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REVIEW

Osteoimmunology in Osteoarthritis: Unraveling the Interplay of Immunity, Inflammation, and Joint Degeneration

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Abstract: Osteoarthritis (OA) is a degenerative joint disease influenced by multiple factors, with its etiology arising from intricate interactions among mechanical stress, inflammatory processes, and disruptions in bone metabolism. Recent research in bone immunology indicates that immune-mediated mechanisms significantly contribute to the progression of OA, highlighting the interactions among immune cells, cytokine networks, and bone components. Immune cells interact with osteoclasts, osteoblasts, and chondrocytes in a variety of ways. These interactions foster a pro-inflammatory microenvironment, contributing to cartilage breakdown, synovial inflammation, and the sclerosis of subchondral bone. In this article, we present a comprehensive review of bone immunology in OA, focusing on the critical role of immune cells and their cytokine-mediated feedback loops in the pathophysiology of OA. In addition, we are exploring novel therapeutic strategies targeting bone immune pathways, including macrophage polarization, T-cell differentiation, and stem cell therapy to restore the metabolic balance between immunity and bone. By integrating cutting-edge research in bone immunology, this review integrates the latest advancements in bone immunology to construct a comprehensive framework for unraveling the pathogenesis of OA, laying a theoretical foundation for the development of innovative precision therapies.

Keywords: OA, bone immunity, immune cells, osteoclasts, chondrocytes

Introduction

The skeletal system, an important part of the musculoskeletal system, forms the body's contours, supports the body's scaffolding, and provides the attachment points for muscles. The bone marrow is abundant in hematopoietic stem cells, which create the milieu essential for the proliferation of these cells, enabling their differentiation into immune cells that perform immunological tasks.[1] The immune system comprises immunological organs, cells, and chemicals that collectively monitor, defend, and regulate the body's defense processes. Osteoblasts are essential for maintaining proper bone structure by regulating the balance between bone remodeling and resorption.[2] Bone remodeling and resorption are maintained in a delicate dynamic balance. Osteoimmunology, as a multidisciplinary field, bridges the immune and skeletal systems, reflecting their intricate interdependence. Given the shared regulatory networks of these systems, including overlapping cytokines and signaling molecules, they collaborate to mediate "bone immunity" and collectively influence both physiological processes and pathological conditions.[3] Osteoimmunology investigates the intricate interactions between the immune system and bone metabolism. This field provides valuable insights into the mechanisms underlying bone diseases and highlights the pivotal role of immune regulation in conditions such as OA, rheumatoid arthritis, and osteoporosis, paving the way for novel therapeutic approaches.

OA is a prevalent chronic joint disorder, marked by the degeneration of articular cartilage, synovial inflammation, and structural alterations in the subchondral bone. OA can cause pain in the patient's joints, affect joint movement, and, in the

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most severe cases, lead to disability.[4] According to epidemiological reports, over 500 million people worldwide suffer from OA, representing a heavy medical burden and seriously affecting public health.[5]

Immunology is central to the pathogenesis of OA, encompassing not only the breakdown of cartilage in the articular cartilage but also the inflammation of the synovium and the structural alterations in the bone. These processes are intricately linked to the dysregulated activation of the immune system. Inflammatory factors are secreted by infiltrating immune cells, promoting a chronic inflammatory response within the joints, accelerating osteoclast formation and activity, and inhibiting osteoblast proliferation and differentiation, resulting in bone loss.[6–8] Simultaneously, In addition to influencing the dynamic equilibrium of bone remodeling, osteoblasts are responsible for regulating the function of osteoclasts through the secretion of substances such as RANKL.[9] In addition, chondrocytes, the main component of articular cartilage, release pro-inflammatory factors after injury, exacerbating synovial cell activation and inflammation, forming a vicious circle.[10] In addition, synoviocyte proliferation and the inflammatory response can directly affect the function of chondrocytes and osteocytes.[11] By the secretion of molecules like RANKL, the interaction between synoviocytes and chondrocytes regulates the bone remodeling process, thus affecting overall joint health. This interplay between immunity and bone metabolism reveals the key role of osteoimmunology in OA, and understanding the mechanism not only helps to elucidate the pathophysiological process of OA, Furthermore, it offers a promising theoretical foundation for the development of innovative therapeutic strategies designed to alleviate pain and enhance joint function in patients with OA.

Osteoimmunology: Interactions Between the Skeletal and Immunological Systems

Osteoimmunology is a multidisciplinary field focused on exploring the complex interactions between the skeletal and immune systems, highlighting their multifaceted interactions and mutual influences, a dynamic relationship known as the "immune-bone axis". Signaling pathways along this axis are involved in normal bone remodeling but also accelerate bone destruction or abnormal bone production under pathological conditions. As early as 1983, Research has demonstrated that cells from both the innate and adaptive immune systems establish a paracrine environment that governs osteoclast genesis and subsequent bone resorption. It was further demonstrated that human peripheral blood leukocytes secrete osteoclast-activating factors, underscoring a significant connection between the immune and skeletal systems.[12] In 2000, The term "osteo-immunology" was initially proposed by Arron and Choi to emphasize the interplay between the skeletal and immune systems, encompassing many cells, mediators, and signaling pathways involved in intercellular communication.[13] The bone marrow plays a pivotal role in bone immunology, acting as the origin of both osteoblasts and immune cells. Within the bone marrow microenvironment, hematopoietic stem cells give rise to various immune cell lineages, including monocytes, macrophages, dendritic cells, T cells, B cells, and natural killer (NK) cells, underscoring its central function in maintaining immune and skeletal homeostasis. Osteoclasts arise through the differentiation of monocytes and macrophages, whereas osteoblasts are formed from bone marrow mesenchymal stem cells (MSCs). Situated in the medullary cavity, the bone marrow harbors diverse immune cells, while osteoblasts remain localized along the bone surface. Consequently, the skeletal and immunological systems coexist within the same microenvironment, sharing an extensive array of cytokines and signaling molecules that mediate their interactions.[14] Immune cells, interact with skeletal cells through both direct and indirect mechanisms, thereby influencing overall bone homeostasis.

Immunomodulation of Osteoclasts

Osteoclasts are cells that facilitate bone resorption and originate from multifunctional hematopoietic stem cells, mostly myeloid progenitor cells or bone marrow-derived macrophages.[15] Osteoclasts serve as the primary drivers of bone resorption. Myeloid progenitor cells can diverge into bone marrow macrophages or osteoclasts, depending on diverse extracellular cues. In turn, these macrophages have the potential to mature further into osteoclasts when exposed to certain environmental triggers, underscoring the dynamic interplay between immune and skeletal systems. Myeloid progenitor cells enhance the expression of transcription factor PU.1 and Microphthalmia transcription factor (Mitf), leading to increased M-CSF receptor levels and the induction of M-CSF binding to c-Fms. This interaction subsequently

upregulates RANK (Receptor Activator of Nuclear Factor-κB) expression on these cells, promoting their differentiation into osteoclast precursors.[16] RANK is a membrane-bound receptor in the tumor necrosis factor (TNF) receptor superfamily. It is predominantly expressed by both osteoclast progenitors and mature osteoclasts, where it orchestrates their differentiation and function.[17] RANK interacts with its ligand, RANKL, and recruits the adaptor protein TRAF6, a TNF receptor-associated factor. This recruitment activates several signaling pathways, including the mitogen-activated protein kinase (MAPK) family, the inhibitor of nuclear factor-κB kinase (IKK) complex, and the PI3K pathway. These cascades ultimately activate essential transcription factors like NF-κB, c-Fos, and c-Jun.[18–20] The activation of these transcription factors modulates nuclear factor of activated T cells c1 (NFATc1), hence facilitating osteoclast genesis.[21] In addition to macrophages, which express RANK and can act directly as osteoclast precursors, dendritic cells also express RANK, and immune cells such as T cells, B cells, and NK cells are able to secrete the NF-κB receptor activator, RANKL, which binds to RANK and stimulates osteoclast formation under certain conditions.[22,23]

