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Fine Line Between Repair & Ruin: How Inflammation Shapes Bone Remodelling?

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Abstract: Inflammation serves as both a stimulus for bone regeneration and a driver of deterioration. Although the process of bone remodelling is strictly regulated by osteoblasts, osteoclasts, osteocytes, and bone-lining cells, immunological signalling significantly affects how it is balanced. Acute inflammation is crucial for initiating bone repair because cytokines such as IL-1, IL-6, and TNF-α draw neutrophils and macrophages to the fracture site, clear debris, and encourage mesenchymal stem cell differentiation into osteoblasts. However, prolonged or dysregulated inflammation promotes bone loss by tilting the RANKL/OPG axis in favour of osteoclastogenesis, a characteristic of diseases such as inflammatory bowel disease, periodontitis, and rheumatoid arthritis. The new field of osteoimmunology shows how immune cells have two different effects: Th17 cells, hyperactivated neutrophils, and pro-inflammatory macrophages speed up bone resorption, while Tregs, osteomacs, and B cell-derived OPG encourage regeneration. This review emphasises how inflammation's temporal, cellular, and molecular context determines skeletal outcomes, highlighting the thin line separating repair from ruin. Comprehending this osteoimmune paradox offers therapeutic options, such as immune cell reprogramming, cytokine modulation, and RANKL inhibition, to promote bone regeneration while reducing inflammation-induced bone loss.

Keywords: *Inflammation, Bone Remodelling, Osteoimmunology, Osteoclastogenesis, RANKL/OPG Axis, Cytokines, T Regulatory Cells, Th17 Cells, Osteomacs, Bone Regeneration.*

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I. INTRODUCTION

Inflammation is the body's natural response to injury, infection, or harmful stimuli. It is a complex biological process that involves the immune system, blood vessels, and various cells to protect the body and promote healing. The ancient Roman doctors Celsus and Galen documented the obvious symptoms of inflammation, which include redness (rubor), swelling (tumour), fever (Calor), pain (dolor), and functional impairment (function loss). [6] Pathological conditions that primarily involve inflammation receive the suffix itis as their classification. [4] There are three different stages to the inflammation, which can be either acute or chronic. Increased vascular permeability causes inflammation, which is then followed by leukocyte infiltration, granuloma development, and tissue healing. [1] Localized increases in leukocyte counts and a variety of intricate mediators are involved in inflammation. Many immune cells can detect the direction and intensity of an extracellular chemical gradient and migrate toward the source of stimulus.

This process is called chemotaxis, which is essential for immune system function and homeostasis. Chemotaxis is initiated, and other mediators are released by adhesion molecules, cytokines, chemokines, platelet activating factor, and metabolites of arachidonic acid. [2] The body's plasma generates several inflammatory mediators, such as kinins and complement proteins, whereas cells create histamine, prostaglandins, and cytokines. When cells become active and biochemical mediators start to show up in the area, the reaction starts. The components of the inflammatory process include transcription factors like NF-κB and matrix metalloproteinases (MMPs), cytokines like Interleukin-1 and TNF-α, and kinases like p38 kinase, JNKs, and MAP kinase. [3]

II. THE GOOD AND BAD INFLAMMATION

When cells close to wounds or infectious agents activate neutrophils, macrophages, Langerhans cells, dendritic cells, and innate immune cells, the initial stage of "good" inflammation starts. By producing cytokines and chemokines, which cause immune cells to migrate to regional lymph nodes and initiate an adaptive immune response, local inflammatory changes are intensified. The biological process that mobilizes additional cells from the peripheral hematopoietic system and immune system locations across

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the body is strengthened by systemic inflammation. The phrase "bad inflammation" refers to strong inflammatory reactions that result in unfavourable prognoses, such as those caused by septic shock, serious infections, and aggressive malignancies. [5]

