

Immunopharmacological Targeting of Immune-Bone Crosstalk in Bone Disorders: Mechanisms and Therapeutic Perspectives

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ABSTRACT

Bone remodeling is a tightly regulated physiological process governed by the coordinated activities of bone-forming osteoblasts and bone-resorbing osteoclasts. Emerging evidence highlights the immune system as a critical regulator of this process through complex cellular interactions and signaling networks, giving rise to the concept of osteoimmunology. Immune cells, including T cells, B cells, and macrophages, modulate bone homeostasis by secreting cytokines and engaging in direct cell-cell communication that influences osteoclast differentiation and osteoblast function. Key molecular pathways implicated in immune-mediated bone remodeling include the RANK-RANKL-OPG axis, Wnt/ β -catenin signaling, and pro-inflammatory cytokine networks involving TNF- α , IL-6, and IL-17. Dysregulation of these pathways contributes to the pathogenesis of bone disorders such as osteoporosis, rheumatoid arthritis, and other inflammatory bone diseases. From a pharmaceutical perspective, targeting immune-bone signaling pathways has emerged as a promising therapeutic strategy. Approved biologics, including monoclonal antibodies against RANKL and inflammatory cytokines, have demonstrated clinical efficacy in reducing pathological bone resorption. In addition, emerging immunopharmacological approaches such as modulation of regulatory T cells, immune checkpoint signaling, and cytokine-driven intracellular pathways offer novel opportunities for drug development. Advances in precision medicine and immunotherapy further support the development of personalized interventions for immune-mediated bone disorders. This review critically examines immune-bone crosstalk with an emphasis on pharmacologically actionable targets and emerging therapeutic strategies, providing insights into future directions for restoring skeletal homeostasis and preventing immune-driven bone loss.

Keywords: Bone turnover, Cytokines, Immune system, Osteoimmunology, RANK-RANKL-OPG.

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INTRODUCTION

The significant increase in bone biology research over the last 20 years has not only helped us better understand how bone remodelling is controlled, However, it has also made it possible for us to answer some of the most important questions that remain unsolved. Numerous biochemical and mechanical factors control the complex process of bone remodelling, which entails the continuous replacement of old bone with new tissue and requires interaction between different cell phenotypes. The

skeletal system, which is made up of bone and cartilage, serves two primary purposes (Bahrami *et al.*, 2024). The first is a structural function that includes maintaining and safeguarding vital internal organs, bone marrow, and the muscular attachment for mobility. Second, by buffering changes in hydrogen ion concentration and serving as a store of calcium and phosphate necessary to maintain serum homeostasis, the skeleton serves a crucial metabolic role. Turning over bone throughout the remodelling process maintains the size, shape, and quality of the skeleton. This is achieved by structural alteration in response to biomechanical stresses and stress, as well as microfracture healing. This process is characterised by the coordinated actions of osteoclasts and osteoblasts organised in Bone Multicellular Units (BMU) that follow an activation-resorption-formation sequence of events (Flores-Silva *et al.*, 2015). By controlling the ratio of bone production to resorption, the immune system is essential for preserving bone homeostasis. Osteoimmunology



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is the term for this relationship, which comprises intricate signalling networks where immune cells and cytokines affect the activity of osteoblasts and osteoclasts. Immune cells such as T cells, B cells, and macrophages help regulate important pathways like RANK-RANKL-OPG and Wnt/ β -catenin, which are essential for bone remodeling (Cai *et al.*, 2024). While anti-inflammatory cytokines like TGF- β and IL-10 support bone growth and repair, pro-inflammatory cytokines like TNF- α , IL-6, and IL-17 encourage osteoclastogenesis and bone resorption (Bhol *et al.*, 2024). Pathological illnesses like osteoporosis, rheumatoid arthritis, and osteolytic bone diseases where excessive inflammation causes bone loss can result from dysregulation of immune responses. Osteoporosis, which is brought on by an imbalance that favours either excessive bone resorption or insufficient bone creation, results in decreased bone mass and an elevated risk of fracture. This imbalance is frequently brought on by altered RANKL/OPG signalling and hormonal alterations such as decreased oestrogen levels (Kareem *et al.*, 2021). The hallmark of Paget's disease is excessive bone turnover brought on by overactive osteoclasts, resulting in structurally weak, disorganized bone. Genetic mutations, particularly in the SQSTM1 gene, and enhanced RANK signaling contribute to this disorder. In bone cancers like osteosarcoma and metastatic bone disease, factors like RANKL and parathyroid hormone-related protein (PTHrP) are secreted by tumour cells, which disrupt normal remodeling, causing either excessive bone resorption or aberrant bone formation (Trout *et al.*, 2023). This pathological remodeling not only fuels tumor growth but also leads to complications such as bone pain, fractures, and hypercalcemia. Developing tailored therapeutics to restore normal bone remodeling and slow the course of illness requires an understanding of these pathways. Malignant mesenchymal cells that produce osteoid and/or immature bone are a hallmark of osteosarcoma, the most prevalent primary solid cancer of the bone. Among the general population, osteosarcoma affects 2-3 million individuals annually; however, it is more common among adolescents, with an incidence of 8-11 million persons between the ages of 15 and 19. Osteosarcomas account for 15% of all solid extracranial tumours in this age group. Males are 1.4 times more likely to be impacted than females. Identification of bone cancer is crucial, although it is challenging to predict (Xiao *et al.*, 2015). Conversely, immune-targeted therapies, including cytokine inhibitors and monoclonal antibodies against RANKL, offer promising approaches for treating immune-mediated bone disorders. Understanding the immune system's role in bone homeostasis is essential for developing innovative therapeutic strategies that restore skeletal integrity and prevent bone loss associated with aging, autoimmune diseases, and chronic inflammation (Jung *et al.*, 2022). This review examines immune system mechanisms in bone turnover and highlights emerging therapies targeting these pathways. In controlling osteoblast and osteoclast activity, it investigates the functions of important immune cells (T cells, B cells, and macrophages) and signalling

pathways (RANK-RANKL-OPG, Wnt/ β -catenin, and cytokine networks) (Tao *et al.*, 2025). Along with immune-driven bone illnesses such as osteoporosis and rheumatoid arthritis, the effects of pro-inflammatory (TNF- α , IL-6, IL-17) and anti-inflammatory (IL-10, TGF- β) cytokines on bone remodelling are covered. Therapeutic approaches, including RANKL inhibitors, cytokine blockers, and immunomodulatory strategies, are reviewed. Advances in precision medicine and immunotherapy offer promising avenues for treating immune-mediated bone disorders (Moulin *et al.*, 2025).

METHODOLOGY

A systematic literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar. Keywords such as Bone turnover, Immune system, RANK-RANKL-OPG, Osteoimmunology, Cytokines, Therapeutic strategies were used with Boolean operators to refine results. Peer-reviewed articles in English focusing on immune mechanisms in bone remodeling and related therapies were included, while non-English and unrelated studies were excluded. Data on immune cells, signaling pathways, disease models, and therapeutic interventions were extracted and synthesized thematically. Study quality was assessed using PRISMA and the Newcastle-Ottawa Scale.

Bone Remodeling Process: Cellular and Molecular Mechanisms

Role of Osteoblasts in Bone Formation

Stem cells are unique cells with self-renewing and differentiation potential. Originating from mesoderm-derived embryonic connective tissue, Mesenchymal Stem Cells (MSCs) can differentiate into a variety of cell types, such as bone and cartilage. They are found in a gelatinous extracellular matrix. Despite being the primary MSC source, bone marrow contains only a small fraction of these cells (Zhou *et al.*, 2023). Osteoblasts, derived from MSCs, produce bone matrix and function in clusters along bone surfaces. They differentiate into fibroblasts, myoblasts, chondrocytes, osteoblasts, or adipocytes (Henry *et al.*, 2023). Runx2 and osterix are essential for osteoblast differentiation. While some mature osteoblasts develop into flat lining cells on the surface of the bone, about 15% of them become osteocytes. The three stages of bone development are mineralisation, maturation, and osteoid formation (Komori *et al.*, 2006). These processes move at the same pace in healthy adult bone. Osteoblasts first create osteoid collagen, which is then followed by increased mineralisation and a final slowdown in collagen production (Salhotra *et al.*, 2020). Growth factors such as IGF (LeRoith *et al.*, 2021), PDGF (Chen *et al.*, 2012), bFGF, TGF- β , and BMP regulate osteoblast activity via autocrine and paracrine signaling. Growth hormone (Brinkman *et al.*, 2023), insulin (Menon *et al.*, 1996), progesterone (Paulino *et al.*, 2020), prolactin (Velkeniers *et al.*, 1998), thyroid hormone (Tanm *et al.*, 2011), parathyroid hormone, and parathyroid hormone-related protein are also

receptors found on osteoblasts. They also contain nuclear steroid hormone receptors for retinoids (Librizzi *et al.*, 2023), androgens (Alemany *et al.*, 2022), estrogens (Lizcano *et al.*, 2022), and Vitamin D3 (Rebelos *et al.*, 2023).

Role of Osteoclasts in Bone Resorption

Osteoclasts are large multinucleated cells (up to 100 μm in diameter) responsible for bone resorption, originating from mononuclear hematopoietic lineage cells (Yahara *et al.*, 2022). Found in Howship's lacunae, they interact with calcified bone surfaces through their ruffled border and sealing zone. Osteoclasts, which are abundant in mitochondria, transport vesicles, and Golgi complexes, release lysosomal enzymes such as tartrate-resistant acid phosphatase and cathepsin K across the ruffled boundary (Everts *et al.*, 2022). Integrins facilitate their adhesion to bone matrix proteins, with $\alpha\text{v}\beta3$ integrin triggering cytoskeletal rearrangement (Gu *et al.*, 2023). Podosomes, dynamic adhesion structures, enable osteoclast migration during resorption, relying on adhesion kinases like Src (Chen *et al.*, 2023). Bone resorption involves acidification and proteolysis, initially releasing hydroxyapatite crystals and subsequently breaking down collagen fibers via cathepsins or collagenases. Degraded components are internalized or transported for exocytosis. Calcitonin (Xie *et al.*, 2020), androgens (Alemany *et al.*, 2022), thyroid hormone (Sabatino *et al.*, 2025), insulin (Rahman *et al.*, 2021), PTH (Dettori *et al.*, 2023), IGF-1 (Bailes *et al.*, 2021), IL-1 (Boraschi *et al.*, 2022), CSF-1 (Sehgal *et al.*, 2021), and PDGF (Pandey *et al.*, 2023) are among the systemic hormones and local cytokines that control osteoclast function.

