



Original Article

The Osteoimmune Axis in Aging: Role of Immunosenescence, Inflammaging and Senescent Cells in the Pathogenesis of Osteoporosis

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ABSTRACT

Background: Age-related osteoporosis is increasingly recognized as a disorder of disrupted immune-skeletal communication rather than solely impaired bone turnover. Immunosenescence, cellular senescence, and inflammaging interact within the bone microenvironment and may contribute to progressive bone loss and remodeling imbalance.

Methods: This narrative review integrates current evidence on the interplay among immunosenescence, cellular senescence, inflammaging, and age-related osteoporosis. Emphasis is placed on inflammatory cytokines, the RANKL/RANK/OPG axis, senescence-associated secretory phenotype (SASP), immune-skeletal interactions, and key signaling pathways, including NF- κ B, JAK/STAT, MAPK, NLRP3 inflammasome, oxidative stress, TGF- β , and Wnt/ β -catenin. Emerging therapeutic strategies targeting these mechanisms are also discussed.

Results: Evidence indicates that age-associated alterations in immune-cell function can reshape the bone marrow microenvironment and enhance osteoclastogenesis through inflammatory cytokines and dysregulation of the RANKL/RANK/OPG axis. TNF- α , IL-1 β , IL-6, and IL-17 may further promote osteoclast activity while impairing osteoblast and mesenchymal stromal-cell function. Accumulation of senescent skeletal, stromal, and immune cells may amplify inflammation through SASP-mediated signaling. These processes converge on interconnected molecular pathways, while epigenetic and miRNA-mediated mechanisms provide additional regulation. Potential interventions include RANKL/OPG modulation, anti-inflammatory therapies, senolytics, senomorphics, immunosenescence-targeted approaches, and nutritional or natural compounds.

Conclusion: Age-related osteoporosis may represent a complex osteoimmune disorder driven by progressive disruption of immune-skeletal communication. Integrating immune, inflammatory, senescence, and skeletal biomarkers may facilitate osteoimmune phenotyping and support personalized therapeutic strategies.

Introduction

Aging is accompanied by progressive deterioration of skeletal homeostasis, in which the balance between osteoclast-mediated resorption and osteoblast-dependent formation becomes increasingly susceptible to inflammatory and immune regulation (1, 2). Various therapeutic strategies, including pharmacotherapy and tissue engineering, are

therapeutic complexity (3-5). Osteoporosis therefore may be viewed not only as a disorder of bone mass and microarchitecture, but also as a consequence of disturbed communication between skeletal and immune compartments within the bone marrow microenvironment (6, 7). Recent osteoimmunological evidence indicates that macrophage activation, T-cell subset imbalance, inflammatory cytokines,



and the RANKL/RANK/OPG system can converge on osteoclastogenesis, with TNF- α , IL-1 β , IL-6, and IL-17 potentially increasing RANKL expression and the RANKL/OPG ratio, thereby establishing a pro-inflammatory, pro-resorptive feedback network (8). This immune-skeletal interaction becomes particularly relevant during aging, when chronic inflammation and immune remodeling may alter the functional state of bone-resident and circulating immune cells. Of particular interest, accumulation of senescent CD28⁻CD8⁺ T cells has been associated with reduced protective IFN- γ production and acquisition of a senescence-associated secretory phenotype, with reported effects on osteoblast differentiation and mesenchymal stromal-cell viability (9). Thus, senescence may not simply represent a consequence of skeletal aging, but could participate in reshaping the inflammatory environment in which bone remodeling occurs.

Accordingly, the osteoimmune axis may provide a useful framework for connecting immunosenescence, cellular senescence, inflammaging, and osteoporosis. Rather than considering these processes as independent contributors, we propose that their interaction may progressively shift the bone microenvironment toward an osteoclastogenic state, in which inflammatory signaling, altered immune-cell function, oxidative stress, and RANKL-dependent pathways reinforce one another. This review therefore examines how aging-associated immune and cellular changes may converge on osteoimmune dysregulation and considers whether interrupting these interconnected pathways could provide more precise strategies for preventing or treating age-related bone loss.

Methods

Literature Search Strategy

A systematic literature search was conducted using PubMed, Scopus, and Web of Science databases. The search covered publications from January 2010 to July 2026, using the following key terms and their combinations: “osteoporosis,” “immunosenescence,” “inflammaging,” “cellular senescence,” “SASP,” “RANKL/OPG,” “osteoclastogenesis,” “bone remodeling,” and “osteoimmunology.” Articles were included if they addressed immunological or senescence-related mechanisms of bone loss in aging populations. Reviews, original research articles, and meta-analyses published in English were considered. Studies focusing exclusively on non-aging-related secondary osteoporosis were excluded.

The Osteoimmune Axis in Bone Remodeling

Bone remodeling is maintained through a tightly regulated interaction among osteoblasts, osteoclasts, osteocytes, mesenchymal stromal cells, and immune populations residing within or recruited to the bone marrow microenvironment. Rather than functioning as anatomically and functionally independent systems, skeletal and immune cells continuously exchange molecular signals that determine whether bone tissue undergoes formation, resorption, or repair (10). Macrophages, T cells, B cells, and other immune populations can therefore influence osteoclast differentiation and osteoblast activity through cytokines, cell-cell

interactions, and modulation of intracellular signaling pathways. Recent osteoimmunological studies further support the view that the net skeletal outcome is determined by the balance among interacting immune-cell populations rather than by the activity of a single immune-cell type (11).

