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The Place of Osteoimmunology in the Pathogenesis of Rheumatic Joint and Bone Diseases

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ABSTRACT

The bone and immune cells all share the same microenvironment, interact with each other, share common signaling pathways, collaborate, performing the functions of an "osteoimmune system". The same cytokines may have different and often opposite effects depending on the specific environment in which they function, the maturation stage of the target cells and/or the influence of other cytokines. Through osteoimmunology, the intimate mechanisms in the pathogenesis of many rheumatological diseases such as Rheumatoid arthritis, axSpA, autoinflammatory diseases, osteonecrosis, osteoarthrosis, osteoporosis are clarified. Osteoimmunology is a conceptual framework for decoding the complex language through which the immune system and bone communicate. This review summarizes the data accumulated to date on the interactions between the immune and bone systems of the human organism and reveals the bidirectionality of these interactions and their role in the pathogenesis of rheumatic joint and bone diseases.

Keywords: Osteoimmunology; Cytokines; Rheumatic Joint and Bone Diseases; Signal Pathways

Introduction: the «Embrace» of the Immune and Bone Systems

The skeletal system and the adaptive immune system developed simultaneously during the evolution of vertebrates. The implication is that certain components of the skeletal system are essential for the proper operation of the immune system (Boehm 2012). About 385 million years ago, the aquatic vertebrates moved to land and the skeletal system evolved to maintain the motor activity in terrestrial conditions. The adaptive immune system first appears in cartilaginous fish. The nuclear factor receptor activator ligand - κB (RANKL) is known from cartilaginous fish (OrthoDB database). The osteoclasts first appear in bony fish. Active bone metabolism, regulated by calciotropic hormones such as vitamin D and parathyroid hormone, has been known since the advent of amphibians. Immunoglobulin classes and lymph nodes are found only in terrestrial animals. The bone marrow serves as a site for communication and collaboration between bone and immune cells, working together to carry out crucial tasks such as strengthening the body, regulating mineral metabolism, and facilitating hematopoiesis (the production of blood cells) (Morrison and Scadden 2014). The concept of osteoimmunology originated from initial research demonstrating that immune cells secrete factors that activate osteoclasts (Horton et al. 1972; Mundy et al. 1974). Similar to other multifunctional cytokines in the TNF superfamily, the influence of RANKL extends beyond its role in regulating bone remodeling. It also plays a part in immune responses and the formation of immune organs. The RANKL/RANK pathway plays a critical role in the formation of important immune organs in mammals, including the thymus and lymph nodes. Additionally, the bone marrow houses hematopoietic stem cells (HSCs) [1]. The bone marrow contains hematopoietic stem cells (HSCs), myeloid and lymphoid progenitors, as well as mature immune cells, neutrophils, macrophages and T lymphocytes. Bone and immune cells share the same microenvironment and interact with each other, cooperating, performing the functions of an «osteoimmune system». In 2000, the term «osteoimmunology» was proposed by Arron and Choi to emphasize the T-lymphocyte-controlled regulation of osteoclastogenesis in the context of rheumatoid arthritis.

Subsequently, it has become evident that the immune and skeletal systems are subject to shared regulation by a variety of cytokines, chemokines, transcription factors, and signaling molecules. In addition, the evidence suggests that bone cells reciprocally regulate immune cells and hematopoiesis [1].

Accumulated scientific evidence on the communication between immune and bone cells has led to a revised understanding of bone remodeling. This new model posits that the phases of bone resorption and formation, which are in a constant state of balance, are subject to precise immunological regulation [2]. The skeletal and immune systems are intricately interconnected through intricate networks that work together to maintain homeostasis. Bone is a constantly changing tissue comprised of bone proteins that are infused with mineral crystals and interwoven with bone cells such as osteocytes (OCs), osteoblasts (OBs), and osteoclasts (OCLs). The osteoblast, which derives from the mesenchymal stem cell (MSC), has the potential to differentiate into other cell types such as chondrocytes, bone marrow stromal cells, and adipocytes [3]. Osteoclasts (OCLs) are specialized myeloid cells with multiple nuclei that are responsible for breaking down mineralized bone tissue through the secretion of lysosomal enzymes like tartrate-resistant acid phosphatase (TRAP) and cathepsin K [4]. OCL originates from a progenitor cell in the bone marrow, which allows differentiation to «professional» antigen-presenting cell (APC), i.e. dendritic cell and macrophage. Based on that data, OCL can also be considered a specialized immune cell. Under normal circumstances, osteoblasts (OBs), osteoclasts (OCLs), and osteocytes (OCs) engage in continuous communication with one another to maintain optimal bone quality and quantity in a homeostatic manner. Osteoblasts (OBs) secrete various signaling molecules such as macrophage colony-stimulating factor (MCSF), RANKL, and other stimulatory factors to direct the differentiation of myeloid lineage progenitor cells into osteoclasts (OCLs) [5]. The receptor activator of nuclear factor Kappa B (RANK) and its ligand (RANKL), along with the nuclear factor of activated T-cell (NFATc1), are essential for the communication between osteoclasts (OCLs) and osteoblasts (OBs). The expressed on the osteoclast precursor RANK interacts with RANKL and forms the RANK-RANKL complex, which activates the Wnt signaling pathway, leading to the stimulation of maturation, differentiation and activation of osteoclasts and inhibits their apoptosis. The activated T cells produce RANKL, which activates OCL, which is not followed by activation of OB, i.e. bone formation did not follow witch is the so-called pathological remodeling.