Bone Remodeling

Bone is a dynamic organ that continuously remodels through the coordinated activity of osteoblasts and osteoclasts. This process, termed "bone remodeling" by Frost in 1990 (Zhu *et al.*, 2021), maintains structural integrity and adapts to mechanical load (Figure 1). Osteoclasts and osteoblasts operate within a Basic Multicellular Unit (BMU), which varies morphologically between cortical and trabecular bone but follows a similar biological process (Sims *et al.*, 2023). The BMU advances through cortical bone at 20-40 $\mu\text{m}/\text{day}$, forming a cylindrical canal, while trabecular bone remodels more aggressively due to its higher surface-to-volume ratio (Oftadeh *et al.*, 2015). Remodeling occurs in three phases: resorption (~2 weeks), reversal (~4-5 weeks), and formation (~4 months). Preosteoclasts migrate, fuse, and resorb bone, followed by mononuclear cells preparing the surface for osteoblasts, which then replace resorbed bone. The cycle concludes with flattened lining cells covering the surface (Borcianni *et al.*, 2020). The interaction between osteoblasts and osteoclasts is mediated by RANKL, a TNF superfamily peptide that binds to RANK on osteoclast precursors, promoting activation and survival (Luo *et al.*, 2018). Osteoprotegerin (OPG), a dimeric glycoprotein secreted by osteoblast-lineage and bone marrow

cells, inhibits RANKL by acting as a decoy receptor, inducing osteoclast apoptosis and suppressing resorption (Aragon *et al.*, 2020). OPG's regulatory actions are still reversible because it is not integrated into the bone matrix.

Role of Osteocytes in Bone Homeostasis

Osteocytes, the primary mechanosensors and regulators of bone remodeling (Choi *et al.*, 2022), are essential for maintaining bone homeostasis (Figure 2). Derived from osteoblasts, they are embedded in the mineralized matrix and interconnected via canaliculi. Osteocytes coordinate osteoblasts and osteoclasts by sensing mechanical stress and converting it into biochemical signals. They produce sclerostin, which inhibits the Wnt signaling pathway, suppressing bone formation (Borcianni *et al.*, 2020). Mechanical loading or hormonal signals reduce sclerostin expression, enhancing osteoblast activity, while disuse or aging increases sclerostin, promoting resorption. By producing Fibroblast Growth Factor 23 (FGF23), which regulates phosphate homeostasis, osteocytes also govern mineral metabolism (Wang *et al.*, 2021). They secrete key regulatory molecules, including RANKL, OPG, and sclerostin. Sclerostin binds LRP5/6 receptors on osteoblasts, inhibiting bone formation, while PTH or mechanical loading reduces its expression, stimulating osteoblast activity. Osteocytes and osteoblasts release RANKL, which binds to RANK on osteoclast precursors, driving osteoclastogenesis. By blocking RANKL and reducing bone resorption, OPG functions as a decoy receptor. In order to regulate bone turnover, the ratio of RANKL to OPG must be balanced. FGF23 further maintains mineral balance by regulating phosphate levels (Wu *et al.*, 2024), ensuring skeletal integrity and homeostasis.

Immune System Components Involved in Bone Turnover

Immune Cells in Bone Turnover

By affecting osteoblast and osteoclast activity through cytokine signalling, T cells, B cells, and macrophages all play important roles in bone metabolism. While regulatory T cells (Tregs) generate anti-inflammatory cytokines such as IL-10 that prevent bone resorption, T cells emit RANKL, which promotes osteoclastogenesis. B cells contribute to bone homeostasis by secreting OPG, which blocks RANKL and suppresses osteoclast formation. Macrophages, particularly osteal macrophages (osteomacs), support osteoblast function and bone repair by releasing growth factors such as TGF- β and BMPs. Additionally, pro-inflammatory macrophages (M1) enhance osteoclastogenesis via TNF- α and IL-1 β , whereas anti-inflammatory macrophages (M2) promote bone formation and healing (Yang *et al.*, 2024).

Interaction between immune cells and bone-resorbing cells (osteoclasts)

To control bone metabolism, immune cells specifically T and B cells interact with osteoclasts, which are cells that break down

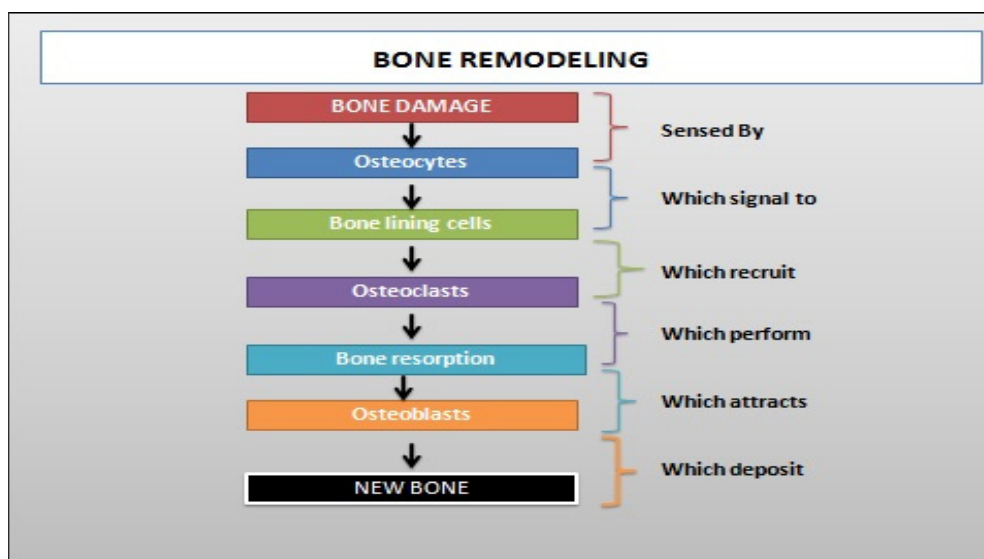


Figure 1: Bone Remodeling.

bone. T cells are essential for increasing osteoclastogenesis and bone resorption, particularly in inflammatory situations, by secreting RANKL (Receptor Activator of Nuclear Factor- κ B Ligand). By generating Osteoprotegerin (OPG), which binds to RANKL and stops it from interacting with osteoclast precursors, B cells, on the other hand, control osteoclast activity and prevent excessive bone resorption. The balance between RANKL and OPG production by immune cells is crucial in maintaining bone homeostasis, with disrupted immune responses contributing to pathological bone loss in conditions like osteoporosis and rheumatoid arthritis. Additionally, immune cell activation, such as through the CD40/CD40L pathway, can modulate OPG production, further influencing osteoclast function and bone remodeling (Komatsu *et al.*, 2022).

Impact of regulatory immune cells (Tregs, dendritic cells) on bone health

Regulatory immune cells, such as Tregs and dendritic cells, play a crucial role in bone health by modulating immune responses and bone remodeling. Tregs suppress pro-inflammatory cells, preventing excessive osteoclastogenesis and maintaining immune tolerance. Dendritic cells influence T-cell differentiation and the balance of pro- and anti-osteoclastogenic signals, impacting bone homeostasis. Dysregulation of these cells contributes to bone loss in conditions like osteoporosis and autoimmune diseases (Yang *et al.*, 2021). DCs develop into immature Langerhans and interstitial DCs from CD34+ bone marrow stem cells. They mature in response to danger signals to trigger immunological responses, absorbing and breaking down antigens for MHC class II presentation (Abbaszadeh *et al.*, 2025). Chemokine receptors regulate DC trafficking, while maturation enhances MHC class II and costimulatory molecule expression, influencing Th1/Th2 polarization (Kumar *et al.*, 2019). DCs are isolated based on low buoyant density and adherence properties, with negative

selection removing macrophages, B, T, and NK cells, and positive selection enriching for MHC class II+ CD11c+ cells (Inaba *et al.*, 2025). DCs can be propagated using growth factors such as GM-CSF, TNF- α , IL-4, SCF, TGF- β , IL-3, and Flt3L, which support differentiation and proliferation (Sabado *et al.*, 2017). GM-CSF and IL-4/TNF- α promote interstitial DCs and LCs, with TGF- β essential for LCs. IL-3 supports plasmacytoid DCs, while Flt3L expands DCs and progenitors in vitro and in vivo (Zanna *et al.*, 2021).

Signaling Molecules and Cytokines in Bone Turnover

Key cytokines (TNF- α , IL-6, IL-1 β) in immune-bone interactions

By influencing osteoclastogenesis and bone resorption, important cytokines like TNF- α , IL-6, and IL-1 β play important roles in immune-bone interactions. TNF- α enhances osteoclast differentiation and activity by synergizing with RANKL, promoting bone loss in inflammatory conditions. IL-6 contributes to osteoclastogenesis by stimulating RANKL expression and is implicated in bone diseases like osteoporosis and rheumatoid arthritis. IL-1 β further amplifies bone resorption by upregulating RANKL and promoting osteoclast survival. Collectively, these pro-inflammatory cytokines disrupt bone homeostasis in pathological conditions, leading to excessive bone loss and skeletal disorders (Kitaura *et al.*, 2020).

Role of RANK/RANKL/OPG signaling in osteoclastogenesis

The primary regulator of osteoclastogenesis and bone remodeling is the RANK/RANKL/OPG signalling pathway. Osteoclast precursors express Receptor Activator of Nuclear factor- κ B (RANK), whereas osteoblasts, osteocytes, and stromal cells produce its ligand, RANKL. By binding to RANK, RANKL triggers downstream signalling pathways that promote bone resorption,

osteoclast differentiation, and survival. By attaching to RANKL and blocking its interaction with RANK, Osteoprotegerin (OPG), a decoy receptor released by osteoblasts and B cells, suppresses osteoclastogenesis. Bone homeostasis depends on the ratio of RANKL to OPG, where too much RANKL causes bone loss and too much OPG guards against conditions linked to resorption (De Leon-Oliva *et al.*, 2023).

Immune signaling pathways involved in osteoblast function (Wnt, BMP, etc.)

Several immune signaling pathways regulate osteoblast function, influencing bone formation and homeostasis. One important regulator is the Wnt/ β -catenin pathway, in which Wnt ligands attach to Frizzled and LRP5/6 receptors to stabilise β -catenin and stimulate osteoblast activity and differentiation. In order to promote osteoblastogenesis and matrix mineralisation, Bone Morphogenetic Proteins (BMPs), specifically BMP-2, BMP-4, and BMP-7, stimulate Smad-dependent signalling. Pro-inflammatory cytokines like TNF- α and IL-6 can inhibit osteoblast differentiation by suppressing Wnt signaling, while TGF- β plays a dual role, initially promoting osteoblast recruitment but later inhibiting their activity. Crosstalk between these pathways ensures a balanced bone remodeling process (Liu *et al.*, 2022).