At the center of this communication is the RANK/RANKL/OPG axis, which provides a major molecular interface between immune signaling and osteoclastogenesis. RANKL, expressed by osteoblast-lineage cells and several immune-cell populations, binds receptor activator of NF- κ B (RANK) on osteoclast precursors and initiates signaling required for their differentiation and activation. Osteoprotegerin (OPG), functioning as a soluble decoy receptor, limits RANKL availability and thereby constrains excessive osteoclast formation (12). Importantly, the activity of this pathway is not regulated in isolation. Pro-inflammatory M1-like macrophages and Th1/Th17 responses can increase RANKL expression and the RANKL/OPG ratio, while M2-like macrophages, Treg/Th2 responses, IL-10, TGF- β , IL-4, IL-13, and OPG may contribute to suppression of excessive osteoclastogenesis (13).

Cytokine signaling consequently provides another critical layer of osteoimmune regulation. TNF- α , IL-1 β , IL-6, and IL-17 have been associated with enhanced osteoclastogenic activity, partly through increased RANKL expression and greater responsiveness of osteoclast precursors to RANKL. Conversely, anti-inflammatory mediators may favor resolution of inflammation and preservation of skeletal homeostasis. Importantly, these effects appear to be context-dependent rather than uniformly destructive or protective. For example, CD8⁺ T-cell-derived IFN- γ has been reported to inhibit osteoclast formation through interference with NF- κ B and MAPK signaling under particular physiological conditions, whereas estrogen deficiency can alter this phenotype through an IL-33/CCL5/CCR3/ERK pathway that promotes bone resorption (14). During aging, this communication network may progressively become biased toward a pro-inflammatory and pro-resorptive state. Immune dysfunction, chronic inflammatory signaling, altered macrophage and T-cell phenotypes, and accumulation of senescent immune cells can collectively disturb the regulatory balance controlling RANKL-dependent osteoclastogenesis (15). Thus, the osteoimmune axis may be conceptualized not simply as communication between two tissues, but as a dynamic regulatory circuit in which aging-associated immune alterations can modify the threshold at which normal remodeling becomes pathological bone loss. This perspective provides a mechanistic bridge to the subsequent discussion of immunosenescence, inflammaging, and cellular senescence as interconnected determinants of age-related osteoporosis.

Aging, Immunosenescence and Inflammaging

Aging is accompanied by a progressive remodeling of the immune system rather than a uniform loss of immune activity. This process, generally described as immunosenescence, involves alterations in both innate and adaptive immunity, including reduced proliferative capacity, differentiation bias, altered migration and homing, impaired phagocytic and clearance functions, and changes in cellular secretory profiles (16). In the skeletal system, these changes



are increasingly considered relevant because immune-cell dysfunction can reshape the bone marrow microenvironment and disturb the coupling between osteoclastogenesis and osteogenesis. In particular, age-associated changes in T cells and myeloid populations may increase osteoclastogenic signaling while weakening immune mechanisms that normally constrain excessive bone resorption (1).

A closely related phenomenon is inflammaging, referring to a persistent, low-grade inflammatory state that develops with advancing age and is characterized by sustained elevation of inflammatory signaling rather than the intense response associated with acute inflammation. In the context of osteoporosis, this inflammatory background has been associated with increased TNF- α and IL-6 and with alterations in bone-regulatory mediators, including RANKL, DKK1, and sclerostin (17). Importantly, the available evidence does not support inflammation as an isolated determinant of skeletal deterioration; rather, inflammatory signaling appears to interact with endocrine, metabolic, cellular, and immune alterations that collectively modify the bone microenvironment. This interpretation is consistent with emerging models in which osteoporosis is regarded as an aging-associated disorder of osteoimmune homeostasis rather than solely a consequence of defective bone turnover (18). Among the inflammatory mediators implicated in this process, TNF- α , IL-1 β , IL-6, and IL-17 are particularly relevant because they can converge on pathways regulating osteoclast differentiation and activity. Within the RANKL-dependent network, these cytokines may increase RANKL expression, alter the RANKL/OPG ratio, and enhance the responsiveness of osteoclast precursors, thereby establishing a pro-osteoclastogenic inflammatory environment. The contribution of individual mediators, however, appears to be highly context-dependent (19). CD8⁺ T cells illustrate this context-dependency: IFN- γ inhibits osteoclastogenesis via NF- κ B/MAPK interference under physiological conditions, while estrogen deficiency redirects this population toward a resorptive phenotype via the IL-33/CCL5/CCR3/ERK pathway (20).

The relationship between immunosenescence and inflammaging may therefore be bidirectional. Aging-associated immune dysfunction can impair inflammatory resolution and clearance of damaged or senescent cells, while persistent inflammatory signaling can further modify immune-cell phenotype and function. As discussed in Section 4, senescent immune cells amplify these effects through SASP-mediated suppression of osteoblast function, providing a mechanistic link between immune dysfunction and impaired bone formation (21).

