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Jerarquías de señalización de los osteocitos: integración de la mecanotransducción con la regulación sistémica

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ABSTRACT

Background and aim: osteocytes are emerging as hierarchical regulators of skeletal and systemic physiology. This review examines the integration of mechanotransduction pathways with endocrine and paracrine outputs.

Methods: a comprehensive narrative review of 2016–2024 literature was undertaken across major biomedical databases.

Results: osteocytes coordinate remodeling through sclerostin-mediated Wnt inhibition and RANKL-driven resorption, while secreting FGF23 to regulate mineral metabolism. Mechanosensation involves fluid shear stress, integrin adhesion complexes, cytoskeletal remodeling, and *PIEZO1* channel activation. Increasing recognition of osteocyte heterogeneity challenges simplified models of signaling dominance. Fundamental questions persist regarding signal prioritization and spatial coordination.

Conclusion: osteocytes represent central signaling hierarchies linking mechanical input to skeletal and systemic output. Emerging spatial and functional technologies will refine mechanistic understanding and inform therapeutic innovation.

Keywords: Osteocyte. Mechanotransduction. Endocrine signaling. Bone remodeling. FGF23.

RESUMEN

Antecedentes y objetivo: los osteocitos están emergiendo como reguladores jerárquicos de la fisiología esquelética y sistémica. Esta revisión examina la integración de las vías de mecanotransducción con las salidas endocrinas y paracrinas.

Métodos: se llevó a cabo una revisión narrativa exhaustiva de la literatura publicada entre 2016 y 2024 en las principales bases de datos biomédicas.

Resultados: los osteocitos coordinan el remodelado óseo mediante la inhibición de la vía Wnt mediada por esclerostina y la resorción impulsada por RANKL, al tiempo que secretan FGF23 para regular el metabolismo mineral. La mecanosensación implica el estrés por cizallamiento del fluido, complejos de adhesión por integrinas, remodelación del citoesqueleto y activación del canal *PIEZO1.* El reconocimiento creciente de la heterogeneidad de los osteocitos cuestiona los modelos simplificados de dominancia en la señalización. Persisten interrogantes fundamentales sobre la priorización de señales y la coordinación espacial.

Conclusión: los osteocitos representan jerarquías centrales de señalización que conectan los estímulos mecánicos con las respuestas esqueléticas y sistémicas. Las tecnologías espaciales y funcionales emergentes permitirán afinar la comprensión de los mecanismos e impulsarán la innovación terapéutica.

Palabras clave: Osteocito. Mecanotransducción. Señalización endocrina. Remodelado óseo. FGF23.

INTRODUCTION

The dominance of osteoblast and osteoclast biology historically overshadowed osteocytes, which were viewed as terminally embedded and largely inactive cells (1). This perception has been decisively

overturned. Contemporary studies establish osteocytes as master regulators orchestrating bone remodeling and systemic mineral homeostasis (2).

Through secretion of sclerostin and receptor activator of nuclear factor-κB ligand (RANKL), osteocytes modulate both bone formation and resorption (3). Their endocrine output, particularly fibroblast growth factor 23 (FGF23), underscores their systemic influence (4). Apoptotic signaling further positions osteocytes as initiators of targeted remodeling responses (5).

Yet the precise mechanosensory architecture and spatial logic of osteocyte signaling remain debated (6). Addressing these uncertainties is essential for translating osteocyte biology into clinical intervention.

This review analyzes current evidence surrounding osteocyte signaling hierarchies and outlines future investigative priorities.

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 uncertainty and emerging consensus. The review does not aim to perform a quantitative meta-analysis but rather to generate an integrated conceptual framework informed by the breadth of available evidence.

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 I).

Cx43 interacts with integrins at dendritic attachment sites, suggesting an integrated mechanotransduction complex (13). Super-resolution imaging demonstrates colocalization of β3 integrin with pannexin 1, Purinergic Receptor P2X7 **(**P2X7R), and calcium voltage-gated channel subunit alpha1 H (CaV3.2) along dendritic processes—structures absent from the cell body (14). Mechanical stimulation of dendrites triggers directional calcium influx through integrin alpha-V beta-3 (αVβ3) 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 β1 is enriched at the cell body, whereas integrin β3 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 αVβ3 integrin attachments (14). The balance between depolarizing cation influx and hyperpolarizing potassium efflux likely determines activation thresholds (19). Certain G protein-coupled receptors (GPCRs) 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 I).

In addition to these established mechanosensors, caveolae—flask-shaped invaginations of the plasma membrane enriched in caveolin proteins—have been implicated in mechanoprotection and signaling in various cell types. In osteocytes, caveolin-1 localizes to the plasma membrane and may participate in integrin signaling and membrane trafficking, although direct evidence for caveolae as primary mechanosensors in osteocytes remains limited compared with

PIEZO1 or primary cilia (5). Further investigation is needed to determine whether caveolae contribute to the hierarchical mechanosensory apparatus of osteocytes.