➢ *Bone Remodelling*

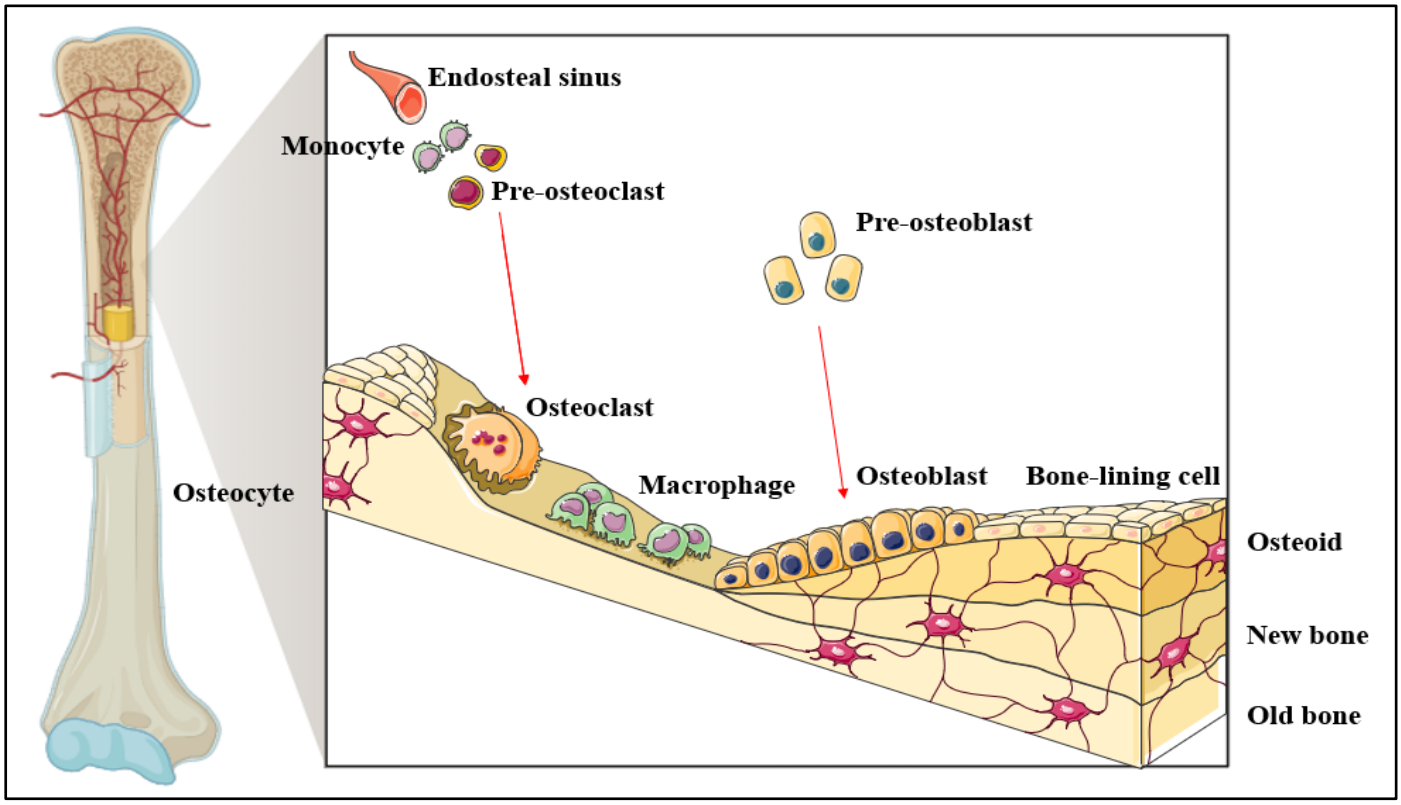

Fig 1 Schematic Representation of Bone Remodelling

III. CONCEPT OF BONE REMODELLING

Four different kinds of bone cells, osteocytes, osteoclasts, osteoblasts, and bone-lining cells cooperate to carry out a complicated process known as bone remodelling. Basic multicellular units (BMUs) are anatomical and functional structures that are in charge of bone remodelling. [7,8] Mature bone cells called osteocytes preserve bone tissue and interact with other bone cells. Osteoclasts break down old or damaged bone tissue, while osteoblasts build new bone tissue. Together, these cells ensure that the bone remains strong and healthy. Osteoblasts were obtained from mesenchymal stem cells (MSCs) via a multistep differentiation process **(Figure 1)**. MSCs develop into osteoprogenitors, then transform into preosteoblasts and subsequently mature into osteoblasts. [11] Osteoclasts, the only cells responsible for bone resorption, are multinucleated giant cells that develop from the mononuclear cells of the monocyte/macrophage lineage when activated by two critical elements: the monocyte/macrophage colony-stimulating factor (M-CSF) and the ligand for the receptor activator of nuclear factor κB, RANKL. [9,10]