T cells do not directly enhance RANKL expression but instead secrete various cytokines, such as IFN-γ, IL-2, and TNF-α, driving their polarization into distinct subtypes, including Th1, Th2, and Th17 cells. Th2 cells predominantly secrete cytokines such as IL-4, IL-5, IL-9, IL-10, and IL-13, while Th17 cells are characterized by their production of IL-17. These cytokines influence immune responses and contribute to the regulation of bone metabolism. These immunological cytokines influence osteoblast differentiation and formation. TNF-α, secreted by Th1 cells, directly stimulates macrophages to enhance RANK expression while simultaneously acting on stromal cells to promote increased production of RANKL.[24] TNF-α can increase RANKL production. Furthermore, TNF-α can activate multiple signaling pathways and promote synergistic effects between M-CSF and RANKL to promote osteoclast genesis.[25] Th17 cells, as key immune components within the bone marrow, facilitate the recruitment of monocytes as osteoclast precursors and actively promote osteoclast genesis.[26] The cytokine IL-17, secreted by Th17 cells, stimulates osteoblasts and other cells to increase RANKL production. Additionally, IL-17 amplifies the local inflammatory microenvironment by promoting the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-23 at the site of inflammation. These factors collectively enhance RANKL expression and drive RANKL-mediated osteoclast differentiation, contributing to bone resorption and tissue degradation.[27] While IFN-γ secreted by Th1 cells can stimulate osteoclast genesis through T cell activity, it paradoxically inhibits osteoclast genesis by activating the classical JAK-STAT1 pathway. This activation augments the ubiquitin-proteasome pathway, resulting in the degradation of the ubiquitin ligase TRAF6. The diminished activity of TRAF6 subsequently impairs downstream signaling pathways, such as NF-κB and STAT, thereby inhibiting osteoclast genesis.[28,29] Th2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13, all type 2 inflammatory cytokines that combat bone loss and inhibit osteoclast genesis. IL-4 targets osteoclast precursors via ligands of peroxisome proliferator-activated receptor γ1 (PPARγ1) and inhibits osteoclast genesis in a STAT6-dependent manner.[30,31] IL-13, which utilizes the same γ receptor as IL-4, suppresses RANKL expression in osteoblasts through a STAT-dependent pathway. Similarly, IL-10 strongly inhibits osteoclast genesis by downregulating the intrinsic expression of NFATc1 and reducing the availability of RANKL and M-CSF produced by surrounding cells, thereby attenuating bone resorption.[32,33]

Under healthy settings, B cells generate fifty percent of the OPG in the bone marrow, which inhibits RANK-RANKL-mediated osteoclast genesis by antagonizing RANKL and preventing excessive bone resorption.[34] In addition, receptor signaling in mature B cells leads to activation of phosphorylated tyrosine residues on Bruton's tyrosine kinase (BTK) signaling.[35] Bruton's tyrosine kinase (BTK) suppresses osteoclast differentiation by modulating the expression and activation of NFATc1. This regulation occurs through the interaction with immunoreceptor tyrosine-based activation motif (ITAM)-associated adapter proteins, such as FcRγ and DAP12, which are critical for osteoclast signaling pathways.[36,37] In inflammatory conditions, B cells produce substantial quantities of RANKL, which directly promotes osteoclast differentiation. Additionally, B cells amplify the production of granulocyte colony-stimulating factor (G-CSF) by increasing the secretion of chemokines such as CXCL12. This enhances neutrophil recruitment, intensifies the inflammatory response, and elevates the number of osteoclast progenitor cells, thereby exacerbating bone resorption.[38] Neutrophils are key cells in the inflammatory response and, in bone resorption diseases, RANKL exhibits high expression levels in neutrophils, stimulating osteoclast genesis.[39] However, when neutrophil recruitment is insufficient, macrophages continue to release IL-23, prompting Th17 cells to secrete more IL-17 and increase osteoclast genesis.[40] Natural killer (NK) cells, actively involved in inflammatory diseases, express elevated levels of M-CSF and RANKL.

These factors enhance IL-15 expression, this process stimulates monocytes to differentiate into osteoclasts, thereby promoting bone resorption.[41,42] Immune cells and their associated factors not only regulate osteoclast activity, but osteoclasts also play a significant role in modulating the immune system. By secreting cytokines such as IL-6, TNF-α, TGF-β, and IL-1β, osteoclasts influence immune cell activity, promote macrophage polarization, and attract immune cells, including monocytes and T cells, to the bone microenvironment, thereby contributing to the dynamic interplay between bone and immune regulation.[15,43]

Immunomodulation of Osteoblasts

Osteoblasts facilitate bone formation by differentiating mesenchymal stem cells into bone progenitors through Wnt signaling and bone morphogenetic protein (BMP) transduction. The binding of bone morphogenetic proteins (BMPs) to their receptors initiates the phosphorylation and activation of Smad1, promoting the nuclear translocation of Runt-related transcription factor 2 (RUNX2). This cascade enhances the expression of osteogenic markers such as alkaline phosphatase (ALP) and osteocalcin (OC), which are essential for osteoblast differentiation. RUNX2, in conjunction with these osteogenic factors, plays a crucial role in the development and function of osteoblasts. Beyond their role in bone formation and mineralization, osteoblasts are pivotal in bone immunoregulation, mediating interactions with various immune cells. Macrophages can promote MSC-mediated osteogenic capacity, and depolarized macrophages induce oncostatin M (OSM) expression.[44] Polarized M2 macrophages secreted various cytokines and chemokines and upregulated prostaglandin E2 (PGE2) expression to promote osteoclast genesis;[45] polarized M2 macrophages secreted various cytokines and chemokines, recruited osteoblast precursors from the bone microenvironment and promoted osteoblast formation and differentiation through the release of factors such as BMP-2, VEGF and TGF-β.[46] Nevertheless, the TNF-α that is released by M1 macrophages leads to the inhibition of the translocation of insulin-like growth factor I (IGF-1) and RUNX2, as well as the suppression of osteoblast development.[47] T cells upregulate intercellular adhesion molecule (ICAM)-1 in osteoblasts and simultaneously downregulate transforming growth factor (TGF)-β1, thereby increasing mineralization.[48] Th2 cells combat bone loss during severe inflammation, mainly by relying on Th2 cell-mediated cytokines. IL-4 and IL-13 promote bone formation by activating OPG expression in endothelial cells and osteoblasts through STAT6 activation.[49] Regulatory T (Treg) cells secrete IL-4 and TGF-β, which enhance osteoblast function by engaging the CD39-CD73-adenosine receptor (AdoR) signaling pathway. This mechanism facilitates the modulation of bone remodeling and contributes to maintaining bone homeostasis.[50] While this is going on, Treg cells are interacting with CD8+T cells in order to control the expression of WNT10b and to encourage bone growth.[51] IL-17 produced by Th17 cells induces RANKL expression, which inhibits osteoblast differentiation and function.

TGF-β secreted by B cells inhibits osteoblast differentiation by upregulating the phosphorylation of Smad2/3 (p-Smad2/3) and simultaneously suppressing the expression of Runx2, a crucial transcription factor required for osteoblast development and function.[52] B cells further inhibit osteoblast differentiation by secreting CC-motif chemokine ligand 3 (CCL3) and TNF. These substances influence the extracellular signal-regulated kinase (ERK) pathway and NF-κB, impairing signaling mechanisms essential for osteoblast growth.[53]

NK cells directly inhibit osteoblast differentiation and mineralization by secreting interferon-γ (IFN-γ). IFN-γ suppresses critical osteoblast signaling pathways, including the Wnt/β-catenin and BMP/Smad pathways, thereby inhibiting bone matrix production and mineralization processes essential for bone formation.[54]

Moreover, osteoblasts engage in intricate regulation with immune cells through the secretion of several cytokines, chemokines, and surface chemicals. The RANKL secreted by osteoblasts binds to RANK receptors on the surface of T cells, promoting osteoclast genesis and enhancing the activation and pro-inflammatory response of T cells. OPG secreted by osteoblasts acts as a RANKL antagonist, inhibiting RANKL binding to T cells and reducing T cell pro-inflammatory activity, thus restoring local immune balance.[55] Osteoblasts also attract different T cell subtypes to the bone microenvironment, where CXCL10 promotes recruitment of Th1 cells and inhibits IFN-γ-mediated mineralization of osteoblasts, thus reducing new bone production.[56] Osteoblasts also have a regulatory role in B cell production, in immature osteoblasts expressing osterix. Decreased IL-7 expression causes abnormal IL-7/Stat5 signaling in early-stage B lymphocytes, leading to heightened death of pre-B and immature B cells.[57] The bidirectional regulation mechanism

between osteoblasts and immune cells is essential for sustaining bone metabolic balance and immunological homeostasis (Figure 1).

Key Roles of Various Immune Cells in OA

OA is a common chronic degenerative joint disease whose pathological process involves not only degeneration of articular cartilage but also synovial inflammation, changes in joint fluid, and remodeling of bone tissue. Recent research indicate that the immune system significantly contributes to the initiation and progression of OA. Various immune cell types participate in the pathogenic mechanisms of OA via a complicated network of immunological responses. Innate and adaptive immune cells collaborate to exacerbate the disparity between damage and repair of joint tissue.