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 nitric oxide synthase activation and is required for subsequent prostaglandin E_2 (PGE_2) synthesis and sclerostin downregulation (21,22).

Mechanical cues further regulate nuclear responses through Yes-associated protein (YAP)/Transcriptional coactivator with PDZ-binding motif (TAZ), which shuttle between cytoplasm and nucleus. Osteocyte-specific deletion of both Yap and Taz 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).

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 (25). Following fatigue-induced microdamage, surviving osteocytes surrounding apoptotic cells upregulate RANKL and related mediators to recruit osteoclasts precisely to damaged sites (26). Mechanotransduction is closely linked to metabolic state. Osteocytes reside in a relatively hypoxic microenvironment and rely largely on glycolytic metabolism (27). 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 (28). In addition, osteolineage cells can transfer functional mitochondria to myeloid cells through tunneling nanotubes and EVs, revealing an additional mechanism of intercellular coordination (29) (Table I).

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 I).

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 (PI3K) 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 focal adhesion kinase-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). 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). 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). 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). Notably, emerging evidence suggests that FGF23 expression is also responsive to mechanical cues. Fluid shear stress suppresses FGF23 transcription in osteocyte-like cells, while mechanical unloading increases FGF23 levels, indicating that the mechanosensitive apparatus—including primary cilia and *PIEZO1* channels—may directly regulate endocrine output. However, the precise molecular links between individual mechanosensors and FGF23 transcription remain incompletely defined and represent an important area for future investigation. Excess FGF23 causes hereditary hypophosphatemic rickets and tumor-induced osteomalacia, whereas deficiency results in hyperphosphatemia and ectopic calcifications (34). In chronic kidney disease, sustained FGF23 elevation contributes to mineral bone disorder and increased cardiovascular mortality (35,36) (Table I).

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

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 (DKK1) expression, contributing to skeletal fragility (35). Osteocytic PPARγ signaling mediates some of these effects (32).

Local inflammation

Periodontal Disease: Periodontal disease provides another example: bacterial infection activates the toll-like receptor (TLR)/myeloid differentiation primary response 88 (MYD88) pathway in alveolar osteocytes, leading to RANKL upregulation and localized bone resorption (36) (Table II).

Having established the molecular toolkit osteocytes use to sense and transmit signals (section “Molecular and cellular mechanisms of osteocyte signaling”) and their systemic reach (section “Osteocytes as systemic regulators”), 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 “Molecular and cellular mechanisms of osteocyte signaling” 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 “Cell fate decisions: apoptosis and senescence as signaling events”, 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 (39,40). Resorption is thus confined to damaged bone and followed by coupled formation to restore structure (41).

This spatial precision depends on the LCN architecture described in section “The lacunar-canalicular network: structural basis for communication”, 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 “Molecular mechanosensors: primary cilia, integrins, and ion channels” and “Intracellular signal transduction: from membrane to nucleus”, 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 (42). 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: PTH, 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 “Cell fate decisions: apoptosis and senescence as signaling events”) 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 (46). 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, IGF-1, and bone morphogenetic proteins (BMPs)— 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 “Cell fate decisions: apoptosis and senescence as signaling events”: 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 “Molecular and cellular mechanisms of osteocyte signaling”), systemic regulation (section “Osteocytes as systemic regulators”), and tissue-level remodeling (section “Osteocyte coordination of bone remodeling”), this final section considers how emerging technologies and conceptual frameworks can unify these layers into a coherent model of skeletal and systemic regulation (51,52).

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 (53).

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. While the majority of these genes have no previously characterized skeletal function, it is precisely this pool of 'unknown function' genes that may hold key insights into osteocyte-specific biology. Importantly, human homologs of several of these genes are linked to monogenic skeletal disorders and complex traits, highlighting the translational relevance of investigating osteocyte-specific gene networks —even when their molecular functions remain to be elucidated (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 cells preferentially express sclerostin (56). Serial collagenase/Ethylenediaminetetraacetic acid (EDTA) digestion combined with fluorescence-activated cell sorting (FACS) 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).

Epigenetic regulation remains poorly defined. Deoxyribonucleic acid (DNA) 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-1α (HIF-1α) 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 (JAK)/signal transducer and activator of transcription (STAT) 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 (Vdr), and fibroblast growth factor receptors (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/Osteoprotegerin (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 extracellular vesicles 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 “Molecular and cellular mechanisms of osteocyte signaling”), through the tissue-level coordination of remodeling units (section ”Osteocyte coordination of bone remodeling”), to systemic endocrine effects on mineral metabolism and distant organs (section ”Osteocytes as systemic regulators”).
- 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 “Future directions: toward an integrated osteocyte

biology”), 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 extracellular vesicles 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.