➢ *Role of Inflammation in Bone Repair*

The body initiates an inflammatory response right after a bone breaks. [12] The fundamental beginning of bone healing requires inflammation to initiate the process. [13,14] The traumatizing event causes blood vessels to break both inside and surrounding the fracture region, where a hematoma forms. Blood vessel ruptures that happen at and near the fracture site result in a hematoma. The hematoma serves as a structural base that draws in inflammatory cells and different types of cytokines. Through the coordinated action of TNFα, CCL2, IL1, IL6, and other chemicals, this area triggers inflammation and starts an inflammatory cascade. [12] Initially, PMNs are recruited, and the call for phagocytic cells like monocytes/macrophages begins as they enter the area surrounding a fracture. [15] Once the dead cells and debris have been cleared by PMNs and macrophages, the inflammatory region becomes resolved. This is an example of a multi-step, highly regulated procedure. The tissue reduces inflammatory-initiating chemicals, inhibits the synthesis of pro-inflammatory mediators, and gradually eliminates immune cells. [16] Special bone-residing macrophage cells known as osteomacs exist among the bone lining cells of endosteum and periosteum, where they support bone maintenance processes. [17,18]

➢ *V. Role of Inflammation in Bone Loss*

The proinflammatory cytokines could promote osteoclastogenesis, which helped explain how inflammation contributes to bone loss. [20] Most attention has been paid to the most prevalent chronic inflammatory illnesses. Numerous disorders, including inflammatory bowel disease, lung inflammation, chronic joint disease, and kidney diseases, have similar processes that can cause bone loss. These

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processes are triggered by immunological signals that can shift the equilibrium of bone homeostasis in Favor of bone resorption. [19] The influence of tumour necrosis factor-α (TNF-α) on osteoblasts' production of RANKL serves as the greatest example of this effect. RANKL can promote bone resorbing activity and cause osteoclast differentiation. Additionally, TNF-α directly promotes osteoclast resorption in vitro. [21,22] RANKL is normally produced by osteoblasts; however, during inflammation, a variety of inflammatory cells can also produce it. Certain cells, such as fibroblasts and lymphocytes, are present in the inflammatory synovium. [23,24,25]

➢ *The Osteoimmune Paradox When Immune Cells Build Vs Destroy*

Osteoimmunology is an emerging field of research that explores the relationship between the immune system and bone health. It focuses on how immune cells influence bone formation, maintenance, and destruction. This interdisciplinary area blends aspects of immunology and bone biology to provide a more comprehensive understanding of how the two systems interact.