Mechanisms of Macrophage Action

Macrophages are pivotal immune cells in the pathogenesis of OA, serving as key mediators in initiating and sustaining the inflammatory response while significantly contributing to bone and cartilage degradation. As a central component of the innate immune system, macrophages are widely distributed in synovial tissues and joint fluids, are highly activated in OA, and contribute to disease progression via multiple mechanisms. Studies have shown that activated macrophages, rather than resting macrophages, are present in the knees of 76% of OA patients and that the number of activated macrophages correlates positively with the severity of OA.[58] Macrophage surface pattern recognition receptors (PRRs) are activated to identify external pathogen-associated molecular patterns (PAMPs) and endogenous pathogen-associated molecular patterns (DAMPs). This cascade triggers downstream cellular inflammatory responses, leading to the secretion and release of substantial amounts of inflammatory cytokines and chemokines, which play a critical role in the

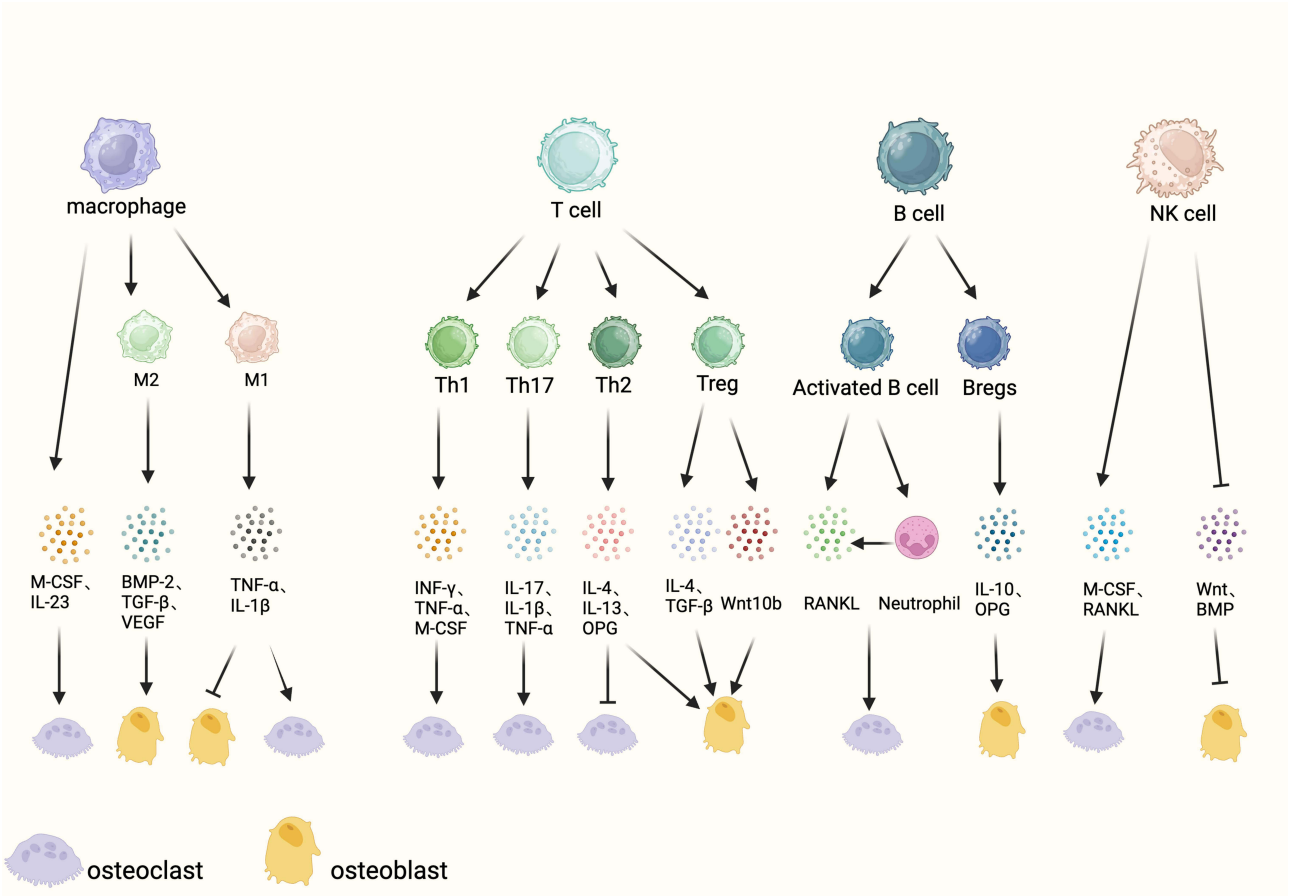

Figure 1 This diagram shows the interaction between macrophages, T cells, B cells, and natural killer cells with osteoclasts and osteoblasts. Different types of immune cells regulate the formation and function of osteoclasts and osteoblasts by secreting various cytokines, chemokines, and growth factors.
Notes: Created in BioRender. Hu, K. (2025) https://BioRender.com/ z29y099.

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progression of OA.[59] M1 macrophages are promptly activated during the inflammatory response, and their stimulation by IFN-γ, TNF-α, and GM-CSF swiftly releases pro-inflammatory molecules TNF-α, IL-1β, and IL-6, initiating synovial inflammation.[60] These variables induce synovial inflammation and OA via signaling pathways including NF-κB and MAPK. TNF-α, through the TNFR1 receptor, stimulates the p38 MAPK and ERK1/2 pathways, increasing the secretion of pro-inflammatory cytokines and upregulating the expression of the matrix-degrading enzyme MMP-13, respectively. The NF-κB and MAPK pathways demonstrate a synergistic connection that stimulates chondrocytes to synthesize matrix-degrading enzymes, such as MMPs and ADAMTS. This leads to the downregulation of type II collagen and aggregated proteoglycan production, thereby hastening cartilage breakdown.[61,62]

M2 macrophages are polarized by Th2 cytokines, including IL-4 and IL-13, facilitating tissue repair and anti-inflammatory responses predominantly through the secretion of anti-inflammatory molecules such as IL-10 and TGF-β.[63] A dynamic equilibrium between M1 and M2 macrophages is maintained in healthy tissue to preserve tissue homeostasis. However, in the chronic inflammatory environment of OA, this equilibrium is disrupted, and sustained activation of M1-type macrophages leads to inflammatory expansion and tissue damage. This M1-based state not only maintains synovial inflammation but also impedes tissue repair by inhibiting the anti-inflammatory function of M2 macrophages.[64]

Synovial macrophages are not only drivers of inflammation; they also amplify the inflammatory response through their interactions with synovial fibroblasts. Factors such as CCL2 and MMP1 secreted by synovial macrophages attract more monocytes to infiltrate the synovium, exacerbating inflammation. The chemokines CCL2, MMP1, and GM-CSF secreted by synovial macrophages attract more monocytes to migrate into the synovium, reinforcing the inflammatory response.[65,66] Furthermore, macrophages promote synovial cell proliferation and enhance the expression of inflammatory markers through the actions of IL-1β and TNF-α, thereby exacerbating synovial tissue damage.[67] A positive feedback loop exists between the pro-inflammatory state of synovial macrophages and synovial angiogenesis. Pro-inflammatory cytokines, including TNF-α and IL-1β, activate synovial endothelial cells to produce VEGF, thereby promoting neovascularization and sustaining the inflammatory response.[68] which not only enhances immune cell migration pathways but also reinforces the chronic inflammatory state in synovial tissue.[69]

During the progression of OA, chondrocytes are directly targeted by matrix metalloproteinases (MMPs) and a disintegrant and metalloproteinase with thrombospondin motifs (ADAMTS) released by macrophages. These enzymes break down the collagen and proteoglycans within the cartilage matrix.[70] In addition, pro-inflammatory factors from M1 macrophages further impede cartilage repair by inhibiting chondrocyte proliferation and inducing apoptosis.[71] This effect is multifaceted and leads to a loss of structural integrity of cartilage tissue. Interestingly, there are interactive signals between chondrocytes and synovial macrophages. Degenerating chondrocytes release DAMPs, which in turn activate macrophages, creating a vicious circle.[72] This transcellular interaction makes OA lesions highly self-perpetuating and accelerates the spread of cartilage damage.

Another pathological feature of OA is subchondral bone remodeling. Macrophages in the subchondral bone act as a bridge between osteoblasts and osteoclasts and regulate osteoclast activity by secreting RANKL and OPG. In OA patients, increased bone mass and structural changes in the subchondral bone result from an imbalance of macrophages. In the early stages, macrophages secrete large quantities of RANKL, which stimulates osteoclast genesis, leading to increased bone resorption, unbalanced bone metabolism and early changes in the trabecular structure of subchondral bone due to altered mechanical loading, with a decrease in trabecular density in certain regions, resulting in microfractures and localized bone lesions.[73] Subsequently, a large number of inflammatory cells infiltrate, releasing inflammatory factors, activating the Wnt/β-catenin and TGF-β pathways, promoting differentiation and mineralization of subchondral bone osteoblasts, leading to excessive subchondral bone growth.[74,75] This alters the mechanical environment of the joint, aggravating cartilage damage. Collectively, these studies underscore the pivotal role of macrophages in the pathogenesis and progression of OA.