RESULTS AND DISCUSSION

Mechanisms of Immune Regulation of Bone Turnover

Immune-Mediated Activation of Osteoclasts

RANK/RANKL pathway in osteoclast differentiation and activation

RANKL belongs to the TNF cytokine superfamily. Its receptor, RANK, was previously found to be involved in T-cell activation and dendritic-cell function. It shares some similarities with the extracellular domain of human CD40, a member of the TNF receptor superfamily (De Leon-Oliva *et al.*, 2023). Due to a whole OC deficiency, severe osteopetrosis is caused by genetic deletion or mutation of RANKL or RANK (Yao *et al.*, 2021). The binding of RANKL with RANK in OCPs causes terminal OC differentiation, fusion, and activation when co-stimulated with M-CSF. However, RANK lacks intrinsic kinase activity to trigger downstream signalling, just like other TNF receptor superfamily members (Choi *et al.*, 2022). The multifunctional adaptor proteins, TNF receptor-associated factors (TRAFs) 1, 2, 3, 5, and 6, as well as kinases like TGF β -activated kinase-1 (TAK1), are among the molecules that are recruited when RANKL binds to RANK. These molecules sequentially activate NF- κ B p50 and p52, c-Fos, and NFATc1, the three sets of transcriptional factors necessary for OC differentiation (Boyce *et al.*, 2023). Since NFATc1 is the master transcription factor that controls OC differentiation (Kitazawa *et al.*, 2021), over-expression of NFATc1 causes OCPs to terminally differentiate and fuse without the addition of RANKL (Zheng *et al.*, 2024). It can also repair the OC formation defect caused by TNF and RANKL that is brought

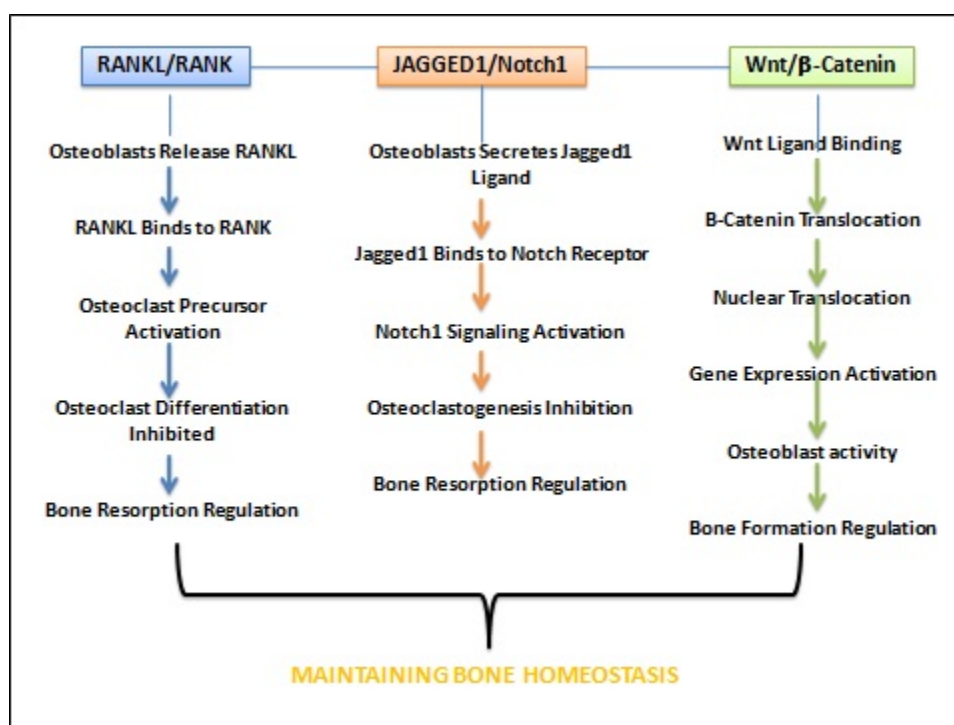


Figure 2: Role of RANKL, Notch1 & Wnt/ β -Catenin in Bone Homeostasis.

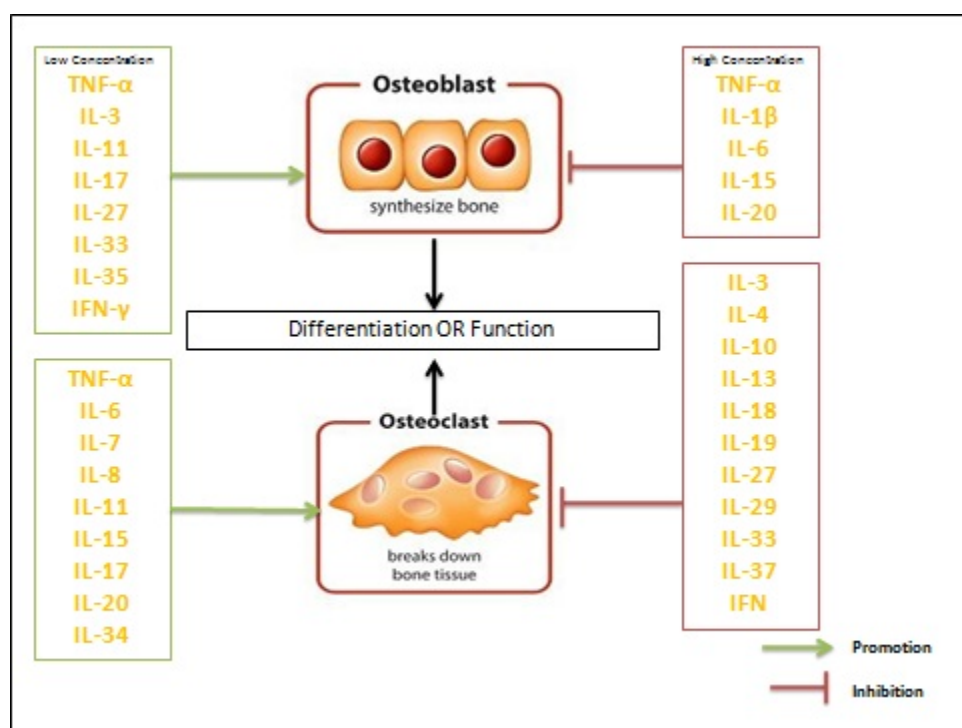


Figure 3: The promotive and suppressive effects of different cytokines on osteoblasts and osteoclasts affecting their differentiation or function.

on by the deletion of NF- κ B p50/p52 or c-Fos (Yao *et al.*, 2021). As a soluble RANKL decoy receptor, OPG binds to RANKL to prevent RANKL-RANK interaction, which in turn prevents OC production and bone resorption (De Leon-Oliva *et al.*, 2023). Therefore, homozygous deletion of 100 kilobases of the OPG gene in humans causes juvenile Paget's disease, which is characterised by osteopenia and fractures (Hoppner *et al.*, 2021), while genetic deletion of OPG causes osteoporosis in mice. Bonemass and OC distinguishing status are believed to be significantly influenced by the RANKL/OPG ratio (Zhivodernikov *et al.*, 2023). In prevalent bone illnesses including osteoporosis and RA, it is believed that RANKL increases as OPG decreases, increasing the ratio of RANKL to OPG and promoting osteoclastogenesis (Tobeiha *et al.*, 2020). Nonetheless, some published data suggests that in postmenopausal osteoporotic women and with ageing, serum levels of OPG are elevated and RANKL are decreased (Veshnavei *et al.*, 2022). Furthermore, despite the fact that joint degeneration was prevented by the OC deficit, synovial inflammation persisted in TNF-Tg animals produced to have a RANKL insufficiency (Yi *et al.*, 2021). According to clinical trials, denosumab, a RANKL inhibitor, caused a prolonged decrease of bone turnover in RA patients, but it had no effect on RA disease activity or joint space narrowing (Takeuchi *et al.*, 2019). These results imply that in pathological circumstances like osteoporosis and RA, mechanisms other than RANKL/OPG may contribute to the enhancement of OC differentiation. Clarifying which mechanisms mediate increased OC production and examining how they are activated and function to cause the observed bone loss and joint deterioration are crucial (Yao *et al.*, 2021).

Influence of pro-inflammatory cytokines on osteoclastogenesis

The ability of osteoclasts to resorb bone is known to be influenced by a number of local and systemic variables. These parameters greatly balance the osteoclast activity in a physiological state. Additional pro-inflammatory cytokines, mostly produced by activated T cells, cause their activity to become dysregulated under pathological situations, such as excessive immune system activation (Wu *et al.*, 2025). As previously stated, pro-inflammatory cytokines are either osteoclastogenic (if they have demonstrated the ability to stimulate osteoclast differentiation and/or activity) or anti-osteoclastogenic (if they have demonstrated the ability to suppress osteoclasts) (de Oliveira G *et al.*, 2024). According to available data, pro-inflammatory cytokines like IL-1, IL-6, IL-8, IL-11, IL-17, TNF- α , and others are thought to be osteoclastogenic, while cytokines like IL-4, IL-10, IL-13, IL-18, IFN- γ , and IFN- β are thought to be anti-osteoclastogenic (Figure 3) (Drafta *et al.*, 2021). The standard Th1 and Th2 cells are regarded as antiosteoclastogenic because they produce IFN- γ (Th1) and IL-4 (Th2), but Th17, a unique subtype of T helper cells, are categorised as osteoclastogenic because they produce IL-17 and RANKL (Luo *et al.*, 2022). It has been demonstrated that several pro-inflammatory cytokines, including TGF- β and IL-7, IL-12, IL-23, and IL-6, have both osteoclastogenic and anti-osteoclastogenic qualities. Their overall impact appears to be dependent on the particular pathophysiological state of the bone under study *in vivo*, whereas *in vitro* experiments rely on the osteoclasts' embryonic stage (Kitaura *et al.*, 2020). Given

that these cytokines have been shown to have both synergistic and antagonistic effects on osteoclasts, determining their precise function in the bone microenvironment is even more challenging (Xu *et al.*, 2023). As was previously established, pro-inflammatory cytokines can either directly or indirectly target osteoclasts by altering the RANK/RANKL/OPG system. By measuring the expression of osteoclast-specific genes that encode RANK, calcitonin receptor, $\beta 3$ integrin, OSCAR, cathepsin K, and TRAP genes involved in osteoclast differentiation, bone-resorbing activity, and survival the osteoclastogenic effect of these cytokines can be evaluated (Gyori DS *et al.*, 2020).

Immune cell-derived factors promoting osteoclast function

Immune cell-derived factors play a significant role in promoting osteoclast function by enhancing osteoclast differentiation and activity. One of the important cytokines is RANKL, which is mostly generated by T and B cells and stimulates osteoclastogenesis by binding to its receptor RANK on osteoclast precursors. Activated T cells and macrophages release TNF- α , which works in concert with RANKL to promote osteoclast survival and development. IL-1 β enhances osteoclast activity by upregulating RANK expression, while IL-6 promotes osteoclast precursor differentiation, particularly in inflammatory conditions (Zhou *et al.*, 2022). Th17 cell-produced IL-17 promotes osteoclastogenesis by causing osteoblasts and stromal cells to express RANKL. Furthermore, depending on the situation, GM-CSF and IFN- γ can either stimulate or inhibit osteoclast development (Wang *et al.*, 2025). Although these immune-derived substances are

essential for maintaining bone homeostasis, they also play a role in the pathological loss of bone in conditions like osteoporosis and rheumatoid arthritis (Tao *et al.*, 2025).