➢ *When Do Immune Cells Build?*

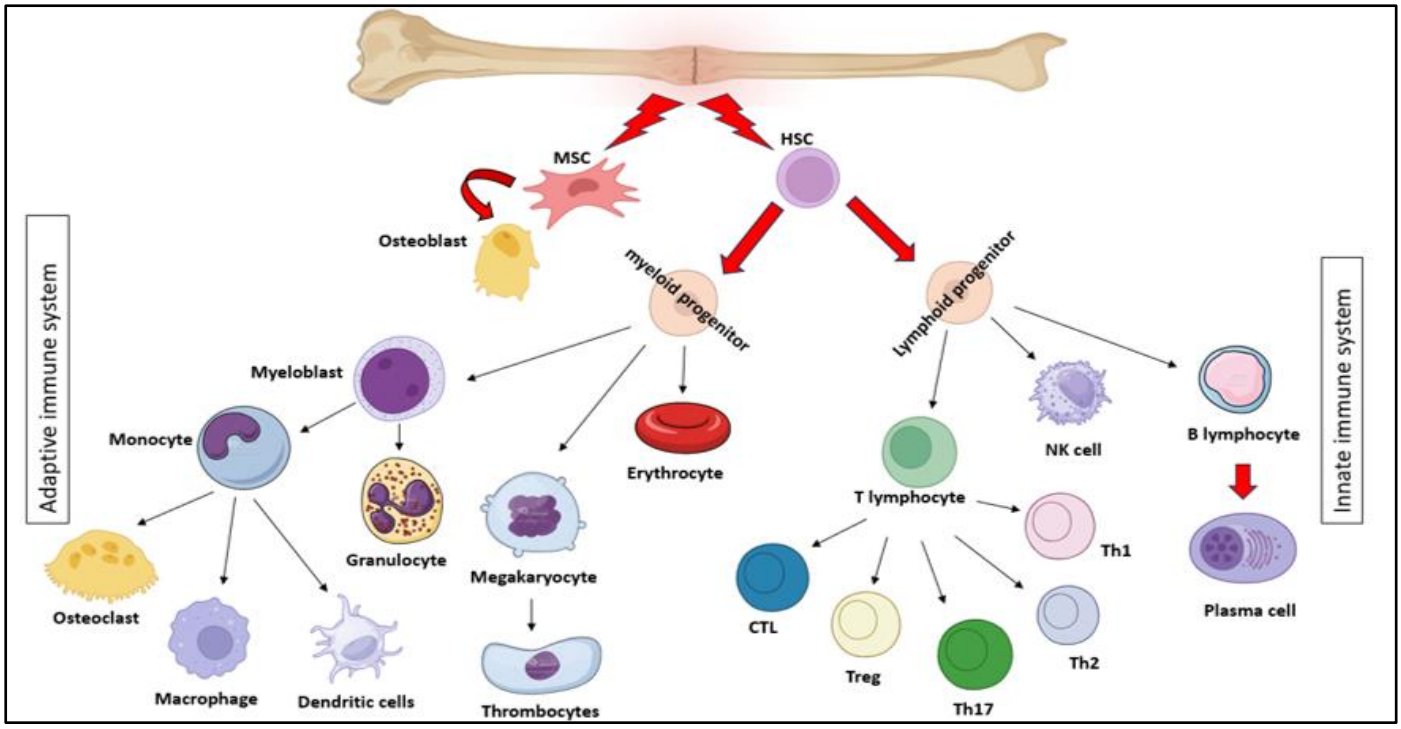

Fig 2 Immune Cell Lineage Development from Hematopoietic Stem Cells (HSCs) and Mesenchymal Stem Cells (MSCs), Showing Differentiation into Innate and Adaptive Immune Cells.

- *Abbreviations:*

MSC-Mesenchymal Stem Cell, HSC-Hematopoietic Stem Cell, CTL-Cytotoxic T Lymphocyte, Treg-Regulatory T Cell, Th1-T Helper Cell 1, Th2-T Helper Cell 2, Th17-T Helper Cell 17.

➢ *When do Immune Cells Build? (Figure 2)*

- *Impactor Cells of the Innate Immune System*

Cell components include innate lymphoid cells, natural killer cells, phagocytic cells, endothelial and epithelial cells, and platelets. Phagocytic cells are composed of dendritic cells, monocytes/macrophages, and granulocytes (including neutrophils, eosinophils, basophils, and mast cells). Most cell components that express PRRs on the cell surface and can produce cytokines exhibit microbicidal actions. These cells are affected by innate immunity effector pathways in both the acquired and innate immune systems. [35,36] In the early stages of bone fracture repair, mesenchymal progenitor cell proliferation and osteoblastic differentiation are accelerated by acute inflammation that produces chemokines. [26]