Cellular Senescence and the Aging Bone Microenvironment

Cellular senescence is increasingly regarded as a biologically heterogeneous state in which proliferative capacity is durably restricted while metabolic activity and intercellular signaling are retained. In bone, senescence may be induced by several age-associated stressors, including telomere dysfunction, DNA damage, oxidative stress, mitochondrial abnormalities, and other forms of cellular injury, with the canonical p16INK4a/pRB and p53/p21CIP1 pathways contributing to the establishment of cell-cycle

arrest. At the same time, DNA-damage responses and signaling through pathways involving NF- κ B, mTOR, JAK/STAT, and GATA4 have been implicated in the development of the secretory phenotype characteristic of senescent cells (22).

The accumulation of senescent cells within the aging bone microenvironment appears to involve several skeletal and stromal populations rather than a single cellular lineage (Figure 1). Increased senescence-associated markers have been detected in osteoblasts, osteoblast progenitors, osteocytes, myeloid cells, B cells, and T cells in aged bone, while osteocytes and myeloid populations appear particularly relevant to the development of a senescence-associated secretory phenotype (SASP). In aged mice, senescent osteocytes have been detected at substantially greater frequency than in young animals, and their accumulation has been associated with increased expression of multiple SASP-related factors (23). Bone marrow mesenchymal stromal cells are also susceptible to senescence, with senescent cells exhibiting impaired osteogenic capacity and, in some experimental settings, a shift toward adipogenic differentiation, potentially contributing to deterioration of the osteogenic potential of the aging marrow niche (24).

The biological significance of senescence, however, extends beyond the arrested cell itself. The SASP comprises a heterogeneous collection of cytokines, chemokines, growth factors, proteases, and other signaling molecules that can act locally or systemically through autocrine and paracrine mechanisms (25). Within bone, this secretory activity provides a plausible mechanism through which a relatively limited population of senescent cells could exert effects disproportionate to their abundance. Experimental evidence indicates that SASP-associated signaling can favor osteoclast-mediated resorption while impairing osteoblast-dependent formation, thereby contributing to the uncoupling of bone remodeling observed during skeletal aging (26). Importantly, this interpretation should not be reduced to a simple equation in which all senescent cells are intrinsically pathological, because cellular senescence can also participate in physiological tissue remodeling and its consequences appear to depend on cellular identity, stimulus, duration, and tissue context (27).

The interaction between senescent cells and immune cells may therefore represent a critical amplification mechanism within the aging bone microenvironment. Senescent immune cells can themselves acquire inflammatory secretory characteristics, while cytokines released by senescent skeletal or stromal cells may alter immune-cell recruitment, activation, and functional polarization. This reciprocal relationship—in which senescent skeletal cells drive immune dysfunction while immune-cell senescence further reinforces the inflammatory and senescent microenvironment—may establish a self-sustaining feedback loop. Consequently, cellular senescence may function as more than a marker of biological aging; it may constitute a self-reinforcing interface between damaged bone cells and the immune system, through which local cellular dysfunction is converted into persistent inflammatory signaling and progressively altered bone remodeling. This possibility provides a mechanistic basis for considering senescent-cell burden, rather than inflammation alone, as a potential determinant of osteoimmune imbalance in age-related osteoporosis (28).