Immune-Mediated Modulation of Osteoblast Activity

Immune cytokines affecting osteoblast differentiation and activity

Under both healthy and pathological circumstances, complex cytokine networks closely regulate osteoblastogenesis. While anti-osteoblastogenic cytokines like Tumour Necrosis Factor- α (TNF- α), TNF- β , IL-1 α , IL-4, IL-7, IL-12, IL-13, IL-23, IFN- α , IFN- β , Leukaemia Inhibitory Factor (LIF), Cardiotrophin-Like Cytokine (CLC), and Ciliary Neurotrophic Factor (CNTF) downregulate osteoblastogenesis. Osteoblastogenic cytokines include Interleukin-10 (IL-10), IL-11, IL-18, Interferon- γ (IFN- γ), Cardiotrophin-1 (CT-1), and Oncostatin M (OSM). One proinflammatory cytokine that is crucial in bone disorders is TNF- α (Amarasekara *et al.*, 2021). In OB precursors and MC3T3-E1 preosteoblastic cells, TNF- α suppresses RUNX2 expression as well as RUNX2-induced osteoblastogenic marker expression. Through the stimulation of RUNX2 by osteoblastogenic mediator β -glycerophosphate through the TNF type 1 receptor, TNF- α inhibits the production of osteoblastogenic markers (Xing *et al.*, 2022). It has also been found that TNF- α suppresses BMP/Smad signalling and activates JNK signalling to prevent BMP-induced osteoblastogenesis. Furthermore, in MC3T3-E1 preosteoblastic cells, TNF- α inhibits the production of nephronectin, an extracellular matrix protein thought to be

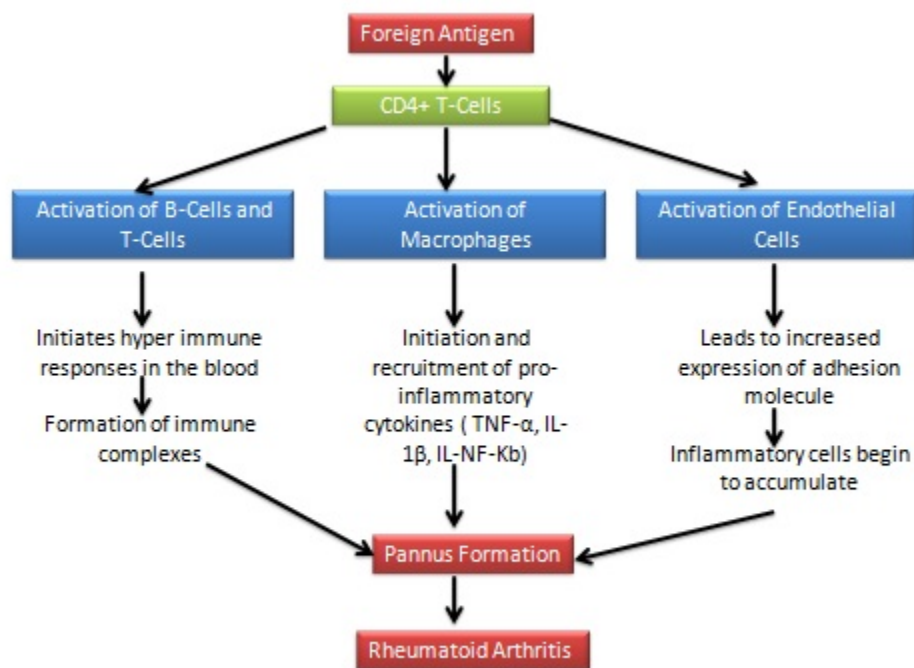


Figure 4: Pathophysiology of Rheumatoid Arthritis.

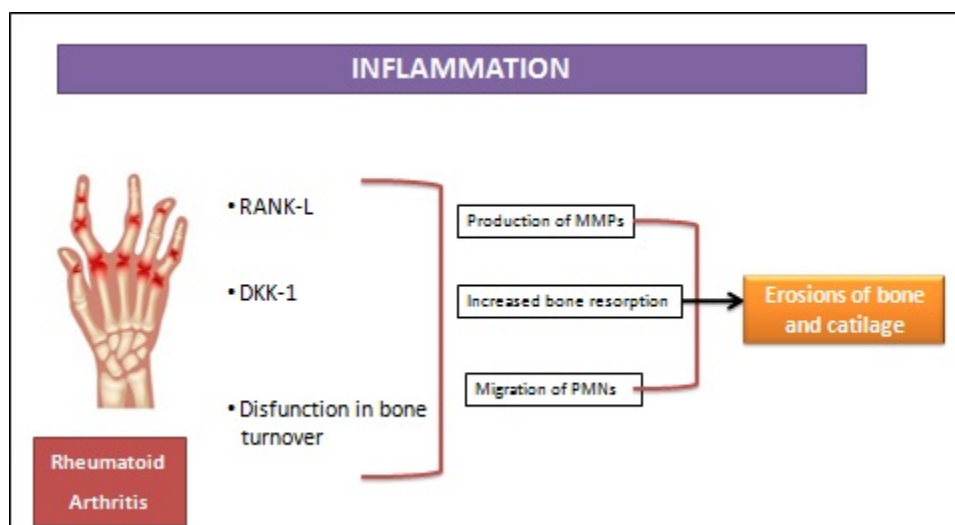


Figure 5: Chronic inflammation.

a positive regulator of osteoblastogenesis (Yao *et al.*, 2024). By enhancing the expression of ubiquitin E3 ligase Wwp1, TNF- α prevents osteoblastogenesis's OB lineage commitment by causing the AP-1 transcription factor to be broken down by proteasomes (Zhao *et al.*, 2021). TNF- α also inhibits the expression of osteoblastogenic transcription factor SATB2 via the BMP/Smad, NF- κ B and MAPK signaling pathways in osteoblastogenesis (Zuo *et al.*, 2017). By upregulating P2YR expression through the ERK/JNK signalling pathways, TNF- α prevents OB proliferation and differentiation in osteoporosis caused by oestrogen deprivation (Ng PY *et al.*, 2018). A recent study found that TNF- β , in addition to TNF- α , suppresses the early stage of osteoblastogenic differentiation from MSCs by activating NF- κ B and downregulating RUNX2 (Zhu *et al.*, 2024). TNF- α and TNF- β are well established to be potent anti-osteoblastogenic cytokines when combined. Although IFN- γ is well known for inhibiting OC differentiation, it has also been shown to play a role in osteoblastogenesis (Li *et al.*, 2021). By stimulating the production of osteoblastogenic markers as RUNX2, OSX, ALP, and OCN, IFN- γ stimulates osteoblastogenesis (Qu *et al.*, 2024). By suppressing RUNX2 expression, IFN- γ deficiency or knockdown in human MSCs prevents osteoblastogenesis (Arya *et al.*, 2024). Furthermore, animals lacking the IFN- γ receptor have a reduced ability to differentiate OB (Stinson *et al.*, 2022). However, it has also been documented that IFN- γ and TNF- α work together to enhance OB apoptosis by downregulating B cell lymphoma 2 expression, activating caspases, and causing nitric oxide generation or mitochondrial cytochrome c release (Ng *et al.*, 2025). By suppressing ALP activity and downregulating BMP-2 expression, IFN- α prevents the proliferation and differentiation of OB progenitor cells (Hu *et al.*, 2017). Furthermore, via decreasing the production of COL1A1, fibronectin, fibulin, fibrillin, and laminin, IFN- β inhibits matrix mineralization (Gillesberg *et al.*, 2025). Furthermore, DEF6, often referred to as IFN regulatory factor 4-binding protein, has been shown in recent studies to

decrease osteoblastogenesis by endogenous type 1 IFN-mediated feedback inhibition (Deng *et al.*, 2020). When considered collectively, these results suggest that IFN- γ is an osteoblastogenic cytokine, albeit there may be some outliers, whereas IFN- α/β is a possible anti-osteoblastogenic cytokine (Han *et al.*, 2023).

Wnt and Notch signaling pathways in osteoblast regulation by immune cells

The Wnt and Notch signaling pathways regulate osteoblast activity, with immune cells influencing their function. Wnt/ β -catenin signaling promotes osteoblast differentiation, but TNF- α and IL-1 β inhibit it by upregulating DKK1 and sclerostin, while IL-17 and IFN- γ enhance it (Zhu *et al.*, 2024). Tregs support Wnt signaling via TGF- β . Notch signaling initially promotes osteoblast proliferation but inhibits differentiation with prolonged activation. TNF- α and IL-6 modulate Notch activity, disrupting bone homeostasis. T cells and DCs regulate Notch ligands (Jagged1, Delta-like 1), influencing osteoblast fate. This immune-bone crosstalk plays a crucial role in skeletal integrity (Zong *et al.*, 2024). Haematopoietic Stem Cells (HSCs) are the source of immune cell formation and control. Survival depends on the latter's ability to maintain self-renewal, which permits differentiation and regeneration to produce adult blood cells (Lee *et al.*, 2019). Murine embryonic haematopoiesis occurs at various anatomical locations during development, including the placenta, Aorta-Gonad-Mesonephros (AGS), and extraembryonic yolk sac. Following a sequence of developmental stages, these HSCs migrate into and seed many organs; typical adult haematopoiesis takes place in bone marrow (Gao *et al.*, 2018). Additionally, the response of HSCs can be separated into two stages: (a) short-term HSCs (ST-HSCs) can perform restoration for a short period of time, and (b) long-term HSCs (LT-HSCs) have the ability to differentiate and self-renew for a long time. While DCs have incomplete lineage connections, these ST-HSCs produce multipotent progenitor cells, myeloid lineage cells (granulocytes

and macrophages), and lymphoid progenitor cells (NK cells, dendritic cells, B cells, and T cells) (Bozhilov *et al.*, 2023). We primarily address the function of Wnt signalling in lymphoid and myeloid progenitor cells in this study. Wnt signaling's role in the immune system was first documented in connection with the thymus's T-cell development (Haseeb *et al.*, 2019). Due to its role in guiding immune cell infiltration and its potential as a novel target for cancer molecular therapies, the Wnt- β -catenin signalling pathway is being extensively researched (Melssen *et al.*, 2023).

Impact of immune modulation on bone formation during aging and inflammation

Aging and inflammation disrupt bone homeostasis through immune modulation, leading to impaired bone formation. Numerous elements, such as systemic and local signalling molecules, osteogenic and resorptive cells, immune cells, and blood microcirculation, affect the intricate process of bone regeneration in ageing (Gibon *et al.*, 2017). Research has demonstrated that ageing can have a detrimental effect on bone repair in a mouse model of femur fractures. Compared to younger mice, aged animals had a worse healing response, as seen by reduced bone density, fewer callus, less total cartilage, and less bone content (Zhang *et al.*, 2023). In a mouse model of rib fracture, ageing has also been linked to an increase in osteoclasts and a decrease in osteoblasts (Cai *et al.*, 2022). For bone repair, there must be sufficient blood flow. Reduced endothelium-dependent vasodilation and altered nitric oxide synthase pathways may be the cause of the decreased local blood

flow in bone that is linked to ageing. Femoral blood flow in the metaphyseal medulla is 45% decreased in old rats (Tomlinson *et al.*, 2013). Increased levels of proinflammatory cytokines in the blood are indicative of a chronic, low-grade, subclinical systemic inflammatory state that is linked to ageing (Zhang *et al.*, 2024). This condition, known as "inflammaging," is defined by a baseline increase in pro-inflammatory, activated monocytes in aged mice (Ahmad *et al.*, 2024). The appropriate inflammation-mediated beginning of fracture repair in the elderly may be disrupted by dysregulated chronic inflammation in ageing tissues. Compared to younger mice, older mice exhibit a greater proportion of activated monocytes in response to femur fractures. Non-classical monocyte activation, which is typified by the overexpression of genes involved in phagocytosis and tissue repair and results in a pro-resolving and anti-inflammatory phenotype, is not exhibited by the mice concurrently (Li *et al.*, 2023). Two weeks after the fracture, inflammatory genes were downregulated in juvenile fracture callus specimens, although they were still upregulated in older specimens (Molitoris *et al.*, 2024).