Other potential inducers of RANKL are the pro-inflammatory cytokines: TNFα, IL 1, 6, 17, VEGF (vascular endothelial growth factor). This association between pro-inflammatory cytokines and osteoclast formation explains why cytokine-targeted therapy delays structural bone damage in IMIDs. It is worth noting that RANKL and RANK also have a significant impact on the development of the lactating mammary gland during pregnancy, highlighting their pleiotropic effects [6]. Additionally, osteocytes (OCs), which were once believed to solely regulate bone remodeling, are now known to regulate immune cells and form the «endosteal niche.» Both osteoblasts (OBs) and osteoclasts (OCLs) play a role in the formation of the endosteal niche, which mobilizes hematopoietic stem cells (HSCs) [7]. Studies have shown that RANKL, which is produced by osteocytes (OCs), contributes to increased osteoclastogenesis and bone loss, as observed in estrogen-deficient conditions. Additionally, there is evidence supporting a link between OCs and the immune system, as in vivo ablation of OCs has been found to result in severe lymphopenia, according to Sato and colleagues. The conversation the relationship between the immune system and bones works in both directions, indicating that immune cells can also be impacted by bone cells. OCL has been shown to regulate the HSC niche directly and indirectly through OB. First, OCLs can increase the mobilization of HSCs by secreting cathepsin K, an important protein for their function. As a result, HSCs enter the circulation. As is known, the differentiation of OCL strictly depends on the RANKL / RANK path [8,9]. Studies have demonstrated that OCL (osteoclasts) can control the HSC (hematopoietic stem cell) niche both directly and indirectly by interacting with the interaction between RANKL and RANK, which are expressed by OCL precursors, leads to the recruitment of TNFR-associated factors (TRAFs). These TRAFs then trigger the differentiation of OCL by promoting the translocation of NF-kB to activated B and T cells. RANKL is also produced by activated T lymphocytes. The significance of RANKL in the context of immunology is highlighted by the fact that mice deficient in RANKL not only exhibit a bone phenotype characterized by osteopetrosis due to the absence of osteoclasts, but also display immunological abnormalities such as impaired lymphocyte development and lack of lymph node organogenesis.

Shared Signal Pathways

Cytokines and transcription factors, which act as mediators, are involved in both inflammation and bone metabolism. RANKL is expressed by immune system cells, particularly activated T and B lymp. TNF-α, IL-1, IL-6, and IL-17 are inflammatory cytokines that play a critical role in acute and chronic inflammation. These cytokines are potent stimulators of bone resorption. T-lymphocytes present in the bone marrow are important immune cells that play a crucial role in regulating bone remodeling. Inflammatory cytokines produced by activated T lymphocytes induce bone resorption during inflammatory diseases or conditions characterized by low-grade systemic inflammation. T helper (Th17) cells are involved in stimulating bone resorption and have a significant impact on bone loss observed in inflammatory diseases such as psoriasis, rheumatoid arthritis, periodontitis, Crohn's disease, and chronic ulcerative colitis. Th17 cells promote osteoclastogenesis by producing cytokines such

as IL-17, RANKL, TNF-α, IL-1, and IL-6, in addition to low levels of IFN-γ. IL-17 triggers the release of RANKL from both osteoblasts (OBs) and osteoclasts (OCs), thereby activating RANK signaling in osteoclasts (OCLs). Conversely, T regulatory (Treg) cells inhibit osteoclastogenesis and promote bone formation. The osteoclast-associated receptor (OSCAR) not only facilitates interactions between osteoblasts (OB) and osteoclasts (OCL), but it also plays a role in regulating both adaptive and innate immunity [10]. OSCAR, initially identified as a regulator of osteoclast differentiation and an immunomodulatory mediator in bone, is believed to be involved in cellular activation and inflammation in atherosclerosis [11]. TNF-α promotes the expression of OSCAR and other receptors on the surface of monocytoid peripheral blood cells that play a crucial role in the differentiation of osteoclasts (OCLs) [12]. Cytokines have inherent pleiotropic functions, and it is not surprising that the same cytokines may have different and even opposing effects depending on various factors such as the specific environment in which they operate, the stage of maturation of target cells, and the influence of other cytokines. It is seen that not only do immune system cells regulate bone remodeling, but also bone cells are able to affect the immune system [13-15].