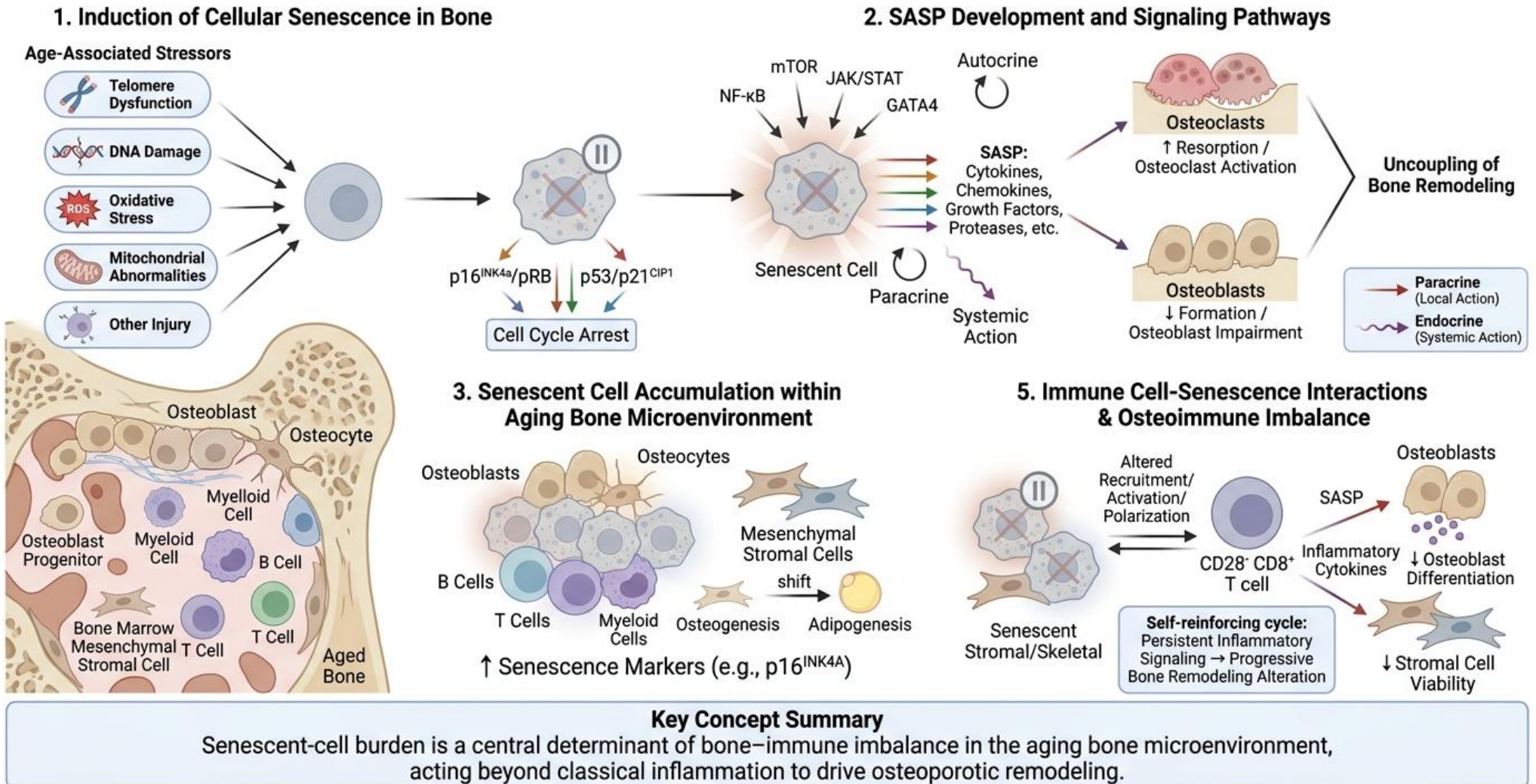


Figure 1. Cellular Senescence and the Aging Bone Microenvironment.

Inflammaging and Immunosenescence in inflammatory bone loss

Inflammatory bone loss may be understood as a progressive disturbance of the cellular and molecular coupling that normally coordinates bone resorption with bone formation. Within this process, immunosenescence and inflammaging appear to modify the behavior of immune cells and their communication with skeletal cells, potentially shifting the bone marrow microenvironment toward persistent osteoclastogenic activity. Rather than representing independent phenomena, altered immune-cell function, inflammatory cytokine production, and senescent-cell accumulation may form interconnected regulatory circuits through which age-associated immune remodeling is translated into skeletal deterioration.

Immune cells exert substantial control over osteoclastogenesis through both direct and indirect mechanisms. Pro-inflammatory macrophage and T-cell responses can increase RANKL expression and enhance the responsiveness of osteoclast precursors to RANKL, with TNF- α , IL-1 β , IL-6, and IL-17 contributing to this pro-osteoclastogenic environment. In contrast, M2-like macrophages, Treg/Th2 responses, and mediators including IL-10, TGF- β , IL-4, IL-13, and OPG may restrain excessive osteoclast formation and favor inflammatory resolution and tissue repair. This balance may become increasingly unstable with aging, when immune-cell composition and functional states are altered (8). The available evidence further suggests that individual immune populations cannot simply be classified as uniformly protective or destructive, because their effects depend on hormonal, metabolic, mechanical, and inflammatory context. The reported dual functionality of CD8⁺ T cells illustrates this principle: IFN- γ can suppress osteoclast formation through interference with NF- κ B and MAPK signaling, whereas estrogen deficiency can promote an IL-33/CCL5/CCR3/ERK pathway associated with bone resorption (29).

Inflammaging and senescence-associated signals may also influence osteoblasts, osteocytes, and mesenchymal stromal cells, thereby affecting the formation side of bone remodeling. Particularly relevant is the accumulation of senescent CD28⁻ CD8⁺ T cells during aging and chronic inflammation. Their reduced IFN- γ production, together with acquisition of a SASP, has been associated with suppression of osteoblast differentiation and reduced mesenchymal stromal-cell viability. Such changes suggest that age-associated immune dysfunction may affect bone mass through two interconnected routes: enhancement of osteoclastogenic signaling and impairment of cellular mechanisms required for bone formation (29). The bone marrow niche consequently represents an important point of convergence. Alterations in immune-cell composition, inflammatory mediators, and stromal-cell function can modify the local signals controlling osteoclast and osteoblast activity. At the molecular level, convergence on the RANKL/RANK/OPG system provides a plausible final common pathway through which diverse inflammatory and immune disturbances can be translated into excessive bone resorption. Recent synthesis of the osteoimmune literature similarly proposes that different forms of osteoporosis may share RANKL-dependent resorption as a common downstream effector while differing considerably in their

upstream immune drivers (30).