Mechanisms of T Cell Action

T cells are adaptive immune cells that play a significant regulatory role in OA lesions. Their influence extends to synovial inflammation, cartilage degeneration, and subchondral bone remodeling through various pathways. T cells are

predominantly located in synovial tissues, where they establish a complex network of interactions with synovial fibroblasts, macrophages, and other immune cells. T cells in OA differentiate into several subtypes, such as Th1, Th2, Th17, and Treg, each contributing uniquely to the regulation of inflammation and tissue damage at various stages.[76]

T cells constituted 22% of the infiltrating cells in the synovial tissue of OA patients and exhibited high levels of activation,[77] High levels of T cells are observed in the peripheral blood and synovial fluid of OA patients, demonstrating a strong correlation with disease severity.[78] T cells are activated when their T cell receptors (TCRs) bind to major histocompatibility complex (MHC) molecules presented by antigen-presenting cells. This interaction initiates an immune response, leading to the secretion of a range of pro-inflammatory and anti-inflammatory cytokines that regulate immune activity and tissue homeostasis,[79] Aggravating synovial inflammation, stimulating bone loss and joint destruction, has a profound impact on the progression of OA.

Th1 cells represent a primary subset of pro-inflammatory T cells and are integral to the inflammatory response associated with OA. Elevated quantities of activated Th1 cells are observed in the synovium of individuals with early OA.[80] A notable elevation in the expression of chemokine receptors (CXCR3/CCR5) and IFN-γ is found.[76] In response to IL-12 and IFN-γ stimulation, Th1 cells release inflammatory factors, which activate synovial macrophages and cause them to polarize towards the M1 type, releasing pro-inflammatory factors such as TNF-α, IL-1β and IL-6. These factors promote synovial inflammation and the secretion of matrix-degrading enzymes (MMP-3, MMP-9, etc). by chondrocytes, resulting in prolonged degradation of the cartilage matrix.[81] Th1 cells inhibit chondrocyte proliferation and induce apoptosis via interferon secretion, further reducing cartilage repair capacity and forming a pro-inflammatory positive feedback loop that maintains the chronic inflammatory state of OA.[82] These factors drive synovial inflammation and stimulate chondrocytes to secrete matrix-degrading enzymes, such as MMP-3 and MMP-9, leading to the persistent degradation of the cartilage matrix.[83,84]

Th2 cells play a key role in reducing inflammation and promoting tissue repair by secreting anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, which help to modulate immune responses and support healing processes. Nonetheless, Th2 cytokine concentrations are diminished in the synovial fluid, synovium, and peripheral blood of OA patients, with only trace amounts of IL-4 and IL-10 detectable.[85,86] In the persistent inflammatory milieu of OA, the anti-inflammatory functions of Th2 cells are typically diminished and ineffective in alleviating ongoing synovial inflammation. IL-4 and IL-10 promote the polarization of synovial macrophages to the M2 phenotype, reducing the release of inflammatory mediators, which alleviates inflammation and indirectly supports cartilage regeneration.[87] Despite the anti-inflammatory function of Th2 cells, their protective role in OA is often reduced, which is linked to multiple factors in chronic inflammation and the immune microenvironment and still requires further research.

Th17 cells, a critical subset of pro-inflammatory T cells, are deeply involved in the pathogenesis of OA. Studies have shown significantly elevated Th17 cell counts and increased serum IL-17 levels in OA patients compared to healthy controls. Furthermore, these elevations positively correlate with disease severity, underscoring their role in driving inflammation and joint degeneration.[88] Th17 cells and secreted IL-17 significantly increase the inflammatory response of chondrocytes and synovial fibroblasts, induce the expression of matrix-degrading enzymes such as MMPs and ADAMTS, and disrupt the integrity of the cartilage matrix, thereby accelerating cartilage degradation.[89] IL-17 was found to induce chondrocyte and fibroblast senescence in the OA model,[90] and senescent cells induced the differentiation of naïve T cells into pro-inflammatory T cells, and the positive feedback between senescent cells and Th17 immune responses reinforced chronic inflammation which actively prevented tissue repair.[91] IL-17 stimulation enhances the polarization of macrophages towards the pro-inflammatory M1 phenotype in a manner dependent on MCP-1. Additionally, IL-17 increases MCP-1 synthesis in synovial macrophages from OA patients. This, in turn, exacerbates the inflammatory response by promoting monocyte migration through the activation of the JAK/STAT3 signaling cascade, further driving the progression of OA.[66] IL-17 synergizes with pro-inflammatory factors including TNF-α and IL-1β to enhance RANKL expression and activate osteoclasts, leading to subchondral osteochondral bone loss.[92] In addition, Th17 cells exacerbate OA lesions by promoting synovial angiogenesis and increasing immune cell infiltration.[93]

Treg cells are key regulatory immune cells that maintain immune homeostasis and limit excessive inflammatory responses. In OA, Treg cells alleviate synovial inflammation and cartilage degeneration by secreting anti-inflammatory mediators such as TGF-β and IL-10, while suppressing the pro-inflammatory functions of Th1 and Th17 cells. However,

in OA patients, the number and function of Treg cells are significantly reduced, leading to uncontrolled inflammation and exacerbated arthropathy.[81,94] Lipid nanoparticles have demonstrated an antigen-specific interaction with Treg cells, effectively regulating cytokine expression and reducing immune cell infiltration into the joint. This approach helps to inhibit chondrocyte apoptosis and prevent cartilage matrix degradation, offering a promising strategy for joint preservation.[95] A Th17/Treg imbalance is often present in OA patients, and its ratio is closely linked to OA progression.[96,97] It was found that the Th17/Treg ratio shifted towards Treg cells after OA patients were treated with saffron phytotherapy, effectively improving the OA condition.[98] However, immunosuppression in chronic inflammatory environments is often insufficient, suggesting that improving Treg cell function could become a new direction for the future treatment of OA.

Mechanisms of B Cell Action

B lymphocytes exhibit a dual involvement in the pathophysiology of OA, possessing both pro-inflammatory and anti-inflammatory capabilities. This dual role means that B cells play a complex and critical role in the pathogenesis of OA.

In a healthy skeletal environment, the immune function of B cells facilitates the balance of bone metabolism. B lymphocytes proficiently obstruct the interaction of RANKL with the osteoclast receptor RANK by secreting OPG, a natural antagonist of the RANKL receptor, hence averting osteoclast activation. The presence of OPG guarantees sufficient osteoclast activity in normal bone metabolism, maintaining bone stability and health.[34] In the pathological context of OA, B-cell function is considerably impaired. In the chronic inflammatory state, B cells tend to promote overexpression of RANKL while their level of secreted OPG decreases. This alteration leads to an imbalance between RANKL and OPG, and RANKL overactivity directly promotes osteoclast genesis,[99] which leads to subchondral bone resorption and joint degeneration. B cell infiltration is present in the synovium of around fifty percent of OA cases, with the degree of lymphocyte infiltration associated with increased synovial inflammation and the occurrence of plasma cells and lymphoid follicles in the most severe cases,[100] It is suggested that the immune response of antigen presentation may promote the progression of OA. By comparing transcriptional patterns, the researchers found that B cells in the OA synovium had a gene expression profile closer to that of plasma cells than circulating B cells, while the expression of their apoptotic genes tended to inhibit B cell apoptosis. Most importantly, the study confirmed, through in vitro experiments, significant functional differences between the circulating B cells of OA patients and those of healthy controls, highlighting their distinct roles in the disease pathology. In both T-cell-dependent and T-cell-independent activation responses, B cells from OA patients did not show a strong proliferative or apoptotic response like T cells. At the same time, B cells from OA patients did not show a strong proliferative or apoptotic response. At the same time, B cells from OA patients differentiated into antibody-secreting plasma cells much more rapidly than healthy controls.[101] TNF-α produced by B lymphocytes is crucial for the activation of synovial fibroblasts within joints. TNF-α secreted by synovial fibroblasts negatively regulates B lymphocytes, whereas synovial fibroblasts activated by TNF-α from B lymphocytes enhance secretion, for example, MMP-3 and lead to increased tissue-destructive properties. In addition, TGFβ secreted by synovial fibroblasts creates a negative regulatory circuit by inhibiting B cell proliferation and activation.[102] In OA patients, there is an immune infiltrate in the subchondral bone, and B and T cells strongly express RANKL, which directly affects bone resorption.[103] As osteoclast activity increases, subchondral bone structure is destroyed, local trabecular density decreases and mechanical loading of joints is abnormal, ultimately contributing to cartilage degradation. Interestingly, in advanced OA, the sclerotic regions of the subchondral bone exhibit a significantly higher abundance of $CD68^+$ macrophages and $CD20^+$ B lymphocytes compared to non-sclerotic areas, highlighting their potential involvement in disease progression.[104]

The function of B cells in OA extends beyond the production of a solitary cytokine; it is more intricately associated with the immunological milieu of OA and the interactions among other immune cells. B cells alter their immune response through a variety of mechanisms. For example, B cells facilitate T cell activation and the release of pro-inflammatory cytokines, notably IL-17 and IFN-γ, via interactions with T cells. B cells alter immune responses via multiple mechanisms.[105] The pro-inflammatory substances released by these T cells can also induce the polarization of synovial macrophages, prompting their transformation into the M1 type and intensifying the inflammatory response in the synovium. This functional change exacerbates local synovial inflammation and impacts bone metabolism via osteoclast

activation, resulting in subchondral bone degradation and joint structure alteration. This cycle exacerbates the progression of OA, rendering lesions difficult to reverse.

