness, yet this area remains underexplored (55). Aging is associated with reduced expression of PTH1r, vitamin D receptor, and FGFRs in cortical bone, potentially blunting hormonal responsiveness (50). Mechanisms governing receptor regulation and sensitivity warrant deeper investigation.

Osteocyte Heterogeneity and Spatial Logic: The functional significance of osteocyte heterogeneity across skeletal sites (cortical vs. trabecular) and depth from bone surface remains poorly understood. How spatial position determines signaling outputs and how this organization is established and maintained are critical unanswered questions.

Translational Horizons

Targeting Osteocyte Signaling: Current and Emerging Strategies

Improved genetic tools are needed to validate osteocyte-specific targets without off-target expression (55). PYK2 inhibition shows promise in preventing glucocorticoid-induced bone loss in preclinical models (53). Bone-targeted modulation of pathways such as Notch may achieve skeletal specificity while limiting systemic toxicity (55).

The therapeutic success of agents targeting osteocyte-derived signals underscores their central role in remodeling. Romosozumab demonstrates that inhibiting an osteocyte-specific signal can simultaneously increase formation and decrease resorption (51). Denosumab, while effectively inhibiting RANKL-driven resorption, does not distinguish between RANKL's cellular sources; whether a strategy selectively targeting osteocyte-derived RANKL could offer advantages in preserving bone formation remains an open question (51). Teriparatide promotes bone formation in part by suppressing osteocyte sclerostin expression, illustrating how even established therapies work through these master regulators (52).

Senolytics and Senomorphics: Senolytic therapies, which clear senescent cells, and senomorphic agents, which suppress the SASP, have prevented age-related and radiation-induced bone loss in mice (49), though the degree to which these approaches selectively target osteocytes remains uncertain (69).

Cancer and the Osteocyte Niche: In oncology, tumor–osteocyte interactions increase sclerostin and shift the RANKL/OPG ratio toward resorption (22). Anti-sclerostin therapy may interrupt this cycle, but whether benefits arise solely from microenvironmental modulation requires clarification.

Osteocytes as Endocrine Therapeutic Targets: Defining causal links between osteocyte-derived factors such as FGF23 and sclerostin and systemic metabolic disease demands interventional human studies (55). Emerging evidence of osteocyte-derived EVs influencing distant organs underscores the need to understand bone as an endocrine regulator of whole-body homeostasis (47). Pathways governing perilacunar remodeling are being explored as targets for conditions requiring rapid calcium mobilization, and the recognition that osteocytes communicate via EVs opens speculative but exciting possibilities for delivering therapeutics directly to the osteocyte syncytium (26).

Toward a Quantitative Systems Framework

Amplified Wnt/ β -catenin signaling in osteocytes increases mineral apposition in craniofacial bone, whereas excessive activation promotes lacunar mineralization, illustrating how signaling amplitude dictates divergent outcomes (70). Future progress will require quantitative frameworks that integrate mechanotransduction, gene regulation, metabolism, and endocrine signaling across skeletal sites. The next phase of osteocyte research must combine single-cell and spatial technologies with functional validation in genetic models and human tissue. Only through this integration will osteocyte-directed therapies move from experimental promise to clinical reality.

Conclusion

Osteocytes have emerged from obscurity to take their rightful place as master regulators of the skeleton, but this review reveals that their influence extends far beyond bone remodeling. Three organizing principles emerge from the current literature: First, osteocyte signaling operates across multiple scales—from the nanoscale organization of mechanosensors along dendritic processes (section 3), through the tissue-level coordination of remodeling units (section 5), to systemic endocrine effects on mineral metabolism and distant organs (section 4). Second, osteocyte functions are context-dependent and heterogeneous. The same cell that suppresses bone formation through sclerostin under unloading conditions can promote formation when mechanically stimulated, while neighboring osteocytes may simultaneously execute apoptosis or senescence programs that shape the local remodeling environment. This heterogeneity, revealed by emerging transcriptomic technologies (section 6), challenges us to move beyond viewing osteocytes as a uniform population. Third, therapeutic targeting of osteocyte pathways has already proven transformative, but realizing the full potential of these cells requires moving beyond single-molecule approaches. Romosozumab's success demonstrates that modulating osteocyte signals can uncouple formation from resorption in ways previously thought impossible—yet this likely represents the first generation of osteocyte-directed therapies. The next decade will determine whether we can translate our growing understanding of osteocyte heterogeneity,

mechanotransduction hierarchies, and systemic communication into therapies that prevent age-related bone loss, mitigate cancer treatment-induced skeletal damage, and harness osteocyte-derived EVs for targeted drug delivery. Meeting this challenge requires the integrated, multiscale approach outlined in this review—one that respects the osteocyte not as an isolated cell, but as the central node in a dynamic network connecting the skeleton to the entire organism.

Footnotes

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