Taken together, these observations support a model in which chronic inflammation is not merely an accompanying feature of inflammatory bone loss but may participate in establishing a self-reinforcing osteoimmune state. Immunosenescence can alter the identity and function of immune populations, senescent cells can modify the inflammatory milieu through SASP-associated signaling, and inflammatory pathways can increase osteoclastogenic pressure while compromising osteogenic competence. The resulting imbalance may progressively move bone remodeling away from physiological coupling toward net bone loss. Importantly, this model remains mechanistically heterogeneous, and the available evidence does not establish that inflammaging alone is sufficient to cause osteoporosis; rather, it may act as an important integrative modifier through which aging-associated immune, cellular, and skeletal abnormalities converge (21).

Molecular Mechanisms of Osteoimmune Dysregulation

The osteoimmune imbalance associated with aging is unlikely to arise from a single signaling pathway; rather, several interconnected molecular networks appear to converge on osteoclast differentiation, inflammatory amplification, and impaired osteogenic activity. Among these crosstalk, NF- κ B–RANKL signaling represents a central point of integration. Pro-inflammatory cytokines, including TNF- α , IL-1 β , IL-6, and IL-17, can increase RANKL expression and enhance the responsiveness of osteoclast precursors to RANKL, thereby reinforcing osteoclastogenesis. Experimental evidence further indicates that inflammatory mechanical conditions can increase RANKL expression and osteoclast differentiation through NF- κ B and JNK signaling, illustrating how extracellular inflammatory or stress signals can be translated into a pro-resorptive cellular phenotype (31).

The JAK/STAT and MAPK pathways provide additional interfaces between cytokine signaling and osteoimmune regulation. STAT3, a cytokine-responsive transcription factor, has been shown to become hyperactivated in macrophages during inflammatory osteolysis, where its inhibition reduced NLRP3 inflammasome activation and macrophage-amplified osteoclast formation. Mechanistically, STAT3 inhibition promoted PINK1-dependent mitophagy, reduced dysfunctional mitochondria and mitochondrial ROS, and consequently suppressed inflammasome activity (32). MAPK signaling also appears to be context-dependent: inhibition of p38 MAPK by isoeugenol reduced macrophage M1 polarization, suppressed cPLA₂ phosphorylation, altered arachidonic-acid metabolism, and was associated with attenuation of ovariectomy-induced bone loss. Similarly, CD8⁺ T-cell-derived IFN- γ has been reported to interfere with NF- κ B and MAPK signaling and thereby inhibit osteoclast formation under particular conditions (29).

The NLRP3 inflammasome provides a mechanistic connection between cellular stress, innate immune activation, and inflammatory bone loss. In macrophages, dysfunctional mitochondria and increased mitochondrial ROS can support NLRP3 activation and IL-1 β processing, whereas enhancement of PINK1-dependent mitophagy has been



associated with suppression of this inflammatory pathway and reduction of osteoclast-mediated bone erosion. This places mitochondrial quality control upstream of an inflammatory circuit capable of influencing the osteoclastogenic microenvironment. Consistently, dysbiosis has been associated with amplification of NF- κ B and NLRP3 signaling together with RANKL/OPG dysregulation and increased oxidative stress (33).

ROS and oxidative stress may therefore function as amplifiers connecting inflammatory signaling, mitochondrial dysfunction, and immune-cell polarization. In the osteoimmune model provided in the literature, hypoxia and oxidative stress favor M1/Th17-associated inflammatory responses, which can intensify RANKL signaling and osteoclastogenesis. At the same time, impaired redox control may interact with other pathways rather than acting independently, suggesting that oxidative stress could represent a reinforcing component of the inflammatory network rather than a single upstream cause (34).

The balance between inflammatory signaling and osteogenic pathways is further influenced by TGF- β and Wnt/ β -catenin signaling. TGF- β is associated with anti-

inflammatory and reparative immune responses, whereas Wnt/ β -catenin activity supports osteoblast differentiation; conversely, chronic inflammation and oxidative stress have been associated with suppression of Wnt/ β -catenin-dependent osteogenic activity (35). In parallel, epigenetic and post-transcriptional mechanisms, including miRNA-mediated regulation and exosomal transfer of miRNAs, provide additional means through which immune and skeletal cells may alter each other's phenotype. For example, miR-1a-3p has been investigated as a regulator of Fcgr4-dependent osteoclast activation, while exosomes can deliver miRNAs, proteins, and lipids that modify inflammatory responses and immune-cell polarization. Collectively, these observations support an axis rather than pathway-centric model, in which inflammatory, metabolic, redox, transcriptional, and post-transcriptional signals converge to determine whether the aging bone microenvironment remains remodeling-competent or progressively shifts toward pathological bone resorption (Table 1).

Table 1. The proposed osteoimmune framework linking aging to osteoporosis. Integrated molecular framework linking immunosenescence, inflammaging, cellular senescence, and osteoimmune dysregulation to age-related osteoporosis.