Mechanisms of Action of Other Immune Cells

Additionally, mast cells, natural killer cells, and neutrophils are all actively implicated in the development of OA. This is in addition to the immune cells that were specifically stated previously. Mast cells were found to be present in large numbers in OA synovial samples, and there was a trend toward correlation with Kellgren and Lawrence (KL) scoring grades.[106] When mechanical loading induces mast cell degranulation and trypsin-like enzymes,[107] MMPs can be activated to disrupt the extracellular matrix and promote cartilage degradation,[108] and PAR-2 secretion promotes bone erosion.[109] PAR-2 secretion promotes bone erosion. Inflammatory factors secreted by mast cells can also exacerbate synovial inflammation, accelerate cartilage degradation, and stimulate the production of osteochondromas in subchondral bone.[110] Although NK cells are less abundant in OA, flow cytometry analysis in a model of collagenase-induced OA in Balb/c mice revealed an increased activation state of the NK cell population during the active inflammatory phase. Subsequently, NK cells differentiated from a cytotoxic phenotype at the onset of OA to an effector phenotype in the chronic phase of the disease,[111] and peripheral blood NK cells showed a pronounced cytotoxic function and an immunomodulator-like phenotype in the synovial fluid of OA patients.[112] Neutrophils secrete neutrophil elastase. This protease contributes to the progression of OA by damaging articular cartilage over time.[113] Neutrophil elastase incubated with cartilage has been found to inhibit chondrocyte proliferation and promote apoptosis by activating intracellular ROS, damaging mitochondrial structure, rapidly dissolving cartilage collagen, and destroying cartilage structure.[114–116] Multiple immune cells collaborate to participate in the pathological mechanisms of OA.

Mechanisms of Bone Immunity in OA

Inflammation of the synovium, cartilage deterioration, bone hyperplasia, and the production of osteophytes are the usual symptoms of OA-related conditions. Evidence is accumulating that bone immunity is integral to the pathogenesis of OA. The immune mechanism of OA in bone comprises various immune cell types, immune factors, and signaling pathways that contribute to the inflammatory response, bone remodeling, and alterations in the structure of subchondral bone.

The Link Between Synovium and Bone Immunity

The synovium is a fragile layer of loose connective tissue that encases the synovial joint cavity and consists of two structural layers: the outer subendothelial layer, made up of loose connective tissue and blood vessels, and the inner layer, primarily containing macrophages and synovial fibroblasts embedded within the tissue. These cells generate synovial fluid, which provides the joint with oxygen and nutrition while removing metabolic waste and matrix degradation byproducts.[117] The complex interaction between synovial and bone immunity is crucial in the progression of OA. As the disease progresses, the synovium not only loses its lubricating and protective functions but also becomes a constant source of inflammation, which in turn significantly affects the homeostasis of articular bone and cartilage. In this context, alterations in the synovial structure are closely associated with the aggregation and activation of immune cells, which influence the local immune response through the secretion of several cytokines that sustain the harmful cycle of OA. Macrophages and T lymphocytes are the most prevalent immune cells in the synovium, followed by smaller numbers of mast cells, B lymphocytes, and plasma cells, and very few neutrophils, which take care of immune homeostasis within the synovium. The synovial immune response extends beyond localized synovial inflammation, directly influencing the evolution of OA by the migration and angiogenesis of immune cells, so establishing a regulatory network involving cartilage, subchondral bone, and the immune system. This process significantly influences intra-articular bone metabolic imbalance and cartilage degeneration via bone immune mechanisms such as the RANKL/RANK pathway.[118]

Synovial macrophages are the primary mediators of the first inflammatory response in OA. When joints are subjected to prolonged mechanical loading or trauma, synoviocytes release large amounts of DAMPs due to force damage and matrix destruction, and DAMPs and various stimuli activate macrophages, polarizing them into M1-type macrophages, which release large amounts of TNF-α, IL-1β, and IL-6.[119] These inflammatory factors regulate the local bone remodeling process.[120] In the initial phases of OA, circulating synovial macrophages can act as progenitors to osteoclasts,

thereby expediting bone resorption and facilitating joint deterioration.[121] Secreted inflammatory factors regulate the interaction between RANKL and RANK, promote osteoclast differentiation and activation, and exacerbate subchondral bone resorption, while the osteogenic process is significantly inhibited. While new osteogenesis has been observed in mid- and late-stage OA, selective depletion of lining macrophages by intra-articular injection of clodronate liposomes has been found to improve cartilage damage and bone matrix formation.[122] This may be because the macrophage activation product, alerting, increases the expression and activation of matrix metalloproteinases during cartilage micro aggregate formation, which may increase cartilage matrix remodeling, leading to greater bone mineral formation.[123] TGF-β, along with related proteins BMP-2 and BMP-4, plays a crucial role in the pathological deposition of type I collagen during osteoid formation and fibrosis. In the synovium, macrophages, in conjunction with fibroblasts, serve as the primary sources of TGF-β. This cytokine stimulates bone formation, promotes the synthesis of proteoglycans and type II collagen, and enhances overall bone remodeling processes.[124–126] Simultaneously, pro-inflammatory mediators released by synovial macrophages, such as CCL2 and CXCL8, attract monocytes and neutrophils to the synovium. These recruited cells aggregate to form clusters of inflammatory cells, further amplifying the local immune response and exacerbating inflammation in OA.[127]

In addition, synovial macrophages and dendritic cells activate synovial T cells through antigen presentation, in particular Th1 and Th17 cells, which account for 20–25% of synovial inflammatory cells.[128] IFN-γ secreted by Th1 cells not only activates synovial fibroblasts and macrophages but also enhances the reactivity of DAMP signaling by increasing PRR expression. Th17 cells, on the other hand, secrete IL-17, which further amplifies pro-inflammatory responses and accelerates cartilage matrix degradation by inducing MMP and ADAMTS expression via IL-17A. In addition, IL-17 acts synergistically with TNF-α to enhance synovial inflammation and increase RANKL expression, thus promoting osteoclast activity. Notably, the number and function of Treg cells in the synovial membrane are often suppressed, leaving the pro-inflammatory effects of Th1 and Th17 out of balance, creating a positive feedback loop for inflammation. Th cells directly produce MIP-1γ, which belongs to the CC chemokine family and may promote osteoclast formation and survival via the RANKL pathway. OA was found to be induced in $CD4^{-/-}$ mice ($CD4^{-/-}$/ACLT model), in which MIP-1γ expression was reduced. MIP-1γ, as a member of the CC chemokine family, plays a key role in the local inflammatory response by binding to the CCR1 receptor. A notable reduction in MIP-1γ correlated with heightened cartilage degradation and bone erosion throughout the advancement of OA.[129] In the synovial tissues of OA, mast cells activate the PAR-2 receptor, a member of the G protein-coupled receptor family, leading to the release of significant amounts of trypsin-like enzymes. PAR-2 is considered pivotal in the pathogenesis of OA. Experimental studies, particularly in mouse models, have demonstrated that PAR-2 activation is a key mechanism driving OA onset. Conversely, PAR-2 deficiency effectively suppresses cartilage erosion and subchondral bone formation, thereby decelerating disease progression.[106,109]

The immune response in the synovium is attributable not only to immune cell activation but is also intricately associated with angiogenesis. The expansion of synovial arteries is considered a vital factor in the movement of immune cells and the intensification of inflammation during OA. Neovascularization facilitates an expanded migration route for immune cells within the synovium, facilitating the rapid infiltration of immune cells, such as macrophages and T cells, into the joint cavity.[130,131] The accumulation of these cells in the synovium creates an environment filled with inflammatory cells and cytokines, which not only exacerbates the local immune response but also promotes degradation of the synovial matrix and resorption of subchondral bone. The interaction between angiogenesis and immune cell migration forms a complex positive feedback loop. Neovascularization facilitates the migration of immune cells and supports the local accumulation of inflammatory factors, which further activate immune cells within the synovium. As the inflammatory response intensifies, these immune cells perpetuate the cycle by secreting additional pro-inflammatory cytokines. This exacerbates local bone resorption and accelerates angiogenesis, creating a feedback loop that drives the progressive escalation of the immune response within the joint cavity, contributing to OA progression. This vicious circle is particularly pronounced in OA patients, where the chronic inflammatory response within the synovium intensifies over time, leading to irreversible damage to joint structure.