Immune System Contribution to Bone Resorption in Inflammatory Diseases

Rheumatoid arthritis and bone erosion via immune-driven mechanisms

Rheumatoid Arthritis (RA) drives bone erosion through immune-mediated mechanisms that enhance osteoclast activity while suppressing osteoblast function (Figure 4) (Komatsu *et al.*, 2022). Pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β stimulate RANKL expression by synovial fibroblasts

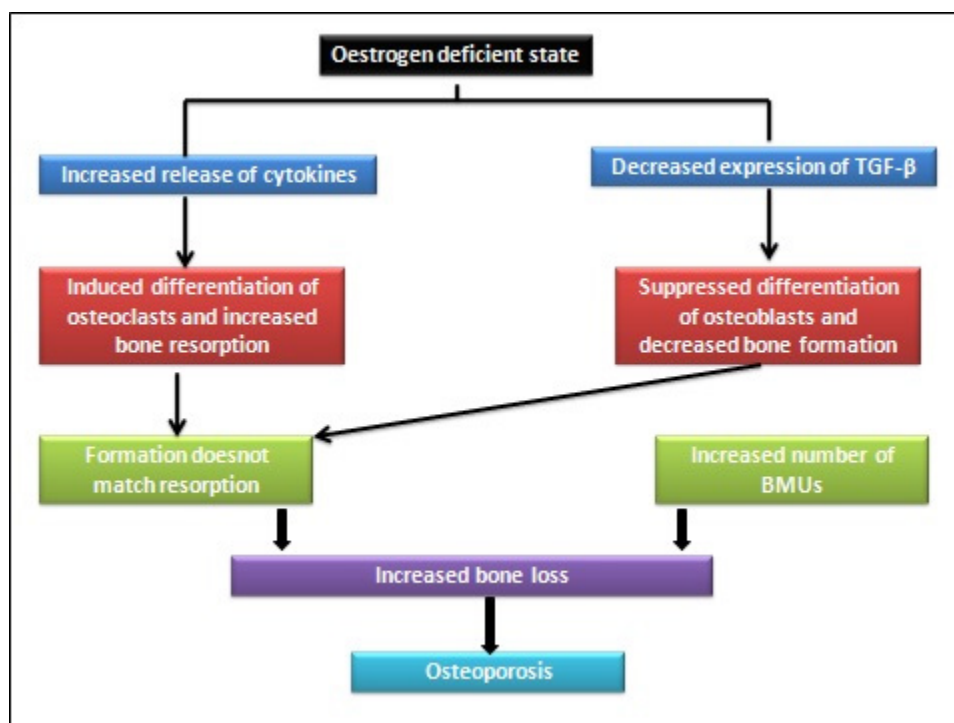


Figure 6: Pathogenesis of Osteoporosis.

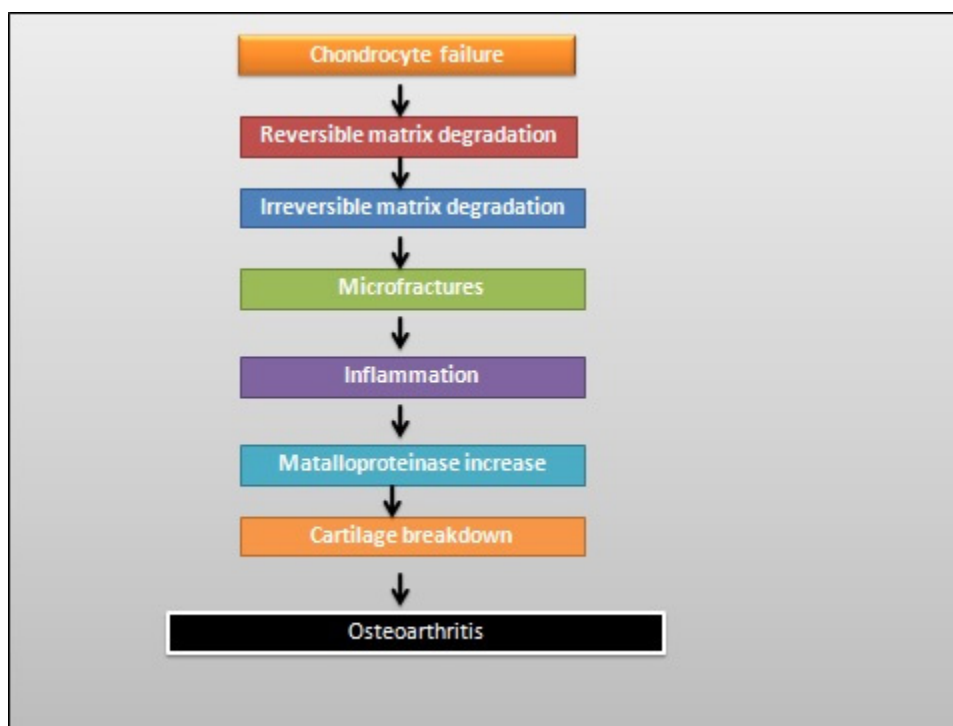


Figure 7: Pathophysiology of Osteoarthritis.

and T cells, promoting osteoclastogenesis and bone resorption. Activated macrophages and dendritic cells contribute to inflammation, while Th17 cells secrete IL-17, further increasing RANKL and inhibiting osteoblast differentiation. Additionally, chronic inflammation suppresses Wnt signaling, impairing bone formation (Silva *et al.*, 2019). The persistent immune activation in RA leads to progressive joint destruction and systemic bone loss, contributing to osteoporosis and increased fracture risk. A chronic, systemic autoimmune disease, Rheumatoid Arthritis (RA) primarily appears as increasing inflammatory pathology in synovial joints. A characteristic immune-mediated inflammation that targets synovial tissues and causes articular cartilage degeneration and osseous resorption is what sets this illness apart. Clinically, RA is characterised by symptoms such joint discomfort, stiffness, swelling of the synovium, persistent pain, and increasing abnormalities of the affected joints. According to epidemiology, RA affects between 0.5% and 1% of people worldwide, highlighting its importance as a significant rheumatologic health issue (Deshmukh *et al.*, 2023). There is a noticeable synovial hyperplasia in the pathophysiology of this articular pathology, which is marked by the infiltration and activation of immune cells, including lymphocytes and macrophages, as well as synovial fibroblasts. Meanwhile, in the osseous marrow compartment, inflammatory cell aggregates, primarily made up of activated macrophages and lymphocytes, develop in the synovium. Synovitis is triggered by this immunopathological cascade and is closely linked to localised osteopenia, which is characterised by a decrease in bone mineral density (Sanchez-Lopez E *et al.*, 2022). In human rheumatoid arthritis, MERT is increased in the serum

(Xu *et al.*, 2022) and synovial membranes (Smith *et al.*, 2011). The study found that patients with RA had significantly higher serum Metrnl values. Rheumatoid Factor (RF), C-Reactive Protein (CRP), and Disease Activity Score 28 (DAS28) all show positive correlations with these elevated levels of Metrnl. This association highlights the role that Metrnl plays in the development and course of RA (Zhang *et al.*, 2022). Moreover, the clinical activity of RA is closely linked to the elevation of serum Metrnl levels. This establishes Metrnl as a key player in the pathophysiological processes of RA as well as a possible biomarker and therapeutic target for next RA management initiatives (Zhang *et al.*, 2022).

Periodontitis and the role of immune cells in bone destruction

The chronic inflammatory illness known as periodontitis is typified by the immune system destroying the bone surrounding the teeth. By upregulating RANKL expression, pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6 which are generated by T cells, dendritic cells, and macrophages promote osteoclastogenesis. Th17 cells play a key role by secreting IL-17, which further promotes RANKL-mediated bone resorption. Additionally, B cells and plasma cells contribute by producing inflammatory cytokines and autoantibodies that exacerbate tissue destruction. The persistent immune activation disrupts the balance between osteoclast and osteoblast activity, leading to progressive alveolar bone loss, a hallmark of severe periodontitis. Histological examination in the 1970s showed that donors with periodontitis had active T and B cells as well as the acquired immune system (Wu *et al.*, 2024). In comparison to healthy controls, periodontal

tissue had higher levels of plasma cells, naive B cells, neutrophils, and activated CD4 memory T cells, according to a recent study (Li *et al.*, 2020). Human peripheral blood cells from individuals with periodontitis were introduced into NOD/SCID mice in order to measure T cell participation. Through RANKL-mediated osteoclast activation, *Actinomyces comitans* stimulated CD4+ T cells, causing alveolar bone degradation (Usui *et al.*, 2021). Th17 cells, one of the CD4+ T cell subsets that produce IL-17, increased in periodontal tissues, whereas Th17-deficient animals showed a suppression of periodontitis. Notably, the majority of tissue damage was caused by Treg-derived Foxp3-negative IL-17+ cells (Crawford *et al.*, 2020). In the periapical tissues of severely damaged teeth, Foxp3+ and IL-17+ cells were consistently seen (Galler *et al.*, 2021).

Chronic inflammation and its effect on bone turnover

Chronic inflammation disrupts bone homeostasis by promoting excessive bone resorption and impairing bone formation (Figure 5). Increased osteoclastogenesis and bone resorption result from the stimulation of RANKL expression by pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. By inhibiting Wnt signalling and raising levels of DKK1 and sclerostin, which are negative regulators of bone formation, inflammation simultaneously prevents osteoblast differentiation. Persistent immune activation, as seen in conditions like rheumatoid arthritis and osteoporosis, skews the balance towards bone loss, reducing bone density and increasing fracture risk. Thus,

targeting inflammatory pathways may help restore bone turnover equilibrium (Terkawi *et al.*, 2022).

Immune System Dysregulation and Bone Disorders

Osteoporosis: Immune dysregulation as a key factor in bone loss

Osteoporosis is increasingly recognized as an immune-mediated condition where dysregulation of immune cells and cytokines contributes to excessive bone loss (Figure 6). Pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 enhance RANKL expression, promoting osteoclast differentiation and bone resorption. Additionally, Th17 cells produce IL-17, which further drives osteoclastogenesis while inhibiting osteoblast function. Meanwhile, reduced Treg activity leads to insufficient suppression of bone-destructive inflammation. Chronic immune activation, as seen in aging, autoimmune diseases, and chronic infections, disrupts bone homeostasis, increasing fracture risk. Targeting immune pathways offers a potential therapeutic approach for osteoporosis management (Saxena *et al.*, 2021). It has long been believed that osteoporosis is a sign of a dysregulated bone remodelling process that is primarily controlled by oestrogen levels. However, new developments in the field have now unequivocally demonstrated the immune system's critical involvement in regulating inflammatory bone loss in osteoporotic disorders, such as Immunoporosis (Wang *et al.*, 2023). One of the most intriguing areas of immunoporosis study is immunomodulatory checkpoints and molecules that mediate the autocrine, paracrine, and endocrine interaction among the bone cells in osteoporosis. The distinct functions and adaptability

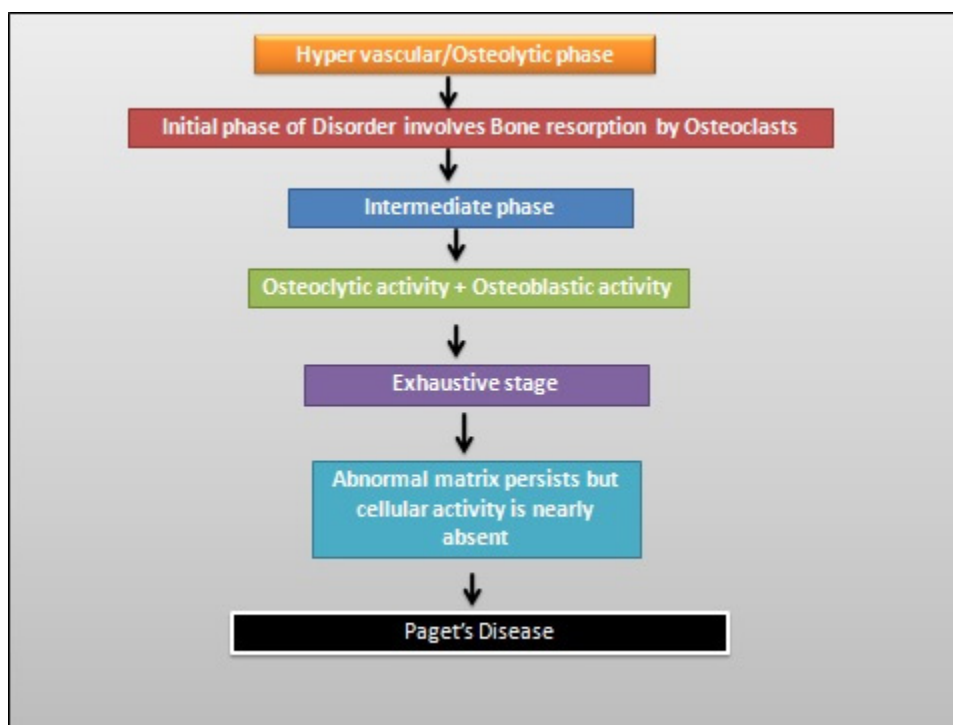


Figure 8: Pathogenesis of Paget's Disease.