Aging-associated alteration	Major cellular/molecular event	Key signaling pathways	Effect on bone remodeling	Potential therapeutic implication
Immunosenescence	Altered T-cell and macrophage phenotype; accumulation of senescent immune populations	NF- κ B, MAPK, cytokine signaling	Increased osteoclastogenic pressure and impaired osteoimmune regulation	Immune-cell-specific modulation
Inflammaging	Persistent low-grade production of TNF- α , IL-1 β , IL-6 and IL-17	NF- κ B, JAK/STAT, MAPK	Enhanced RANKL signaling and osteoclastogenesis	Selective anti-inflammatory strategies
Cellular senescence	Accumulation of senescent osteoblast-lineage, stromal, osteocytic and immune cells	p16/pRB, p53/p21, NF- κ B, mTOR	Reduced osteogenic competence and altered bone microenvironment	Senolytics / senomorphics
SASP activation	Release of cytokines, chemokines and other inflammatory mediators	NF- κ B, JAK/STAT and related inflammatory networks	Persistent inflammatory signaling and remodeling uncoupling	SASP suppression
RANKL/OPG imbalance	Increased RANKL availability relative to OPG	RANK-NF- κ B signaling	Increased osteoclast differentiation and bone resorption	RANKL/OPG targeting
Oxidative stress	Mitochondrial dysfunction and increased ROS	ROS-NLRP3, NF- κ B, MAPK	Inflammatory amplification and impaired bone homeostasis	Redox/mitochondrial interventions
NLRP3 activation	Inflammasome activation and IL-1 β maturation	NLRP3-IL-1 β axis	Macrophage-mediated inflammatory osteoclastogenesis	Inflammasome inhibition
Impaired osteogenic signaling	Reduced osteoblast differentiation and function	Wnt/ β -catenin, TGF- β	Reduced bone formation	Restoration of osteogenic pathways
Epigenetic dysregulation	Altered miRNA and other regulatory mechanisms	miRNA-dependent post-transcriptional regulation	Changes in immune-cell and osteoclast phenotype	Epigenetic/miRNA targeting
Integrated osteoimmune dysregulation	Convergence of immune, inflammatory, senescent and skeletal abnormalities	Multiple interconnected pathways	Persistent shift toward net bone loss	Combination and phenotype-guided therapy

Therapeutic Targeting of the Aging Osteoimmune Axis

Current osteoporosis therapies primarily target either excessive bone resorption or inadequate bone formation, yet the evidence reviewed in the preceding sections suggests that skeletal deterioration during aging may also reflect persistent dysregulation of immune-bone communication. Antiresorptive approaches can therefore be interpreted within

the broader context of the RANKL-dependent osteoimmune crosstalk, whereas anabolic strategies may partially counteract the downstream consequences of inflammatory and osteogenic imbalance. The RANKL/RANK/OPG system represents a particularly important therapeutic node because diverse upstream immune abnormalities, including macrophage activation, Th1/Th17 responses, and inflammatory cytokine signaling, may converge on increased



RANKL activity and osteoclastogenesis (19).

From this perspective, anti-inflammatory intervention represents a potentially complementary strategy rather than a replacement for established osteoporosis treatment. Suppression of excessive TNF- α , IL-1 β , IL-6, or IL-17 signaling could theoretically reduce the inflammatory amplification of osteoclastogenesis, although the context-dependent functions of individual cytokines should be considered before broad immune suppression is pursued (36). The dual behavior of CD8⁺ T cells provides an important example: IFN- γ can inhibit osteoclast formation through NF- κ B and MAPK interference under certain conditions, whereas estrogen deficiency can redirect these cells toward a CCL5/CCR3/ERK-associated bone-resorptive phenotype. Thus, therapeutic precision may be more informative than indiscriminate suppression of immune activity. Targeting the RANKL/OPG axis remains particularly attractive because it represents a convergent downstream effector of several osteoimmune abnormalities (31). The available literature proposes that different forms of osteoporosis may have distinct upstream immune drivers while sharing RANKL-dependent osteoclastogenesis as a final common process. This framework suggests that future interventions could combine direct inhibition of osteoclastogenic signaling with approaches designed to modify the immune state that sustains RANKL elevation, potentially reducing the likelihood that the inflammatory axis simply re-establishes the same pathological phenotype. Senolytic and senomorphic strategies provide a conceptually different therapeutic direction by targeting the cellular source or consequences of age-associated inflammatory signaling. If senescent osteoblast-lineage, stromal, osteocytic, or immune cells contribute to SASP-mediated disruption of the bone microenvironment, selective elimination of senescent cells or suppression of their detrimental secretory activity could theoretically restore aspects of osteoimmune homeostasis. However, the heterogeneity of cellular senescence and the physiological functions that senescence can perform indicate that indiscriminate elimination of senescent cells should not yet be considered equivalent to therapeutic correction of aging (37).

Similarly, targeting immunosenescence may ultimately require cell- and pathway-specific approaches. The accumulation of senescent CD28⁻ CD8⁺ T cells, together with their altered secretory phenotype and reported effects on osteoblast differentiation and mesenchymal stromal-cell viability, suggests one possible target population. Rather than globally restoring immune activity, future strategies could aim to selectively eliminate pathogenic senescent immune subsets or interrupt their osteotoxic signaling while preserving protective immune functions (38).