The interaction of these immune cells with bone immunity is not unidirectional. During the pathological process of OA, bone tissue itself also regulates synovial immune cells via locally released cytokines. The synovial immunological milieu serves as a crucial regulator of bone and cartilage deterioration, influencing the advancement of OA.

The Cartilage-Bone Immunity Link

The interplay between cartilage and bone immunity is a critical mediator in the pathological progression of OA. The fundamental architecture of the joint, cartilage is responsible for maintaining the low-friction movement of the joint, and its integrity is critical to joint function. However, during the pathological process of OA, cartilage is not only a passively damaged structure but also participates in local immune regulation through the release of DAMPs, which directly results in bone immune imbalance and ultimately leads to increased bone resorption and bone matrix formation.

Chondrocytes are highly specialized cells that are at rest under normal physiological conditions. During the progression of OA, chondrocytes are activated by various stimuli, including inflammation, aging, oxidative stress, and mechanical trauma. These triggers initiate a pro-inflammatory response, leading to the release of numerous DAMPs. These DAMPs include high-mobility group protein B1 (HMGB1), heat shock proteins (HSPs), and degraded cartilage matrix components such as hyaluronic acid (HA) fragments and collagen breakdown products, which further propagate inflammation and cartilage degradation. These DAMPs directly activate immune responses in the synovium and subchondral bone by interacting with PRRs.[132–134] Notably, HMGB1 and low-molecular-weight hyaluronic acid (HA) fragments play a significant role in cartilage degeneration by binding to Toll-like receptors (TLR2 and TLR4) on synovial macrophages and dendritic cells. This interaction induces the release of pro-inflammatory cytokines, including IL-1β and TNF-α, thereby perpetuating local immune responses and contributing to the inflammatory environment in OA.[135,136] The connection between the immune system and bone not only worsens cartilage destruction but also hastens the advancement of OA by elevating RANKL expression, which directly influences osteoclast activity and facilitates subchondral bone resorption. When cartilage is damaged, chondrocytes release inflammatory cytokines and chemokines, which recruit immune cells, such as neutrophils, macrophages, and dendritic cells, to the subchondral bone region. This recruitment amplifies the local inflammatory response and contributes to the progression of OA. Neutrophils are the first immune cells recruited to the site of cartilage injury, where they initiate the local inflammatory response by secreting pro-inflammatory mediators. These mediators attract additional immune cells, including macrophages and dendritic cells, which further intensify the inflammatory environment. Through the secretion of pro-inflammatory factors, these immune cells exacerbate chondrocyte apoptosis and contribute to a local imbalance in bone immunity, driving the progression of OA.[137] Chondrocytes influence bone homeostasis by secreting cytokines such as TNF-α, IL-1β, and IL-6. Among these, IL-1β plays a dual role in promoting osteoclastogenesis. It increases RANKL expression in osteoblasts, thereby indirectly inducing osteoclast formation. Additionally, IL-1β directly stimulates the differentiation of osteoclast precursors into multinucleated osteoclasts, contributing to bone resorption and the disruption of bone homeostasis.[137] TNF and IL-6, on the other hand, promote osteoclast differentiation through activation of signaling pathways such as MAPK, NF-κB and activator protein 1 (AP-1), and indirectly promoting osteoclast genesis by stimulating osteoblasts to secrete RANKL, thereby exacerbating the bone resorption process,[137–139] Further promote cartilage and subchondral bone damage, thus forming an immune-bone vicious cycle. In addition, chondrocytes participate in the regulation of bone immunity by regulating the expression and function of osteoclast receptors. The osteoclast-associated receptor (OSCAR) is a receptor found on osteoclast lineage cells that can be activated by collagen produced by chondrocytes to enhance osteoclast activity and production. In osteoarthritic cartilage, OSCAR expression increases significantly, particularly in damaged areas. Studies have shown that inhibiting or reducing OSCAR expression can attenuate cartilage damage and subchondral bone loss in OA.[140]

Cartilage matrix degeneration is intricately associated with structural changes in the subchondral bone. The cartilage matrix primarily consists of type II collagen and proteoglycans, which are essential for maintaining the tissue's elasticity and resistance to compressive forces. Their degradation weakens the cartilage's biomechanical properties, contributing to joint dysfunction and disease progression.[141] As OA progresses, MMPs and ADAMTS are hyperactivated, leading to significant degradation of collagen fibers and proteoglycans. The degradation products released by this matrix breakdown can themselves act as DAMPs, further activating the local immune response in a vicious circle. Degradation of the

cartilage matrix also directly affects the distribution of mechanical loads on the subchondral bone. Cartilage damage remodels the mechanical environment of the joint surface, increasing the load on the subchondral bone. This change in mechanical load activates signaling pathways in subchondral bone cells via mechanoreceptors such as integrins, Piezo1, and TRPV4,[142] stimulating YAP-dependent control of type II and type IX collagen.[143] Tnfrsf11b (encoding the anti-osteoclastogenic protein OPG) regulates osteoclast differentiation,[144] which induces an imbalanced activity of osteoclasts and osteoblasts, leading to increased bone resorption and abnormal bone growth.[145,146] These changes in mechanical load combine with immune cell activation to bring about the structural remodeling of the subchondral bone. Deregulation of bone immunity further accelerates the OA process through this dynamic link.

Association of Subchondral Bone with Bone Immunity

In the pathological process of OA, changes in the subchondral bone are closely linked to the disruption of bone immunity. Subchondral bone is a dynamic structure composed of subchondral bone plates and bone trabeculae that support the joint. Subchondral bone is not only a support and shock-absorbing structure for the joint but also an important zone where bone remodeling and immune responses converge. With the progression of OA, osteoclasts and osteoblasts become abnormally active under the regulation of immune signals, and this abnormally active bone metabolism directly affects the structure and function of subchondral bone, accelerating degenerative joint disease. In particular, the imbalance between osteoclasts and osteoblasts leads to disturbances in bone proliferation and repair, with a profound effect on the progression of OA due to bone immune imbalance.[147]

Different changes in subchondral bone microstructure occur at different stages of OA, with increased bone resorption by osteoclasts and microfractures of subchondral bone in the early stages. It has been shown that, although the degree of immune infiltration in subchondral bone is lower in patients with OA than in those with rheumatoid arthritis, a large number of immune cells are also present.[148,149] In an anterior cruciate ligament (ACL)-transected OA mouse model, T cells were activated early in the disease process, accompanied by increased expression of IFN-γ. Additionally, MIP-1γ expression was observed in the T cell-infiltrated synovium. This contributed to an increased number of osteoclasts, thereby enhancing bone resorption and exacerbating the pathological changes associated with OA.[129] T cells also stimulated the recruitment of osteoclast progenitor cells by increasing chemokines derived from bone marrow mesenchymal stromal cells.[26] Furthermore, IL-17 released by T cells enhances RANK expression on progenitor cells, augmenting their responsiveness to RANKL stimulation and the quantity of osteoclasts.[150] IL-7 and G-CSF, secreted by B cells, play a significant role in bone remodeling by increasing the population of osteoclast progenitor cells and promoting osteoclast genesis, thereby contributing to enhanced bone resorption.[151] B lymphocytes also target ERK and NF-κB by secreting CCL3 and TNF, thus hindering osteoblast differentiation.[53] Neutrophil infiltration is observed in microfractures of bone.[152] Following neutrophil infiltration, monocytes are instructed to rapidly form osteoclasts based on Toll-like receptor 4 and NET-associated protein signaling.[153] Additionally, inflammatory mediators such as IL-6 and PGE2, secreted by immune cells, can enhance osteoclast differentiation by disrupting the balance of the OPG/RANKL/RANK system. These factors inhibit the secretion of OPG by B cells while stimulating the production of RANKL on various cell types, thereby promoting osteoclast genesis and contributing to bone resorption.[154] These processes accelerate bone resorption, leading to the destruction of trabecular bone structures and osteoporosis. As osteoclast activity increases, subchondral bone progressively loses its original volume and bone density, and trabeculae become sparse and fragile, creating favorable conditions for the development of OA.