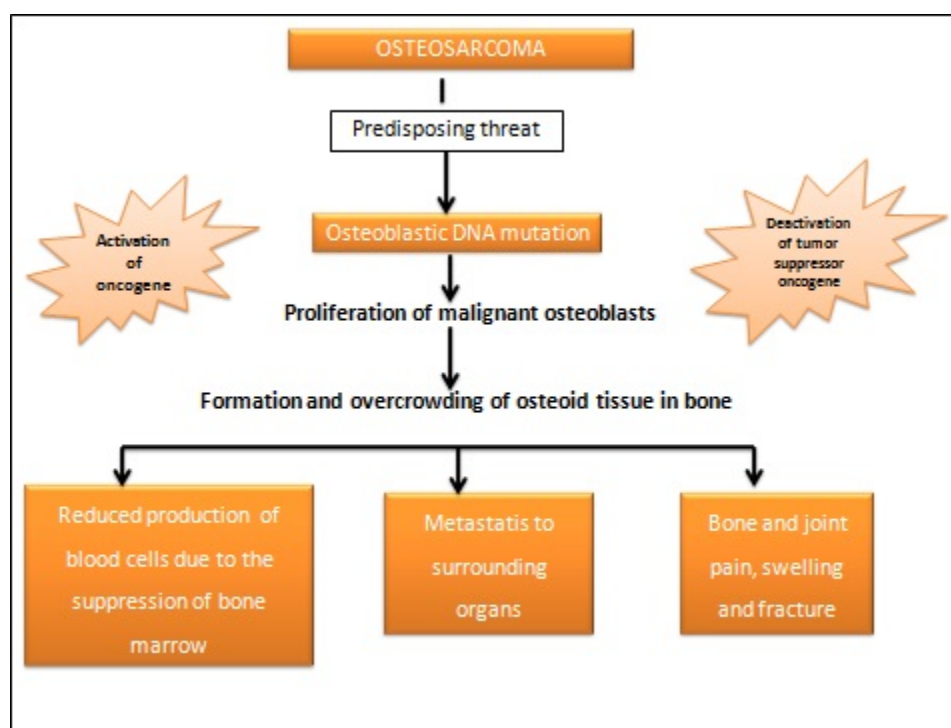


Figure 9: Pathogenesis of Osteosarcoma.

of diverse innate and adaptive immune cells are highlighted in later parts, along with their applicability in various bone pathological diseases, such as osteoporosis, and new therapeutic prospects for clinical interventions (Srivastava *et al.*, 2022). As the host's first line of defence against any invasive infections, innate immune cells are also the main source of pro-inflammatory mediators, which serve as catalysts for the emergence of several bone diseases, including osteoporosis. According to a study, because Mφs, OCs, and DCs all have a common progenitor, they are clinically significant cells. In addition, granulocytes, Natural Killer (NK) Cells, and Innate Lymphoid Cells (ILCs) all contribute to osteoporosis development by generating different inflammatory mediators (Saxena *et al.*, 2021).

Autoimmune diseases and their impact on bone metabolism

Autoimmune diseases significantly disrupt bone metabolism by altering the balance between bone resorption and formation. RANKL-mediated osteoclastogenesis is promoted by chronic inflammation in diseases such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, which causes excessive osteoclast activation through increased TNF-α, IL-1β, IL-6, and IL-17 (Skubica *et al.*, 2023). Simultaneously, impaired Wnt and BMP signaling reduces osteoblast differentiation, hindering bone formation. Additionally, dysregulated Tregs fail to suppress inflammatory bone loss, while excessive Th17 responses exacerbate osteoclast activity. This immune-mediated imbalance increases the risk of osteoporosis and fractures, making immune-targeted therapies a potential

strategy for preserving bone health in autoimmune conditions (Maeda *et al.*, 2019).

The role of inflammatory mediators in diseases like osteoarthritis, Paget's disease, and bone cancer

Osteoarthritis (OA)

The slow deterioration of articular cartilage, frequently coupled with synovial membrane inflammation, is the hallmark of Osteoarthritis (OA) (Figure 7). Macrophages, synovial cells, and chondrocytes all emit pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. These cytokines promote the degradation of cartilage matrix by upregulating matrix Metalloproteinases (MMPs) and inhibiting cartilage repair. Additionally, they stimulate the formation of osteophytes and subchondral bone changes, further exacerbating joint dysfunction. The inflammatory response in OA also leads to synovitis, which can amplify the progression of cartilage breakdown and increase pain through the sensitization of nociceptors (Xue *et al.*, 2023). Patients with Rheumatoid Arthritis (RA) experience progressive articular bone and cartilage deterioration, leading to disability and increased morbidity due to systemic and periarticular bone loss. Unlike other rheumatic disorders, inflammation in RA causes both periarticular bone demineralization and articular bone erosion due to excessive bone resorption and inadequate bone formation (Shim *et al.*, 2018). Disease-modifying drugs, including biologics and small compounds, have made significant progress in reducing inflammation and preventing osteoclastogenesis, thereby stopping RA-related bone loss. However, existing bone erosions rarely repair, as mechanisms promoting bone

resorption also suppress osteoblast activity and bone creation. Bone remodeling involves a balance between Osteoclasts (OCs) and Osteoblasts (OBs), with RANKL promoting OC formation and function, while Osteoprotegerin (OPG) inhibits RANKL binding to RANK, regulating OC activity (Ben Mrid *et al.*, 2022). Proinflammatory cytokines like TNF- α and IL-6 contribute to OC generation, bone resorption, and osteoblast inhibition in RA. IL-6 is prevalent in serum and synovial fluid, driving joint destruction and bone erosion. RA patients show lower bone density and higher osteoporosis prevalence, with RANKL expression and OC formation linked to autoimmune reactions (Llorente *et al.*, 2020). Early-stage peri-inflammatory bone loss and osteitis are predictors of erosive bone deterioration, while nonhealing erosions result from decreased bone production, exacerbating inflammation and bone loss. Elevated RANKL expression in RA synovium is a key driver of inflammatory bone destruction, with OCs playing a central role in the disease pathophysiology (Panagopoulos *et al.*, 2018).

Paget's Disease

Excessive and disordered bone resorption followed by compensatory bone production are hallmarks of Paget's disease, a chronic condition of bone remodeling (Figure 8). The primary cause of the disease is aberrant osteoclast activity, and inflammatory mediators like RANKL and IL-6 are essential to this process. RANKL is essential for osteoclast differentiation and activation, and its overexpression in Paget's disease leads to hyperactive osteoclasts that resorb bone at an accelerated rate (Banaganapalli *et al.*, 2023). By encouraging osteoclastogenesis

and upsetting the natural equilibrium between bone formation and resorption, IL-6, a crucial pro-inflammatory cytokine, also plays a role in the disease. This imbalance results in weaker, larger bones that are more likely to break and develop abnormalities. Localised regions of excessive bone remodelling, with anomalies at every stage of the process, are the hallmark of Paget Disease of bone (PD), the second most common bone disease after osteoporosis (Zhou *et al.*, 2022). Osteoblasts rapidly produce new bone, but it is weak and asymmetrical. This cycle leads to enlarged, misshapen bones prone to fractures and deformities, particularly in the pelvis, spine, skull, and long bones. Genetic mutations like SQSTM1 and possible viral triggers contribute to the disease. Most people who are diagnosed with Parkinson's Disease (PD) are older, typically over (Miao *et al.*, 2021). Males are slightly more likely than females to be affected. 10-30% of patients with Parkinson's disease (Figure 5) have pain, skeletal deformities, neurologic symptoms, pathologic fractures, or hearing, despite the fact that PD is frequently asymptomatic (Zirra *et al.*, 2022).

Bone Cancer

In bone metastasis or primary bone cancers such as osteosarcoma (Figure 9), inflammatory mediators like Prostaglandin E2 (PGE2), IL-11, and TNF- α are implicated in driving bone destruction. Tumor cells often secrete these inflammatory molecules to create a favorable microenvironment for their growth. For instance, PGE2 enhances osteoclast activity by promoting the expression of RANKL, which in turn activates osteoclasts to resorb bone. IL-11 also promotes osteoclastogenesis and bone resorption, while TNF- α contributes to both the local inflammation and

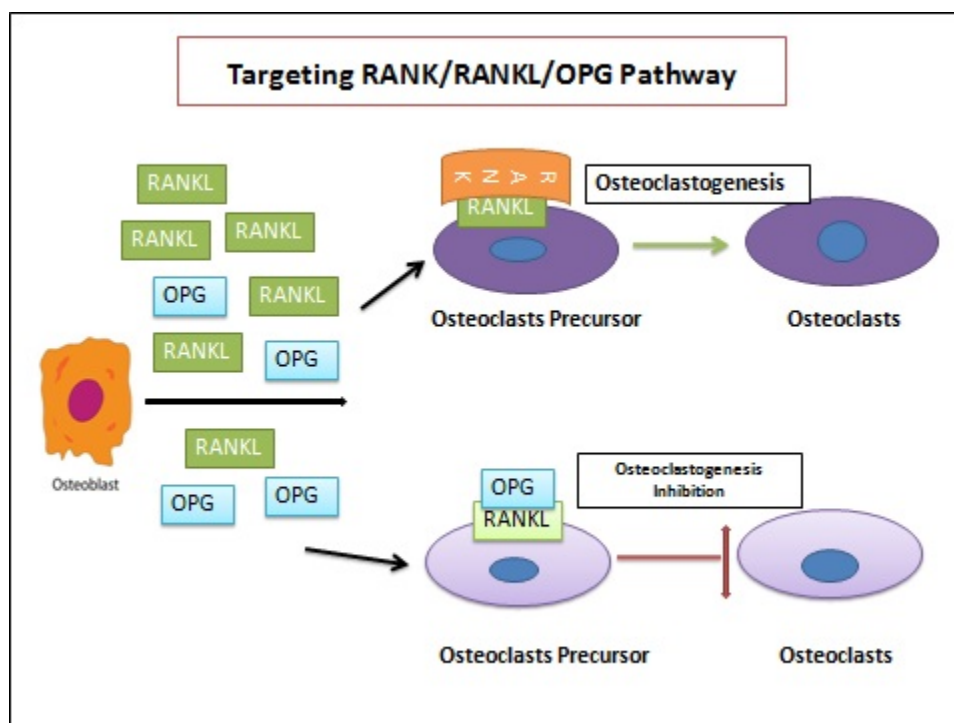


Figure 10: Targeting Rank/Rankl/Opg Pathway.