- *Neutrophils*

When chemotactic stimuli are applied to the site of inflammation, neutrophils (PMN) are the first cell line to be recruited. These stimuli encompass chemokines like IL-8, complement factors like the C5a factor, and leukotrienes (L), such as L-B4, which affect other neutrophils in both paracrine and autocrine mechanisms. Certain receptors, also known as PRRs, recognize all of these chemicals that permit migration to the site of injury. This makes it possible for antibodies (mostly IgG) to phagocytose tagged (opsonized) bacteria. [37,38,39,40] Neutrophil granulocytes have a brief lifespan of three days. Upon contact, several defence mechanisms are secreted, including lysosomal enzymes and myeloperoxidase, which is a component of the oxidative burst and destroys bacterial membranes. [31] In the early stages of bone damage, neutrophils not only serve as immune cells but also control bone homeostasis. [27] Numerous animal studies and clinical examples have demonstrated that neutrophil infiltration and aggregation occur in bone injury and are crucial for the initial phases of bone regeneration. [28] According to several studies, after trauma, bacteria release endotoxin-

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lipopolysaccharide, which causes neutrophils to express receptor activator of nuclear factor kappa B ligand (RANKL). Osteoclasts then carry out bone resorption. [29,30]

- *Macrophages*

There are three groups of macrophages according to their biological role: i) macrophages that are conventionally activated, also known as type 1-activated macrophages; ii) macrophages that are alternatively activated; and iii) macrophages that are type 2-activated. (41) Type 1-activated macrophages are thought of as beneficial cells in the Th1 immune response and are typically triggered by IFN-γ or TNF-α in conjunction with microbial products like LPS. Type 1 macrophages, upon activation, increase the production and expression of pro-inflammatory cytokines and chemokines. They also improve their capacity to eliminate microbial pathogens by producing NO and ROS. [41,42] The precursor cells of dendritic cells and macrophages (MP) are monocytes (MC). Monocytes exit the circulation after around a day to develop into macrophages in extravascular tissue.

Both macrophages and monocytes are capable of phagocytosis, and they can do it with or without the aid of antibodies. When MCs come into contact with microbial antigens, they release IL-12, TNFα, and iNOS. [32] When endogenous or exogenous stimuli are applied, macrophages change into the M1 and M2 phenotypes. While M2 macrophages are anti-inflammatory, M1 macrophages are typically pro-inflammatory. [33] The M1 phenotype can occasionally be changed to the M2 phenotype both in vitro and in vivo, and vice versa. [34] Osteocytes maintain touch with bone surface cells by gap junction-coupled cell processes that travel through tiny channels in the matrix that establish connections between the lacunae in the cell body and the external environment. It actively participates in bone turnover and is essential for bone's functional adaptability. [43] The monocytes and macrophages are among the key cells linked to this process. [44] The preservation of bone health depends on the interaction between macrophages and osteocytes, and M1 macrophages prevent osteocyte maturation [45]

- *B Cells*

Hematopoietic cells called osteoclasts (OCs), which break down bone, and osteoblasts (OBs), create new bone. Hematopoietic stem cells are also the source of immune cells such as B cells, T cells, and macrophages. [48,49] Hematopoietic stem cells in the bone marrow give rise to B cells, which mature and then enter the spleen and lymph nodes. B lymphocytes are stimulated by antigens to proliferate and mature into plasma cells. B-cell development and maturation are intimately linked to bone cells in addition to immunological activity. [46] Osteoclast precursors (OCPs) must differentiate into OCs for the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a crucial protein that is heavily involved in controlling immunological responses, to function. [47] Bone tissue mostly contains osteoprotegerin (OPG) from B cells and plasma cells. B cells secrete OPG, which promotes bone tissue repair and antagonistically blocks the impact of RANKL. Through the CD40/CD40L signalling pathway, activated T cells encourage B cells to produce OPG in an inflammatory environment, which aids in the repair of bone structure. [50] In conclusion, the precise function of B cells in bone regeneration is still up for debate and may vary depending on the clinical circumstances in a given area.