Finally, nutritional and natural compounds may provide relatively accessible approaches for modulating multiple components of the osteoimmune network simultaneously. The evidence in the provided literature includes compounds capable of altering macrophage polarization, inflammatory signaling, oxidative stress, or osteoclastogenesis; notably, isoeugenol was reported to suppress macrophage M1 polarization through the p38 MAPK–arachidonic acid pathway and to attenuate ovariectomy-induced bone loss in experimental models (39). Such approaches are particularly interesting because the aging osteoimmune phenotype is

network-based, but their clinical relevance should not be inferred from preclinical efficacy alone. A more promising future framework may therefore involve combining bone-directed treatment with selective immune or senescence-directed modulation, with therapeutic selection guided by measurable inflammatory, immune, and senescence-associated phenotypes rather than by bone mineral density alone (Figure 2).

Emerging Perspectives and Research Gaps

A major challenge in translating the concept of inflammaging into clinically actionable osteoporosis research is the absence of a validated biomarker framework capable of simultaneously capturing inflammatory burden, immunosenescence, and cellular senescence within the aging bone microenvironment. Current evidence suggests that combinations of inflammatory cytokines, immune-cell phenotypes, senescence-associated markers, and osteoimmune mediators such as RANKL/OPG may provide greater biological information than any single marker, but their predictive value for skeletal outcomes remains insufficiently established (40).

Future therapeutic strategies may therefore need to move beyond single-target inhibition toward combination and phenotype-guided interventions, integrating antiresorptive or anabolic treatment with selective modulation of inflammatory signaling, senescent-cell activity, or pathogenic immune populations. However, much of the mechanistic evidence currently available derives from murine models, macrophage or osteogenic cell lines, and experimentally induced inflammatory bone-loss models, limiting direct extrapolation to heterogeneous human aging. The STAT3/mitophagy/NLRP3 pathway, for example, has demonstrated compelling mechanistic effects in experimental osteolysis, but its therapeutic relevance in age-related osteoporosis remains to be established in human studies (32). A particularly important research direction will therefore be the development of longitudinal human studies integrating immune profiling, senescence-associated biomarkers, bone remodeling markers, and imaging-based skeletal outcomes. Such studies could determine whether osteoimmune alterations precede measurable bone loss or primarily emerge as consequences of skeletal deterioration. Ultimately, identifying these temporal relationships may allow inflammaging and immunosenescence to be treated not merely as correlates of osteoporosis, but as potentially modifiable determinants of its progression (41).