Key Cellular and Humoral Participants in the Cross Communication Between the Immune System and the Bones

T cells are a key component of the adaptive immunity. The links between T cells and the bone biology are numerous: essentially all T cell subtypes are able to affect bone cells (mostly OCLs). However, the role of Th17 and T-reg cells is particularly important. Th17 cells are thought to be the majority of osteoclastogenesis-inducing T cells. These cells stimulate the expression of macrophage-colony-stimulating factor (M-CSF) and RANKL in osteoblasts and stromal cells, resulting in the production of RANKL and TNF-α. Furthermore, they increase the expression of RANK in osteoclast precursor cells [16]. These characteristics make them potent inducers of osteoclastogenesis, which is why they have already been described as «players» in the bone lesions in RA [17] and multiple myeloma [18]. The role of T-reg cells in inhibiting osteoclastogenesis is well established. This is achieved through both soluble factor-mediated mechanisms as well as contact-mediated mechanisms [19]. Dendritic cells (DCs) are a type of antigen-presenting cells that play a crucial role in directing cell-mediated immunity towards appropriate targets with speed and accuracy while preventing autoimmunity [20]. Historically, the role of dendritic cells (DCs) in bone biology has been considered to be indirect, primarily through their interaction with T cells [21]. Later studies have shown that dendritic cells not only present antigens to T cells but also play a role in regulating the activity and balance of T cell subtypes through cytokine signaling [22]. The common myeloid origin of DCs and OCLs should not be overlooked. Neutrophils are also involved in bone biology, particularly in inflammation-induced bone loss [23]. Neutrophils are typically the first type of immune cell to migrate to the site of bone damage, where they release chemokines, cytokines, and other small molecules that act as immunomodulatory factors. The secretion of chemokines CCL2 and CCL20 by neutrophils attracts Th17 cells, which contributes to bone loss. However, the absence of neutrophils can also result in bone loss due to the activation of IL-17-mediated local inflammation [24].

Activated neutrophils express RANKL at the site of inflammation, which leads to their active involvement in osteoclastogenesis. This process can increase juxta-articular osteoporosis associated with rheumatoid arthritis [25]. In summary, however, the role of neutrophils in osteoimmunology is not fully understood, the general consensus is that activated neutrophils are inducers of osteoclastogenesis, directly and indirectly. B-cells: B-cell development is regulated by various factors, including RANKL, OPG, IL-7, and CXCL12, which are secreted by bone marrow stromal cells and osteoblasts [26]. New research indicates that B cells not only rely on RANKL for their development, but they also produce RANKL and use it as an autocrine signaling molecule [27]. Natural killer (NK) cells: Natural killer (NK) cells participate in the regulation of bone homeostasis along with other lymphocytes. NK cells play a role in regulating bone homeostasis and are also involved in the pathogenesis of bone damage in rheumatoid arthritis by inducing osteoblast cell death [28]. NK cells have a dual role in RA-induced bone loss as they can induce OB cell death, making them a potential therapeutic target for reducing bone loss [29]. However, NK cells are also necessary for delaying RA progression, which raises doubts about the effectiveness of anti-NK therapy in RA. Inflammation and inflammatory factors: IFN-γ, produced by various immune system cells such as T and B cells, NK cells, monocytes/macrophages, and dendritic cells, plays a crucial role in both innate and adaptive immunity as well as in the regulation of inflammation [30,31]. In bones, IFN-γ affects both OB and OCL. IFN-γ has a positive effect on OBs, which usually produce low levels of this cytokine. This is because IFN-γ can activate genes that are involved in osteoblast differentiation. IFN-γ has been found to have an inhibitory effect on the differentiation of osteoclasts (OCLs) by counteracting the effects of M-CSF on OCL precursors [31]. It does so by reducing the expression of c-fms receptor, which leads to a reduced number of pre-OCLs that are positive for RANK [32]. In addition, IFN- γ induces osteoclast apoptosis. The importance of IFN type I in bone homeostasis was underscored by the observation that mice deficient in type I-IFN-receptor component (IFNAR1) spontaneously developed osteopenia accompanied by enhanced osteoclastogenesis [33].