- *T Cells*

Numerous studies have demonstrated that T cells are essential for bone remodelling and regeneration because they generate a variety of cytokines and growth factors. T cells are separated into two groups based on distinct T cell receptors: αβ T cells and γδ T cells. Additionally, αβ T cells can be further divided into CD4+ and CD8+ T cells, which both promote and hinder regeneration. A tiny subset of T cells known as γδ T cells is thought to encourage regeneration; however, it's unclear. [51,52] T cells are classified according to the differences in the chemicals on their cell surface (CD = Cluster of Differentiation). [53]

- *T Help Cell 1 (Th1)/Th2 Cells*

Naive T cells undergo Th1 and Th2 cell differentiation in response to antigen stimulation. For the primary purpose of eliminating intracellular infections, Th1 cells release interferon γ (IFN-γ), IL-2, and tumour necrosis factor α (TNF-α). Th2 cells secrete IL-4, IL-5, IL-6, and IL-10, which aid in B cell activation and the removal of external pathogens. [54] According to Sato et al., Th1 and Th2 cells' production of IFN-γ and IL-4 inhibits osteoclast differentiation and promotes bone formation by breaking down TNF receptor-associated factor 6 (TRAF-6). [55] According to earlier studies, Th1 cells are the main source of RANKL. Through TNF-α, Th1 cells primarily promote the growth and activity of osteoclast precursor cells, which indirectly leads to bone tissue absorption and destruction. In inflammatory or estrogen-deficient conditions, Th1 cells also play a major role in osteoclastogenesis. [56,57]

- *T Regulatory Cells (Treg)*

Treg assumes a key positive regulatory function in the healing and regeneration of bone wounds. Since they generate cytokines like IL-4 and TGF-β, T regulatory cells (Treg) are a type of T cell that has a functional inhibitory effect. They also maintain the immune system's homeostasis and immunological tolerance to autoantigens. In comparison to mice of the wild type, transgenic mice with higher levels of Treg have longer bones with more bone mineral density and less bone resorption (Zaiss et al) [58] In a study on the healing of calvarial abnormalities in mice, Treg injections given routinely were found to successfully lower inflammatory factor levels in the local trauma area, boost the osteogenic potential of transplanted stem cells, and ultimately result in functional bone regeneration. [59] Uncontrolled inflammation after tissue damage can lead to impaired healing and tissue remodelling. During bone repair, Tregs are attracted to the damaged location to help reduce inflammation and regulate immunopathologic reactions after damage. [60] Tregs regulate neutrophil behaviour and macrophage polarization, which indirectly aids in tissue regeneration. [61,62] Treg also promote bone regeneration by reducing levels of Th1, Th17, and pro-inflammatory cytokines in local tissue, inducing immune tolerance, and efficiently inhibiting

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over-activated T cells in inflammatory lesions like tissue trauma, inflammation, and tumors. Tregs have been shown to promote MSC-based bone repair by blocking CD4+ T-cells, which release TNF-α and IFN-γ. [63]

➢ *When Do Immune Cells Destroy?*

- *Neutrophils*

Kovtun, Anna, et al found that reduced neutrophil counts resulted in poor bone repair following fractures in a mouse model. [64] Furthermore, unlike CD3+ T cells, activated neutrophils only express the membrane protein RANKL and do not produce soluble RANKL, suggesting that neutrophils only support osteoclast function through intercellular contact. [65,66] However, bone homeostasis may be harmed by the hyperactive neutrophils brought on by infection or damage. Neutrophils directly prevent bone growth in osteoporosis brought on by long-term glucocorticoid therapy and chronic gout by interfering with osteoblast function. [67,68]

- *Macrophages*

Originating from the monocytic lineage, macrophages identify and eradicate harmful germs to carry out immunological sentinel and homeostatic tasks. A study discussing the formation and role of MPs in organs, including joints, was published in Nature. CX3CR1+ positive tissue resident MPs create an immune barrier by forming a layer at the synovial coating that mimics an epithelial layer. In contrast to illuviated MPs, these MPs use tight connections to prevent inflammation. They also self-renew locally and don't depend on circulating recruitment. [75] Using a mouse model of a femur fracture, researchers found that macrophages inhibit the final endochondral ossification by preventing the formation of hard callus, but they are not involved in the early phases of fracture healing. [69] However, by delaying the initial inflammatory response and blocking neovascularization, long-term, persistent inflammation mediated by M1 macrophages reduces the healing effectiveness of bone fractures. [70] Additionally, the bone microenvironment limits the growth of macrophages, while the enhanced myeloid differentiation of HSCs results in continuous recruitment of monocytes; consequently, the macrophages take on a pro-inflammatory phenotype that hinders the healing process. [71,72,73,74]