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Table I. 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)	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	Remodeling balance

Molecule	Primary action	Target cells	Key references	Physiological context	Disease relevance
				signals	
PTHrP	Local calcium regulation	Osteocytes, osteoblasts	(20,43)	Perilacunar remodeling	Lactation, calcium demand

RANKL: receptor activator of nuclear factor-κB ligand; FGF23: fibroblast growth factor 23; PGE_2: prostaglandin E_2; 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.

Table II. 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), senomorphi

Disease state	Key osteocyte changes	Molecular mediators	Key references	Therapeutic implications
				cs
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; PGE_2: prostaglandin E_2; LCN: lacunar-canalicular network; PTHrP: parathyroid hormone-related protein.

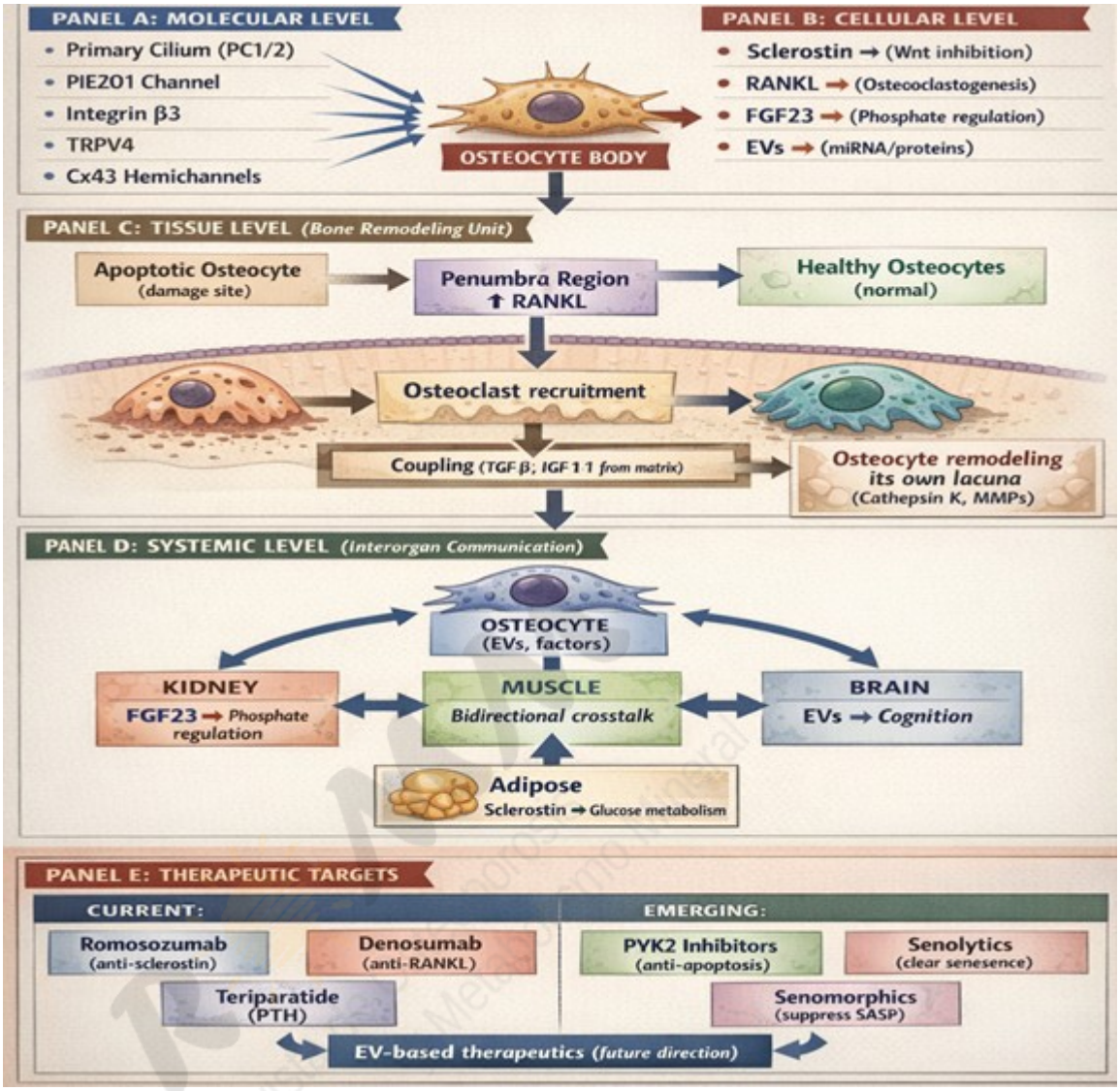

Figure 1. The osteocyte as a multiscale signaling hub. Osteocytes integrate mechanical and biochemical signals across multiple organizational levels. Panel A depicts molecular mechanosensors including the primary cilium, *PIEZO1* ion channels, integrin β3 attachments, TRPV4 channels, and connexin 43 (Cx43) 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.