In advanced stages of OA, osteoblast activity surpasses bone resorption, resulting in subchondral bone sclerosis and osteophyte formation. Studies have demonstrated that the sclerotic regions of the subchondral bone in OA exhibit a higher density of macrophages and B cells compared to non-sclerotic areas, suggesting their involvement in the pathological bone remodeling process.[104] Their involvement in the pathological bone remodeling process is further highlighted by the role of macrophages in promoting osteoblast differentiation. Macrophages synthesize PGE2, which induces the expression of oncostatin M, a cytokine that stimulates the differentiation of bone marrow mesenchymal stem cells into osteoblasts, contributing to abnormal bone formation in OA,[155] and supporting osteoblast differentiation and proliferation by releasing cytokines, notably BMP-2, BMP-4, and TGF-β1, to increase bone-forming capacity. Activated T cells promote OPG production by B cells via the CD40/CD40L signaling pathway, thereby promoting osteoblast

formation and enhancing bone formation.[156] Compared to normal osteoblasts, OA osteoblasts tend to produce more type I collagen, an atypical matrix that cannot be fully mineralized, leading to the formation of sclerotic bone.

The Wnt/β-catenin pathway plays a dual role in osteosclerosis and osteoid formation in the subchondral bone. Overactivated Wnt signaling in osteoarthritic subchondral bone was found to induce translocation of β-catenin into the nucleus and activate expression of osteogenesis-related genes RUNX2 and COL1A1 through the synergistic action of the Frizzled receptor and the Lrp5/6 coreceptor, thereby promoting abnormal mineralization and proliferation of trabecular bone.[157] Moreover, in advanced OA, the Wnt pathway synergizes with TGF-β secreted by T cells, further aggravating subchondral bone sclerosis and altering matrix production.[158] Furthermore, osteoblasts in OA exhibit elevated expression of inflammatory cytokines, including TGF-β1, TNF-α, IL-1β, and IL-6. This cytokine overproduction drives the excessive activation and proliferation of immune cells, fostering a persistent immuno-inflammatory environment. This dysregulated interplay significantly contributes to subchondral bone abnormalities and exacerbates disease progression.[103]

Immune imbalance disrupts the subchondral bone microenvironment, compromising both its physical and biological properties. The inflammatory response, coupled with osteoclast hyperactivity in the subchondral bone, drives degenerative changes in the bone matrix and leads to abnormal bone mineralization. These pathological alterations further accelerate cartilage degradation and destruction, contributing to the progression of OA. As OA progresses, subchondral bone degradation and osteoclast formation exacerbate structural damage to the joint, ultimately leading to loss of joint function.

Although the mechanism of bone-immunity interaction has been extensively studied, a systematic theoretical framework is still lacking. Based on the pathology of synovium, cartilage, and subchondral bone in OA, the "immune-bone axis" links the entire pathogenesis and pathological manifestations, and the circular model of the "immune-bone axis" reveals not only the mechanism of immune cells in OA but also the dynamic interactions between synovium, cartilage and subchondral bone in the progression of OA: in the early stage, synovial macrophages trigger synovial inflammation by secreting TNF-α, IL-1β and other factors, destroying the balance of the joint's immune microenvironment and activating the expression of chondrocyte-degrading enzymes while regulating the production of subchondral osteoclasts by synovial fibroblasts; in the intermediate stage, immune cells and chondrocytes accelerate cartilage and chondrocyte cell degeneration by secreting matrix-degrading enzymes, while chondrocytes induce M1-type synovial macrophage polarization and osteoclast formation through the release of DAMPs in the damaged state, forming a positive feedback loop; at an advanced stage, immune cells promote abnormal subchondral bone remodeling and sclerosis by modulating osteoclast and osteoblast activity, while factors such as IL-6, TGF-β and others are released in the bone resorption process, Reversing enhancement the inflammatory response of the synovium. This dynamic process persists throughout the course of OA, underscoring the central role of immune regulation in disease progression. Employing a loop model, it highlights the intricate interplay between immunity and bone metabolism, providing valuable insights into the mechanisms underlying their imbalance during OA development (Figure 2).

Potential Targets and Therapeutic Prospects for Bone Immunomodulation in OA

As the pathological mechanisms of OA have been intensively studied, the immune system's central role in OA's progression has become increasingly evident, with imbalances in bone immunity emerging as a key factor. Such dysregulation contributes to the disruption of bone remodeling, exacerbates inflammation, and accelerates joint degeneration, has been identified as a significant factor in early and late OA. As a result, immunomodulation has become a new direction in the treatment of OA. By obstructing immune cell activation and the release of inflammatory mediators, synovial inflammation, cartilage degeneration, bone resorption, and bone matrix formation should be slow, thereby reducing joint pain and improving dysfunction.

Therapy Targeting Immune Cells

T cells play an important role in the immune response to OA. Studies have shown that immunomodulatory nanoparticles can effectively induce the conversion of T cells into anti-inflammatory Treg cells, thereby improving the immune

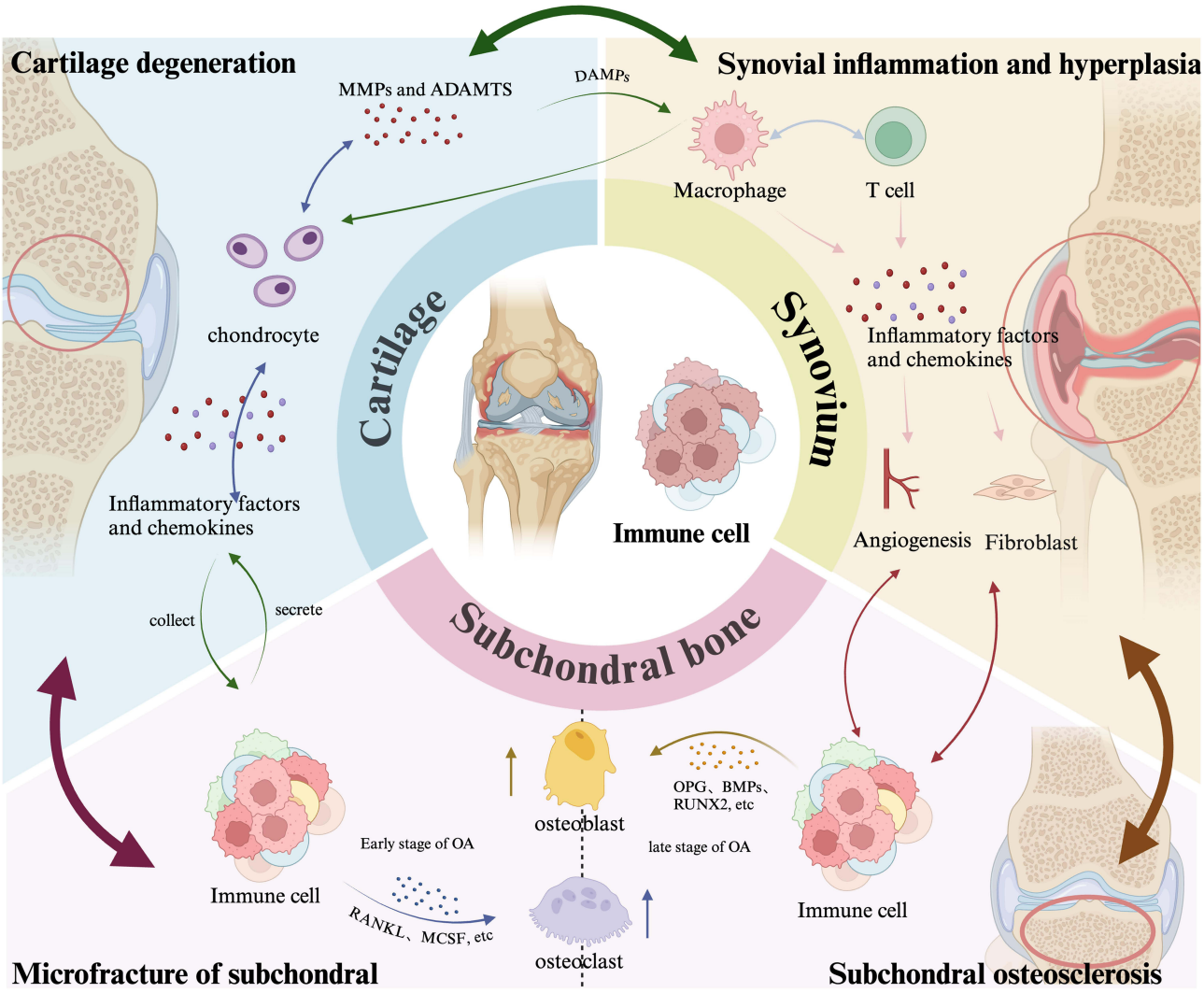

Figure 2 This diagram illustrates the complex interactions and immunomodulatory mechanisms among cartilage, synovial membrane, and subchondral bone in the pathological course of OA. Chondrocytes release MMPs and ADAMTS in response to various stimuli to mediate cartilage degeneration, produce inflammatory factors and chemokines, release DAMPs, and activate immune cells in the synovial membrane, leading to synovial inflammation, angiogenesis, and fibroblast proliferation, thus aggravating the inflammatory environment. At the same time, inflammatory factors and chemokines mediate the aggregation and infiltration of immune cells in the subchondral bone. The early manifestation of OA is increased osteoclast activity leading to increased bone absorption, and the late manifestation is increased osteoblast activity leading to osteosclerosis. Immune cells act as a link between cartilage, synovial membrane, and subchondral bone, driving the progression of OA by amplifying feedback loops of inflammation and tissue destruction.
Notes: Created in BioRender. Hu, K. (2025) https://BioRender.com/ v22z224.