- *Dendritic Cells*

DCs are absent from bone tissue and the nearby BM matrix in the physiological state. [80] DCs and osteoclasts both originate from progenitor cells of monocytes and macrophages. Dendritic cells are essential for the start and control of T cell immunity against infections and malignancies, as well as for blocking immune reactions against environmental antigens or own tissues. [77,78] Dendritic cells (DCs) are the best at presenting antigens. Major Histocompatibility Complex II (MHC II), which effectively promotes T cell immunological activity and initiates the immune response, is highly expressed on the surface of DC membranes. [76] DCs don't seem to be involved in bone remodelling and are hardly ever observed in the bone itself or the surrounding stroma. Animals without DCs have no skeletal defects, according to observations. [79] However, a study on rheumatoid arthritis found that a considerable number of both immature and mature DCs were scattered across the surrounding bone tissue and gathered at the synovium's active lesion site. [81] DCs are found in the mouth's gingival tissue. In chronic periodontitis, DCs and T lymphocytes congregate in the tissue of the periodontal lesion, destroying the structure of the periodontal bone. [82] Consequently, it is thought that DCs may activate and regulate T cell function to indirectly influence inflammation-related bone loss. [83]

- *B Cells*

It is commonly known that B cells primarily contribute to humoral immunity, while T cells are essential for cellular immunity. The two can work together to strengthen the immune system and possibly accelerate conditions like Rheumatoid arthritis. [84] Furthermore, B cell dysregulation in autoimmune diseases such as rheumatoid arthritis can increase RANKL expression and osteoclastogenesis, leading to joint degradation and bone loss. Furthermore, periprosthetic joint infections contain B lymphocytes. [85] B-cell depletion raises inflammation and alveolar bone loss in mice with periodontitis, according to studies, suggesting that B cells may have a protective role in the development of periodontitis. [86] However, because it inhibits osteoblast activity, TGF-β1 generated by B cells may partially contribute to alveolar bone loss in periodontitis. [87]

- *T Help Cell 1 (Th1)/Th2 Cells*

The primary source of RANKL is Th1 cells. Through TNF-α, Th1 cells primarily stimulate the development of osteoclast precursor cells and activate osteoclast activity, which indirectly results in the absorption and destruction of bone tissue. [88] According to a thorough investigation by Sato et al., Th1 and Th2 cells both demonstrated the ability to prevent OC development by producing the classical cytokines IFN-γ and IL-4, respectively. [89] In inflammatory arthritis, IL-4 suppresses osteoclastogenesis and improves bone erosion by blocking NF-κB and JNK activation through a STAT-6-dependent mechanism. [90] The bone remodelling process will inevitably be impacted once pathogenic stimuli induce the imbalance in Th1/Th2 and Th17/Treg, leading to a variety of bone disorders. [91]

- *Th17*

Transformational growth factor β (TGF-β) and IL-6 stimulate naive T cells to develop into Th17 cells, which primarily release IL-17, IL-22, and IL-26 and encourage bone resorption. [96] Th17-cell-produced IL-17 stimulates the expression of RANKL on the surface of osteoblasts, bone marrow stromal cells, and osteoclast precursors, hence boosting osteoclast formation and preventing osteoblast differentiation and function. [97] Compared to Th1 cells, Th17 cells secrete more active RANKL, which directly accelerates the bone resorption process. [98]

Through the recruitment and activation of more immune cells, IL-17 indirectly promotes bone resorption by increasing the levels of TNF-α and IL-1 in bone tissue. [99] Along with the conventional Th1 and Th2 subsets of helper T cells, Th17