Integrative Strategies for Modulating Immune–Bone Communication During Aging

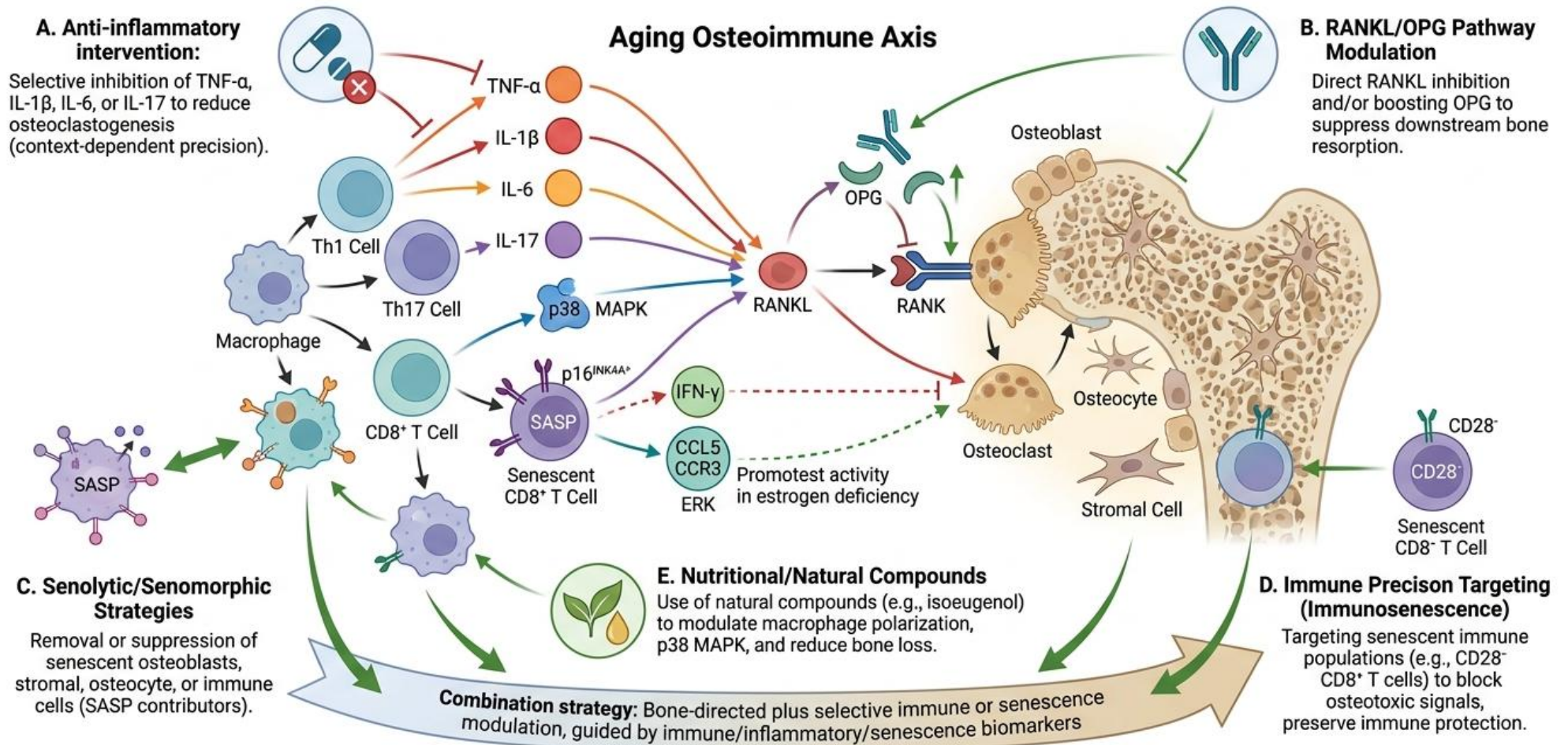


Figure 2. Therapeutic Targeting of the Aging Osteoimmune Axis in Osteoporosis.

Conclusions

Age-related osteoporosis is increasingly understood as a disorder in which skeletal deterioration is closely connected to progressive alterations in immune regulation and the bone microenvironment (42). The evidence considered in this review supports an integrated view in which immunosenescence, cellular senescence, and inflammaging converge on the osteoimmune axis, potentially shifting physiological bone remodeling toward persistent osteoclastogenic activity. Within this network, inflammatory cytokines, altered immune-cell phenotypes, RANKL/RANK/OPG signaling, oxidative stress, and pathways including NF- κ B, JAK/STAT, MAPK, and NLRP3 may interact rather than operate as independent mechanisms.

An important implication of this framework is that senescent cells may represent a mechanistic link between systemic aging and local skeletal dysfunction. Their accumulation within bone and immune compartments, together with SASP-associated signaling, may create a microenvironment in which inflammatory and osteoclastogenic signals are repeatedly reinforced. Nevertheless, the available evidence remains heterogeneous, and the extent to which these mechanisms directly drive human age-related osteoporosis rather than accompany its progression remains incompletely resolved.

Future research should therefore move beyond isolated measurements of bone density or individual cytokines and investigate multidimensional osteoimmune phenotypes incorporating immune-cell states, senescence markers, inflammatory mediators, and bone-remodeling signals. Such an approach may ultimately enable identification of individuals in whom inflammaging and immunosenescence are therapeutically modifiable. Rather than treating osteoporosis solely as excessive bone resorption, the emerging osteoimmune perspective suggests that restoring communication between aging immune and skeletal compartments may become an important component of precision strategies for preserving bone health during aging.

Abbreviations

RANK: Receptor Activator of Nuclear Factor- κ B, **RANKL:** Receptor Activator of Nuclear Factor- κ B Ligand, **OPG:** Osteoprotegerin, **NF- κ B:** Nuclear Factor- κ B, **TNF- α :** Tumor Necrosis Factor- α , **IL-1 β :** Interleukin-1 β , **IL-4:** Interleukin-4, **IL-6:** Interleukin-6, **IL-10:** Interleukin-10, **IL-13:** Interleukin-13, **IL-17:** Interleukin-17, **IL-33:** Interleukin-33, **IFN- γ :** Interferon- γ , **TGF- β :** Transforming Growth Factor- β , **CCL5:** C-C Motif Chemokine Ligand 5, **CCR3:** C-C Chemokine Receptor Type 3, **ERK:** Extracellular Signal-Regulated Kinase, **MAPK:** Mitogen-Activated Protein Kinase, **JAK:** Janus Kinase, **STAT:** Signal Transducer and Activator of Transcription, **STAT3:** Signal Transducer and Activator of Transcription 3, **NF- κ B:** Nuclear Factor- κ B, **mTOR:** Mechanistic Target of Rapamycin, **JNK:** c-Jun N-terminal Kinase, **GATA4:** GATA Binding Protein 4, **p16INK4a:** Cyclin-Dependent Kinase Inhibitor 2A, **p21CIP1:** Cyclin-Dependent Kinase Inhibitor 1A, **pRB:** Retinoblastoma Protein, **PINK1:** PTEN-induced Kinase 1, **NLRP3:** NOD-like Receptor Family Pyrin Domain Containing 3, **ROS:** Reactive Oxygen Species, **DKK1:**

Dickkopf-related Protein 1, **SASP:** Senescence-Associated Secretory Phenotype, **Wnt:** Wntless-related Integration Site, **miRNA:** MicroRNA, **Treg:** Regulatory T Cell, **Th17:** T Helper 17 Cell, **M1:** Classically Activated Macrophage, **M2:** Alternatively Activated Macrophage.

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Ethical Approval

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Conflict of Interests

The authors declare that they do not have any conflict of interest.

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