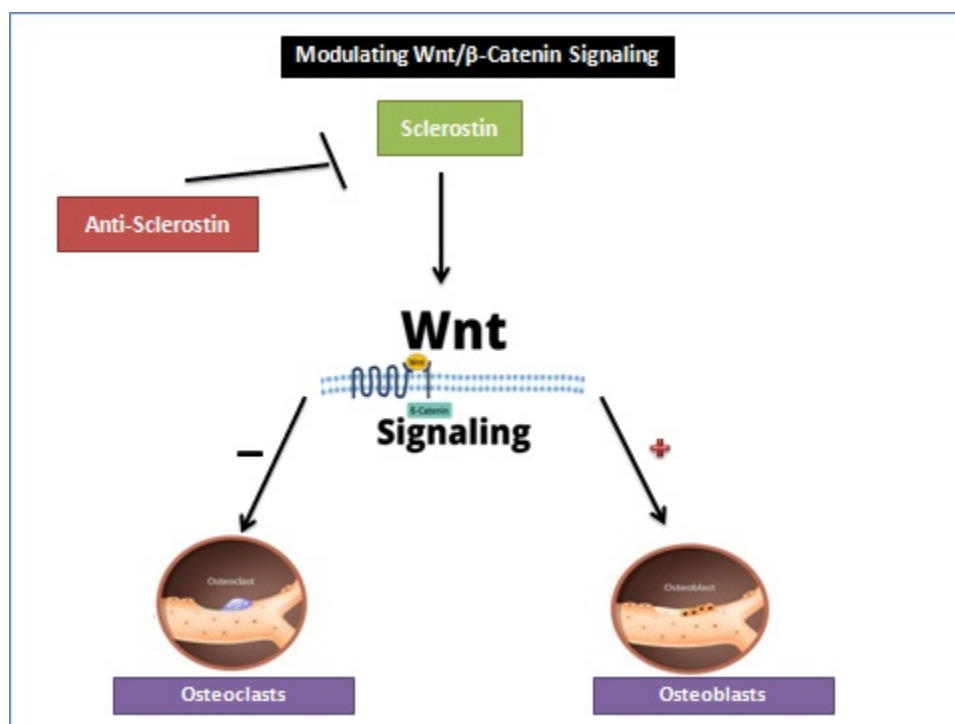


Figure 11: Modulating Wnt/β-Catenin Signaling.

the bone loss associated with the disease (Jing *et al.*, 2023). In addition to promoting osteoclast-mediated resorption, these inflammatory mediators can induce a vicious cycle of bone destruction, where bone loss further facilitates tumor growth and metastasis. Inflammatory mediators like VEGF, TNF- α , and IL-6 exacerbate pro-tumorigenic settings, which might hinder anti-tumor immunity by attracting immune-suppressive cells such as regulatory T cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs) (Maurizi *et al.*, 2018). Hypoxia within the TME further activates Hypoxia-Inducible Factors (HIFs), driving angiogenesis and metabolic reprogramming. Since this dysregulation not only encourages cancer development and metastasis but also lessens the efficacy of conventional therapy, strategies that target these aberrant signalling networks must be developed (Zhuang *et al.*, 2023). Osteoclast activation plays a key role in the formation and spread of bone metastases, promoting tumor growth and bone deterioration. Cancer cells release RANKL, PTHrP, and TGF- β , which stimulate osteoclasts and increase bone resorption. As osteoclasts break down bone, growth factors like IGFs and TGF- β stored in the bone matrix are released, further fueling the process. These growth factors further promote the survival and multiplication of tumour cells. This creates a feedback loop where bone resorption feeds tumor growth, and the tumor amplifies osteoclast activity. This process not only results in osteolytic lesions, characterized by bone destruction, but also contributes to skeletal-related complications such as fractures, pain, and hypercalcemia (Russo *et al.*, 2022). Targeting osteoclast activity using drugs like bisphosphonates or RANKL inhibitors (e.g., denosumab) has become a key therapeutic strategy in managing

bone metastases, aiming to break this destructive cycle and reduce skeletal morbidity. More knowledge of the molecular processes controlling osteoclast activation, however, may result in better therapies for patients with bone metastases (Liu *et al.*, 2024). Table 1 highlights emerging immunopharmacological targets beyond classical anti-resorptive therapy, emphasizing translational opportunities for drug development in bone disorders.

Potential Therapeutic Strategies Targeting Immune System and Bone Turnover

Targeting RANK/RANKL/OPG Pathway

The RANK/RANKL/OPG pathway regulates bone remodeling by balancing bone resorption and formation (Zhang *et al.*, 2022). RANKL, expressed by stromal and osteoblast cells, binds to RANK on osteoclast precursors, promoting osteoclastogenesis and bone resorption. Osteoblasts release Osteoprotegerin (OPG), which inhibits RANKL binding to RANK, reducing osteoclast activity and preserving bone mass. Dysregulation of this pathway is linked to bone diseases like osteoporosis, rheumatoid arthritis, and bone metastases, where excessive RANKL activity leads to bone loss. A possible treatment strategy is to target the RANK/RANKL/OPG pathway (Takegahara *et al.*, 2022). At the end of the previous millennium, it was discovered that the receptor-ligand pairs of the TNF receptor superfamily, RANK (TNFRSF11A, OFE, ODFR, TRANCE-R, ODAR, CD265) (Ming *et al.*, 2020) and RANKL (TNFSF11, TRANCE, ODF, and OPGL), were significant regulators of osteoclast production and bone metabolism (De Leon-Oliva *et al.*, 2023). Among the substances that may contribute to bone resorption

include progesterone, vitamin D3, PTHrP, IL-1, IL-11, IL-17, and TNF- α (Umur *et al.*, 2024). In order to cause preosteoclasts to mature into multinucleated, fully functioning osteoclasts, these substances act on osteoblasts to create RANKL, which attaches to its receptor RANK on the surface of osteoclast progenitor cells. Additionally, RANKL is crucial for osteoclasts ongoing survival and functionality (Figure 10) (Takegahara *et al.*, 2022). RANKL can be released as a soluble trimeric protein (Munasinghe *et al.*, 2017), but it is first generated as a membrane-bound protein. In mice produced with sheddase-resistant RANKL, soluble RANKL is not detected in the blood. Although these mice's bone mass or structure remained unchanged during development, adult mice showed more cancellous bone density and fewer osteoclasts. Crucially, the absence of soluble RANKL had no effect on the bone loss brought on by oestrogen deprivation (Xiong *et al.*, 2018). These findings thus demonstrate that while the soluble version of RANKL can aid in bone remodelling in adult mice. The physiological effects of the protein are mostly caused by its membrane-bound form (Ono *et al.*, 2020). Osteoprotegerin (OPG, TNFRSF11B), a RANKL decoy receptor, can be increased by oestrogen, IL-4, or Transforming Growth Factor beta (TGF- β). OPG competitively binds to RANKL to inhibit bone resorption

and disrupt RANKL-RANK interactions (De Leon-Oliva D *et al.*, 2023). To maintain healthy bone, the proportions of OPG and RANKL are carefully regulated. For example, denosumab, a monoclonal antibody against RANKL, is frequently used to treat osteoporosis and metastatic bone disorders because it efficiently inhibits osteoclast-mediated bone resorption. The most recent antiresorptive drug, denosumab, has a distinct way of working (Yasuda *et al.*, 2021). A completely human monoclonal antibody called briedenosumab helps control turnover in healthy bone by blocking RANKL. Bone resorption slows down and osteoclast recruitment, maturation, and activity are reduced as a result of denosumab's high specificity and affinity for the cytokine RANKL. Denosumab is administered to postmenopausal women with osteoporosis who are at high risk of fracture, as well as to patients who have not responded to or are intolerant of conventional osteoporosis treatments (Zhang *et al.*, 2020). Denosumab is recommended as a first-line treatment for preventing hip, non-vertebral, and vertebral fractures in the OC Clinical Practice Guidelines. The creation of innovative treatments meant to restore bone homeostasis is still influenced by our growing understanding of the molecular complexities of this pathway (Lamy *et al.*, 2025).

Table 1: Immunoregulatory Drug Targets and Pharmacological Compounds Modulating Bone Pathophysiology.

Immune Target / Pathway	Role in Bone Remodeling	Key Drugs / Compounds	Status	Disease Relevance
RANK-RANKL	Osteoclast differentiation & resorption	Denosumab	Approved biologic	Osteoporosis, RA, cancer bone loss
TNF- α	Inflammation-induced bone erosion	Infliximab, Etanercept, Adalimumab	Approved biologics	RA, inflammatory bone loss
IL-6 / IL-6R	↑ Osteoclastogenesis, ↓ osteoblasts	Tocilizumab, Sarilumab	Approved biologics	RA-associated erosion
IL-17	Th17-mediated bone destruction	Secukinumab, Ixekizumab	Approved biologics	SpA, psoriatic arthritis
NF- κ B	Inflammatory osteoclast activation	Bortezomib, Curcumin	Approved / investigational	Osteolytic disease
JAK-STAT	Cytokine-driven immune-bone crosstalk	Tofacitinib, Baricitinib	Approved small molecules	RA-related bone damage
PD-1 / PD-L1	Checkpoint-regulated osteoclast activity	Nivolumab, Pembrolizumab	Approved (oncology)	Cancer bone remodeling
CTLA-4	T-cell-mediated bone resorption	Abatacept	Approved biologic	RA bone loss
mTOR / AMPK	Immunometabolic control of bone turnover	Metformin, Rapamycin	Approved / investigational	Osteoporosis, aging bone
Trained immunity	Epigenetic-driven inflammation	HDAC, BET inhibitors	Investigational	Chronic inflammatory bone disease
SASP pathways	Senescence-driven bone degeneration	Dasatinib + Quercetin	Investigational	Osteoporosis
Natural modulators	Cytokine & oxidative stress control	Flavonoids, Curcumin	Preclinical / nutraceutical	Metabolic bone loss