response and slowing the progression of OA. Intradermal injection of lipid nanoparticles (LNPs) encapsulating type II collagen (Col II) and rapamycin (LNP-Col II-R) significantly enhanced the expression of anti-inflammatory cytokines. This approach reduced immune cell infiltration and the release of pro-inflammatory factors within the joints, effectively inhibiting chondrocyte apoptosis and mitigating cartilage matrix degradation. Such targeted therapy demonstrates potential for modulating immune responses and preserving cartilage integrity in OA.[159] In addition, sphingosine-1-phosphate (S1P) receptor inhibitors effectively reduced cartilage degradation by decreasing T-cell localization in the synovial membrane, offering new therapeutic possibilities for T-cell immunomodulation.[160] DJ-1 is a ROS scavenger with modulation of the redox response and has been shown to induce Treg cell differentiation and inhibit pro-inflammatory cytokine production by modulating the production of Th cell subsets. After DJ-1 treatment, angiogenesis in the synovial membrane was significantly reduced and osteoclast production was inhibited, thus alleviating the destruction of cartilage and bone.[161] Histone deacetylase inhibitors (HDACi) have demonstrated their potential as a drug delivery system in the treatment of OA. Histone deacetylase inhibitors (HDACi) have shown efficacy in

mitigating joint destruction and cartilage degeneration by penetrating physical and chemical barriers at the cartilage surface and enabling sustained drug release. This therapeutic approach slows OA progression by suppressing inflammatory responses and enhancing immune regulation, offering a promising avenue for disease management.[162] NSAIDs reduce the inflammatory response by inhibiting prostaglandin synthesis. In OA, NSAIDs (eg, ibuprofen and indomethacin) improve immune disturbances and clinical symptoms in OA models by modulating the Th17/Treg balance, reducing pain, and inhibiting synovial inflammation.[163]

In a mouse model of OA constructed by surgical destabilization of the medial meniscus (MMD), methacryloyl gelatin hydrogels (GelMA) containing MSC-derived nanovesicles (MSC-NVs) successfully induced the polarization of M1-type macrophages into M2-type macrophages, thereby suppressing the inflammatory response in vivo and effectively ameliorating the severity of OA.[164] Additionally, TPP-Se-CQDs (SCT), A selenium-containing compound exhibited the capacity to inhibit osteoclast differentiation and function by scavenging mitochondrial reactive oxygen species in mononuclear macrophages. This action reduced early chondrocyte apoptosis and preserved the balance between cartilage matrix synthesis and degradation. In vivo studies further confirmed that the SCT@AHAMA delivery system, combining microspheres and high-permeability nano-hydrogels, effectively suppressed osteoclast genesis and H-vessel invasion. This system regulated the initiation and progression of abnormal bone remodeling, ultimately mitigating cartilage degeneration in OA.[165] Moreover, the application of golden sage saponin in OA treatment has been found to inhibit the phosphorylation of IκBα, thereby suppressing activation of the NF-κB signaling pathway. This mechanism reduces the infiltration of pro-inflammatory M1 macrophages into the synovial membrane while promoting the accumulation of anti-inflammatory M2 macrophages, contributing to a more balanced immune response. This action not only improved the immune environment but also effectively inhibited the destruction of subchondral bone.[166]

Targeted Antiresorptive Therapy

The use of antiresorptive drugs in the treatment of OA is still relatively limited, but studies have shown them to be effective in some patients. For example, alendronate is an antiresorptive drug that has been shown to improve clinical symptoms in postmenopausal OA patients. Treatment with alendronate significantly reduces bone wear and bone marrow edema of subchondral bone and improves WOMAC scores in the knee, leading to relief of knee pain.[167] In addition, teriparatide, used in the treatment of osteoporosis, may also be helpful in the treatment of OA. Teriparatide can prevent cartilage damage by reducing the accumulation of senescent cells in the subchondral bone, inhibiting excessive bone reconstruction, and inducing chondrocyte differentiation.[168,169] This can be achieved by increasing expression of the parathyroid hormone one receptor (PTH1R), OPG, and RANKL via the OPG/RANKL/RANK signaling pathway and by inhibiting activation of the p38 and p-AKT signaling pathways, thereby inhibiting chondrocyte differentiation towards hypertrophy.[170] The use of this drug suggests that it could constitute a new therapeutic tool for early intervention in OA by modulating bone resorption.

Stem Cell Therapy

Stem cells possess remarkable immunomodulatory properties, enabling them to regulate immune cells and their associated immuno-inflammatory factors. In OA treatment, MSCs inhibit the maturation of monocyte-derived dendritic cells and impede the development of functionally mature dendritic cells. This is achieved through selective interference with immature dendritic cell production via the secretion of PGE2. Additionally, MSCs promote the upregulation of HLA class I molecules, which suppress NK cell proliferation and diminish NK cell cytotoxicity, thereby contributing to a more balanced immune environment and mitigating disease progression.[171,172] It also inhibits Th1 cell activation, slows B cell development, and regulates adaptive immunity.[173] Stem cell derivatives and exosomes can also modulate the immuno-inflammatory response and effectively treat OA via different pathways.[174]

Immunomodulation offers new perspectives for the treatment of OA. By targeting immune cells and factors, bone immune pathways, and stem cell therapies, among other strategies, future therapeutic options should radically improve the pathological course of OA.

Summary

The advent of osteoimmunology has significantly advanced our understanding of the pathological mechanisms underlying OA. The immune system plays a central role in the progression of OA, particularly through the dysregulation of bone immunity. Immune cell infiltration, including T cells, macrophages, and B cells, contributes to chronic inflammation, cartilage degeneration, and abnormal bone remodeling, creating an "immune-bone axis" that accelerates joint destruction. Studies indicate that targeting immune cells, bone immune pathways, and utilizing stem cell therapies could substantially alter the course of OA. Various therapies, such as immunomodulatory nanoparticles, S1P receptor inhibitors, and HDACi, demonstrate the potential to modulate the immune response and alleviate OA symptoms. Additionally, stem cells, through their immunomodulatory properties, hold promise in restoring immune balance and promoting tissue regeneration in OA.

While current research highlights the potential of immunomodulation in OA treatment, clinical validation remains scarce. Integrating immune modulation into clinical practice for OA is still in its nascent stages, with challenges in demonstrating consistent long-term efficacy and safety. The complex and heterogeneous nature of the immune response in OA, along with individual variations in patients, makes it difficult to predict treatment outcomes. Moreover, immune suppression therapies may lead to unwanted side effects, such as increased infection risks and impaired tissue repair. Clinical translation of these therapies also faces hurdles, including difficulties in assessing long-term effects and variations in patient responses.

With the further application of bone immunology in OA research, future studies should focus more on the following key directions: systematically resolving cell-cell communication networks in synovium, cartilage, and subchondral bone by integrating multi-omics techniques to reveal mechanisms of dynamic change in the bone immune microenvironment. Secondly, it will explore the role of immune cells in regulating bone resorption and osteogenesis. In addition, the development of novel combination therapies based on bone immunomodulation, such as biologics targeting RANKL in combination with immunomodulatory factors, may attenuate bone resorption and potentially restore immune homeostasis in synovial inflammation. Advancing these lines of research will provide a new theoretical basis and technical support to reveal the pathological mechanisms of OA and develop precise treatment strategies. The research and clinical translation of bone immune mechanisms, one of the main drivers of OA, will be an important direction for improving the disease and quality of life of OA patients in the future.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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