Both types of interferons (IFNs) inhibit osteoclastogenesis through the activation of the signal transducer and activator of transcription 1 (STAT1) in the skeletal system [34]. In the skeletal system, both types of IFN inhibit osteoclastogenesis by STAT1. INF-γ

also inhibits the effect of PTH and IL-1 on stimulating OCL formation in bone marrow cultures [35]. INF-γ inhibits RANK signaling but does not directly inhibit bone resorption from mature OCLs [36]. It has been reported that INF-γ can also stimulate bone resorption by enhancing the production of RANKL and TNF-α in T lymphocytes [37]. Inflammatory cytokines, which are produced mainly by macrophages such as IL-1, TNF and IL-6, stimulate osteoclastogenesis. They are called osteoclastogenic cytokines because of their resorptive effect on the bone [38]. IL-1 stimulates TRAF6 (and therefore activates NF-κB and MAPKs) and synergizes with RANKL to induce mature OCL. Activated T cells expressing RANKL have the potential to induce osteoclast differentiation by directly affecting osteoclast progenitor cells. T cells also secrete various anti-inflammatory cytokines such as IL-4, so the effects of T cells on the osteoclastogenesis depend on the balance between pro- and anti-inflammatory factors produced by them. For example, CD4 + T helper cell subgroups Th1 and Th2 produce IFN-γ and IL-4 with an anti-osteoclastogenic effect. Recently, researchers have been considering the role of T cells in non-inflammatory metabolic bone diseases and postmenopausal osteoporosis. TNF and other inflammatory cytokines not only cause local inflammation but also play a direct and indirect role in activating OCLs. Such osteoimmunological pleiotropy may explain the efficacy of RANKL-specific antibody not only in postmenopausal osteoporosis but in rheumatoid arthritis and also its preventive effect on the bone metastases [39]. TNF-α stimulates the formation of OCL and enhances the bone resorption in vivo [40-42]. The ability of TNF-α to stimulate OCL formation from osteoclast precursor is dependent on IL-1 [43], while TNF-α-induced osteolysis is dependent on M-CSF [44].

The results of studies with RANK-deficient mouse cell cultures show that TNF-α directly stimulates the formation of OCL, independent of RANK [45]. TNF-α also inhibits osteoblast differentiation and collagen synthesis [46-48]. In addition, TNF-α is highly proapoptotic to osteoblasts [49], possibly by signaling Fas-Fas ligand (FasL). Fas ligand (FasL), also known as CD95L or CD178, is a protein that is found on the surface of cells and belongs to the TNF family. When FasL binds to its receptor, it can induce a process called apoptosis, which is a type of programmed cell death. The normal bone development does not seem to be affected by TNF-α, as the absence of abnormal bone phenotypes has been observed in TNF receptor 1 and TNF receptor 2. However, TNF-α can affect bone in inflammatory conditions. IL-7, which plays roles in B- and T-cell lymphopoiesis, also regulates the bone homeostasis [50]. The mechanisms by which IL-7 affects bone cells are controversial. The systemic application of IL-7 stimulates the creation of OCLs by boosting the production of cytokines that promote osteoclastogenesis in T cells [51]. IL-8 is a chemokine of the CXC family, which is produced by osteoclasts. It has been found to stimulate the process of osteoclastogenesis and bone resorption, and this effect is not dependent on the RANKL pathway [52,53]. Activated T and B lymphocytes produce IL-10, which has a direct inhibitory effect on the differentiation of osteoclasts and osteoblasts. IL-17 and IL-23 belong to a group of six cytokines called the IL-17 family, which are critical for the adaptive immune system's response [54]. They are produced by a specific subset of CD4+ T lymphocytes called Th17, and they have a strong ability to promote the formation of osteoclasts that rely on IL-17 [55]. IL-17A promotes the development of osteoclasts in cultures that include both hematopoietic cells and osteoblasts, by inducing the production of prostaglandins and increasing the expression of RANKL [56]. IL-23 is linked to IL-12 in its effect, as both cytokines are critical for the differentiation and proliferation of Th17 cells, along with TGF-β and IL-6 [57]. IL-18, which belongs to the IL-1 superfamily, is found to be elevated in inflamed areas such as those affected by rheumatoid arthritis. While osteoblasts produce IL-18, it can inhibit the formation of osteoclasts through different mechanisms. This includes an increase in the expression of GM-CSF in T cells. IL-18 has been shown to stimulate the production of INF-γ in OB cultures in vitro.