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T cells play a significant role as physiologists in several autoimmune disorders, including systemic lupus erythematosus and rheumatoid arthritis. [92] Halvorsen et al. concentrated on Th17 cells seen in RA patients' synovial tissue. They isolated a polyclonal T-cell line that produced IL-17. In addition to IL-17, these CCR6-positive cells also released IL-6, IL-10, TNF-α, and interferon-γ (IFN-γ) in vitro. The production of IL-17 is increased by exogenous IL-15. These findings demonstrate that RA patients' synovial tissue contains Th17 cells. [93] In vivo, Pollinger et al. demonstrated that Th17 cells have a more significant role in bone loss in collagen-induced arthritis. In subchondral regions, Th17 cells are found close to osteoclasts. Similar contributions from these T cells have been observed in RA patients' synovia. [94] Zwerina et al have demonstrated that IL-17 neutralization reduces local and systemic bone loss in TNF-α–mediated murine arthritis. These mice have enhanced Th2 differentiation, IL-4 and IL-12 expression, and more regulatory T cells, suggesting a central role of IL-17 in TNF-α–mediated arthritis. [95] In conclusion, osteoclastogenesis-supporting T cells, or Th17 cells, and the pro-inflammatory cytokine IL-17 they produce have a negative regulatory function in bone regeneration.

IV. DISCUSSION

The review states that acute inflammation is fundamental to the early stages of bone repair, as cytokines such as IL-1, IL-6, and TNF-α promote neutrophil and macrophage migration to the site of injury, facilitating the formation of hematomas and the migration of healing-related mesenchymal cells. [12,13,14,15] Specialized macrophages like osteomacs further illustrate the coordinated role of immune cells in coordinating early bone regeneration. [17,18] Additionally, through chemokine signalling, acute inflammation stimulates the osteogenic differentiation of mesenchymal progenitor cells [26], underscoring the need for controlled inflammation for successful bone remodelling. However, the very mediators that promote healing begin to tilt the scales in Favor of pathological bone resorption when chronic inflammatory diseases take over, especially in illnesses like rheumatoid arthritis, periodontitis, or inflammatory bowel disease. [19,20,21,22] By simultaneously decreasing osteoblast function and increasing bone-resorbing activity, key cytokines like RANKL, TNF-α, and IL-17 either directly or indirectly increase osteoclastogenesis. [23-25,88,95,97] Different immune cells have different effects.

Neutrophils can suppress osteoblast function in chronic inflammation or when exposed to glucocorticoids, despite being necessary for the initial response. [67,68] Macrophages exhibit adaptability; M1 types promote tissue regeneration and resolution, while M2 types contribute to chronic inflammation and poor healing. [33,34,70] T cells, particularly Th17 cells, worsen bone loss through IL-17-mediated mechanisms, whereas regulatory T cells (Tregs) counteract this by lowering inflammation and encouraging osteogenic activity. [58-63,92-99] Despite being mostly associated with humoral immunity, B cells can regulate bone remodelling by either producing osteoprotegerin (OPG) or increasing RANKL mediated osteoclastogenesis, depending on their activation state. [46,50,85] Furthermore, whereas dendritic cells are largely absent in healthy bone, they can accumulate in inflammatory areas and indirectly influence bone resorption through T cell control. [76-83] The discussion highlights bone remodelling as a dynamic process influenced by immunological signalling networks, forming the foundation of osteoimmunology, which could lead to advanced therapy for inflammatory bone disorders.

V. CONCLUSION

Inflammation has a dual function in bone remodelling, both a cause of damage and a catalyst for repair. commenced by studying the characteristics of inflammation, such as its stages, significant mediators, and the distinction between "good" and "bad" inflammation. This sets the stage for understanding its complex role in bone health. The concept of the osteoimmune paradox highlights the duality of immune cell influence, wherein the same mediators that promote healing can also drive degeneration under different conditions.

It became clear that inflammation isn't always the enemy; in fact, a well-controlled inflammatory response is essential for proper bone repair. But when it goes unchecked or becomes chronic, it can lead to bone damage and disease. This work emphasizes how inflammation influences bone's destiny by balancing the delicate line between repair and destruction by combining these elements. Although inflammation is context-dependent and depends on timing, severity, cellular actors, and molecular cues, it is not always harmful. More research in this field may result in targeted therapies that optimize inflammation's beneficial effects while minimizing its detrimental ones, improving the prognosis of bone-related diseases and accidents.

➢ *Data Availability Statement:*
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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