Modulating Wnt/B-Catenin Signaling

By maintaining a balance between osteoblast activity (bone creation) and osteoclast activity (bone resorption), the Wnt/ β -catenin signalling system controls bone remodeling (Figure 11). When Wnt ligands attach to osteoblast precursors' Frizzled receptors and co-receptors, such as LRP5/6, β -catenin builds up in the cytoplasm and moves into the nucleus, where it stimulates the production of osteoblast genes. Wnt signalling is divided into two branches: the β -catenin-independent (non-canonical) pathway, which does not need β -catenin transcriptional activity, and the β -catenin-dependent (canonical) system, which depends on β -catenin (Hu *et al.*, 2024). Another name for the canonical Wnt signalling route is the Wnt/ β -catenin signalling pathway. The Wnt/calcium (Ca^{2+}) route and the Wnt/PCP pathway are the two primary types of non-canonical Wnt signalling pathways. Signal transduction is triggered in different ways by Wnts in these pathways. Other proteins, include Norrin proteins (Najafi *et al.*, 2020) and R-spondin (RSpo) proteins (TerSteege *et al.*, 2021), which belong to two distinct families of growth factors, have been identified as activating Wnt signalling in addition to Wnts. Furthermore, it is shown that FOXB2, an unidentified transcription factor belonging to the forkhead box family, and Strong activators that promote Wnt signaling include Microtubule Actin Crosslinking Factor 1 (MACF1), a multifunctional spectraplakins (Moparthy *et al.*, 2023). The bulk of the secreted inhibitors are composed of six families: the Dkk protein family, secreted Frizzled related proteins (sFRPs) (Zhang *et al.*, 2023), Wnt Inhibitory Factor 1 (WIF-1) (Poggi *et al.*, 2018), Wise, Sclerostin (SOST) (Kim *et al.*, 2020) insulin-like growth factor binding protein 4 (IGFBP-4) (Wang *et al.*, 2023) and Cerberus (Azbazdar *et al.*, 2023). One hundred Sclerostin is produced by the *Sost/SOST* gene, which is located on the human chromosome between 17q12 and q21 (Yu *et al.*, 2022). Osteocytes express this glycoprotein (Thompson *et al.*, 2015). Sclerostin was once believed to be an antagonist of Bone Morphogenetic Protein (BMP) signalling because it lowers BMP signalling and competes with type I and type II BMP receptors for binding to BMPs. Later research, however, shows that it is also an antagonist/inhibitor of Wnt signalling by binding to Wnt co-receptors LRP5 and LRP6 (Ren *et al.*, 2021) and preventing the formation of the Wnt-receptor complex. Additionally, sclerostin's inhibitory effect on Wnt signalling is facilitated by LRP4, another member of the LRP family (Katchkovsky *et al.*, 2022). Sclerostin has been shown to both paracrinely and autocrinely inhibit Wnt signalling transduction in osteoblasts and osteocytes (Gao *et al.*, 2023). The Wnt/ β -catenin pathway is dysregulated in disorders like osteoporosis, osteogenesis imperfecta, and osteosarcoma. Suppression of the pathway leads to bone loss and increased fracture risk, while hyperactivation causes excessive or abnormal bone growth. Therapeutic modulation of this pathway shows potential, with small molecules, monoclonal antibodies, and biologics being developed to enhance osteoblast activity or

inhibit osteoclastogenesis (Wang *et al.*, 2024). For example, romosozumab, an antibody blocking sclerostin (a Wnt antagonist), promotes bone growth and reduces fracture risk in osteoporosis by increasing bone formation and reducing resorption. These treatments improve bone mineral density and lower fracture risk. Romosozumab has demonstrated effectiveness in enhancing hip and spinal bone mineral density and averting fractures. However, its use requires caution due to potential cardiovascular risks, making it suitable for high-risk individuals or those unresponsive to other treatments (Wu *et al.*, 2023). Further exploration of this pathway continues to provide valuable insights for designing novel treatments aimed at maintaining or restoring bone health (Vermeulen *et al.*, 2022).

Anti-Inflammatory Therapies

Inflammation-induced disruption of bone remodeling often leads to bone loss and disorders like osteoporosis, rheumatoid arthritis, and periodontitis. Cytokines and growth factors are released by inflammatory cells such neutrophils, lymphocytes, and macrophages. These substances control cell communication, encourage migration to damage sites, and aid in the healing processes of angiogenesis, fibrosis, and extracellular matrix production (Torres *et al.*, 2023). A crucial part of the healing cascade, cytokine expression peaks in the first 24 hr following a fracture and subsequently declines as cartilage develops (Maruyama *et al.*, 2020). Cytokine expression increases again during the bone remodelling phase (Row *et al.*, 2022). Pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α promote osteoclastogenesis and tip the scales in favour of bone resorption by upregulating RANKL expression and suppressing osteoblast activity. In general, a number of inflammatory cytokines, such as Interleukin-1 α (IL-1 α), IL-1 β , IL-6, IL-18, and Tumour Necrosis Factor alpha (TNF- α), are produced in response to bone fractures. The release of these cytokines is controlled by both time and location (Zhou *et al.*, 2022). The inflammatory response that initiates osteogenesis depends on the expression of these cytokines. Tumour necrosis factor alpha stimulates osteoclasts, causes hypertrophic chondrocytes to undergo apoptosis, and encourages the recruitment of MSCs. Animals lacking the tumour necrosis factor alpha receptor exhibit noticeably slower bone repair, with delayed resorption of mineralised cartilage that prevents the creation of new bone (Daniele *et al.*, 2017). Immunosuppression of the Th-1 pathway, which is regulated by a reduction in Interleukin-12 (IL-12), has been linked in several studies to femur fractures. The key to regaining the immune system's capacity to combat infection in a traumatized setting may lie in IL-12, the gatekeeper for innate immunity (Wang *et al.*, 2025).

Using an open femur fracture model (Lee *et al.*, 2020), shown that systemic IL-12 therapy may be used to immunomodulate the environment and really induce bone regeneration in mice (Yang *et al.*, 2021). The significance of a single cytokine in fracture

healing has been the subject of numerous research; nevertheless, these components are part of a complex physiological system that involves a great deal of feedback and cross-talk. Anti-inflammatory therapies aim to restore this balance by targeting inflammatory mediators or signaling pathways involved in bone metabolism. In diseases like rheumatoid arthritis, drugs like IL-6 blockers (like tocilizumab) (Frade *et al.*, 2023) and TNF- α inhibitors (like etanercept and infliximab) (Gerriets *et al.*, 2023) have demonstrated effectiveness in lowering inflammation and maintaining bone density. TNF- α , a key mediator in conditions like rheumatoid arthritis, promotes osteoclastogenesis by enhancing RANKL expression and suppressing osteoblast activity resulting in decreased bone production and increased bone resorption. TNF- α inhibitors, such as etanercept and infliximab, effectively reduce inflammation, alleviate symptoms, and preserve bone density by directly targeting and neutralizing TNF- α . Similarly, IL-6, another pro-inflammatory cytokine, contributes to osteoclast activation and bone loss in diseases like osteoporosis and arthritis. IL-6 blockers, such as tocilizumab, inhibit IL-6 signaling, thereby reducing osteoclast-mediated bone resorption and inflammation (Luo *et al.*, 2018). These biologic therapies not only improve clinical outcomes in inflammatory bone diseases but also help prevent long-term structural damage by restoring the equilibrium between bone production and resorption. Furthermore, in addition to pharmaceuticals like corticosteroids and Nonsteroidal Anti-Inflammatory Medications (NSAIDs), natural substances like curcumin and omega-3 fatty acids, also modulate inflammatory responses, indirectly benefiting bone health (Xu *et al.*, 2023). By addressing the inflammatory component of bone disorders, these therapies contribute to the maintenance of skeletal integrity and offer significant potential in the management of bone remodeling diseases (Epsley *et al.*, 2021).

Emerging Therapies: Stem Cells and Gene Therapy

Stem cell-based approaches for regenerating bone via immune modulation

Stem cell-based approaches for bone regeneration through immune modulation leverage Mesenchymal Stem Cells (MSCs) to both repair damaged bone and regulate immune responses. MSCs differentiate into osteoblasts to promote bone formation and modulate the immune environment by suppressing inflammation (Shang *et al.*, 2021). They achieve this by enhancing regulatory T cells (Tregs) activity and altering macrophage and dendritic cell function, thereby reducing pro-inflammatory cytokines like TNF- α and IL-6. This creates a favorable environment for bone regeneration. MSC-based therapies, particularly for osteoporosis and rheumatoid arthritis, also show promise when combined with biomaterials that support tissue healing and cell integration, further enhancing regenerative outcomes (Li *et al.*, 2022).

Gene editing (CRISPR) for targeting immune-related bone turnover pathways

Gene editing technologies like CRISPR offer a precise method for targeting immune-related bone turnover pathways. By modifying genes involved in bone resorption and formation, such as the RANK/RANKL/OPG signaling pathway, CRISPR can reduce excessive RANKL expression, which contributes to osteoclast activation and bone loss in inflammatory diseases. Additionally, CRISPR can target inflammatory genes like TNF- α , IL-6, and IL-17, reducing inflammation-driven bone destruction. It can also modulate immune cells like Tregs and dendritic cells to restore immune balance and promote bone health. Furthermore, CRISPR can enhance the regenerative potential of stem cells by optimizing their differentiation into osteoblasts, offering promising treatments for immune-related bone diseases (Chehelgerdi *et al.*, 2024).

FUTURE DIRECTIONS AND CHALLENGES

Future research in immune regulation of bone turnover should focus on personalized immunotherapy for bone-related disorders, leveraging advances in precision medicine to tailor treatments based on individual immune profiles. Understanding the role of immune cells and cytokines in bone remodeling across different patient populations, including those with osteoporosis, rheumatoid arthritis, and metabolic bone diseases, will be crucial for developing targeted therapies. Additionally, exploring immune-bone interactions in aging and age-related bone loss could provide insights into novel interventions for osteoporosis and fracture prevention. Despite significant progress, challenges remain in translating immune system research into clinical therapies, such as optimizing immune (Aljabali *et al.*, 2024).

CONCLUSION

With immune cells, cytokines, and signalling pathways preserving a balance between bone creation and resorption, immune modulation is essential to bone turnover. While regulatory T cells and dendritic cells aid in preserving bone homeostasis, pro-inflammatory cytokines such as TNF- α , IL-6, and IL-17 stimulate osteoclast activity. Osteoclastogenesis depends on the RANK/RANKL/OPG axis, and immunological dysregulation can result in bone diseases such as rheumatoid arthritis and osteoporosis. Targeting immune pathways offers therapeutic potential to reduce bone resorption and promote bone formation, with treatments like biologics, gene editing, and stem cell-based therapies showing promise. Future advancements in precision medicine and combined immune modulation with regenerative therapies hold the potential for more effective management of bone disorders.

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ABBREVIATIONS

MSC: Mesenchymal Stem Cells; **RANKL:** Receptor Activator of Nuclear Factor- κ B Ligand; **OPG:** Osteoprotegerin; **BMU:** Bone Multicellular Units; **TNF- α :** Tumor Necrosis Factor-alpha; **MSCs:** Mesenchymal Stem Cells; **PTHrP:** Parathyroid Hormone-Related Protein; **HSCs:** Haematopoietic Stem Cells; **TME:** Tumor Microenvironment; **RA:** Rheumatoid Arthritis; **OA:** Osteoarthritis; **PD:** Paget's Disease; **Tregs:** Regulatory T Cells; **BMPs:** Bone Morphogenetic Proteins.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Kaniga Pandi, Yokesh Shanmugam, MahaSwetha Kannuchamy, Arunpandiyan Jeyakumar, Inigo Pathuvairajan - "Writing", **Binoy Varghese Cheriyan, Jubilee Ramsamy, Mathesvaran Thirunavukarasu** - "Data Curation". **Sudharshini Srinivasan, Praveen Kumar Ramesh, Bhuvanesh Raj, Preethi Harikrishnan, Sharmila Sakthisivanandhan** - "Conceptualization".

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