The inhibitory effect of IFN-γ on osteoclastogenesis is further enhanced by the presence of IL-12. Studies have demonstrated that IL-18 can increase the production of osteoprotegerin (OPG). The effects of IL-18 on osteoclastogenesis are indirect and mediated through its effects on T lymphocytes [58]. IL-13 and IL-4 decrease bone resorption that is stimulated by IL-1 by reducing the levels of prostaglandin and the activity of cyclooxygenase-2. Toll-like receptor stimulators (TLRs): TLRs (Toll-like receptors) play a crucial role in initiating innate immune responses and are prominently expressed on cells responsible for presenting antigens, such as macrophages and dendritic cells [59]. Since macrophages, dendritic cells, and OCLs have common progenitors, it is not surprising that TLRs are also found in the bone cells. Direct TLR signaling on OCL precursors, including TLR4, inhibits RANKL-mediated osteoclastogenesis [60], which seems controversial as bacterial infections cause inflammation by inducing proinflammatory cytokines in response to TLR ligands [60]. Although TLR stimulation inhibits osteoclast differentiation, TLR ligand treated OCL precursors retain pronounced phagocytic activity. Therefore, TLR stimulation of OCL precursors is likely to differentiate them into non-immune cells, such as mature OCLs. Cathepsin K is a cysteine protease identified in OCLs. Cathepsin K inhibition was recently reported to suppress not only osteoclastic bone resorption but also the autoimmune inflammation. Further studies revealed a role for cathepsin K in regulating Th17 differentiation by mediating TLR9 activation of dendritic cells and the production of cytokines such as IL-6 and IL-23 [61]. This is another example of a molecule originally found in the bones that was later shown to play a role in regulating the immune system. Cathepsin K is a key osteoclast collagenase. The signal for OCL migration to the future site of resorption are the microfractures, as a result of which OCs matrix metalloproteases

enter the extracellular matrix of the bone. Cytokines such as RANKL, OPG, M-CSF and TGFα are released under the action of these metalloproteases. Specific products of matrix protein proteolysis by metalloproteases serve as signals for OCLs attachment. After the attachment, OCLs change their functional activity and switch to bone resorption. The primary enzyme involved in bone resorption is cathepsin K. Cathepsin K is expressed in pre-OCL, epithelium of bronchi, bile ducts and thyroid gland, chondrocytes and smooth muscle cells of the arteries affected by atherosclerosis.

Cathepsin K is able to cleave many proteins: elastin, gelatin, osteopontin, osteonectin, collagen, aggrecan. A characteristic difference between cathepsin K and other proteases that only cleave collagen telopeptides is that it is also capable of cleaving 3-helix collagen [62]. In the field of osteoimmunology discovering of new molecules continues in recent years. This is the case with another bone mass regulator that has been discussed in the last few years: LipoCaliN-2 (Lcn2). The protein, known as lipocalin, is connected with neutrophil gelatinase (NGAL) as it has the ability to attach to and stabilize the MMP9 factor, which is responsible for the movement of neutrophils out of the bloodstream and into tissues (extravasation). Furthermore, Lcn2 is upregulated during inflammation, and its function in inflammatory disorders still needs to be investigated. This molecule's role in innate immunity is clear. In vitro mechanical overburden resulted in the upregulation of Lcn2 in osteoblasts, as demonstrated in a study conducted in 2009 [63]. It was unexpected that removing the production of Lcn2 genetically actually leads to a decrease in bone mass instead of an increase, as it was previously believed that Lcn2 was detrimental to bone health. This paradoxical effect is thought to be caused by Lcn2 overexpression damaging osteoblasts and interfering with their energy balance, ultimately leading to osteoblast dysfunction [64]. Osteoimmunology clarifies the intimate mechanisms in the pathogenesis of various diseases such as rheumatoid arthritis [65], ax SpA, autoinflammatory diseases, osteonecrosis, recovery from bone fractures, myelodysplasia, leukemia, neoplasms, metabolic syndrome. The field of osteoimmunology provides a novel perspective for investigating bone-related disorders like osteoporosis (OP) and osteoarthritis (OA), which have not conventionally been recognized as inflammatory conditions [66]. Understanding the intricate communication between the immune [67-73] system and bones is crucial for identifying potential therapeutic targets in various rheumatic and non-rheumatic diseases that involve [74-82] similar mediators and signaling pathways [83-92]. This review summarizes the currently accumulated data on the mutual «embrace» of the immune and skeletal systems of the human body [93-102]. And as it is with any hug, there is a two-way interaction [103-116]. All this again tells us that when studying human health in depth, we must always strive to reveal the integrity and interconnectedness of the processes in the human body in health and disease [117-130].

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