Paget’s disease of bone: an osteoimmunological disorder?

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Abstract: Osteoimmunology represents a large area of research resulting from the cross talk between bone and immune systems. Many cytokines and signaling cascades are involved in the field of osteoimmunology, originating from various cell types. The RANK/receptor activator of nuclear factor Kappa-B ligand (RANKL)/osteoprotegerin (OPG) signaling has a pivotal role in osteoimmunology, in addition to proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, and IL-17. Clinically, osteoimmunological disorders, such as rheumatoid arthritis, osteoporosis, and periodontitis, should be classified according to their pattern of osteoimmunological serum biomarkers. Paget’s disease of bone is a common metabolic bone disorder, resulting from an excessively increased bone resorption coupled with aberrant bone formation. With the exception of the cellular responses to measles virus nucleocapsid protein and the interferon-gamma signature, the exact role of the immune system in Paget’s disease of bone is not well understood. The cytokine profiles, such as the increased levels of IL-6 and the interferon-gamma signature observed in this disease, are also very similar to those observed in other osteoimmunological disorders. As a potential osteoimmunological disorder, the treatment of Paget’s disease of bone may also benefit from progress made in targeted therapies, in particular for receptor activator of nuclear factor Kappa-B ligand and IL-6 signaling inhibition.

Keywords: Paget’s disease of bone, SQSTM1/p62, osteoimmunology, osteoclast, RANKL

Introduction

Osteoimmunology at a glance

This narrative review of the literature presents first, data on osteoimmunology and osteoimmunological disorders, and second, discusses why Paget’s disease of bone should be considered as a potential osteoimmunological disease. Osteoimmunology is an emerging research area that is the result of the cross talk regarding the relationship between bones and the immune systems. Various cell types are involved in osteoimmunology processes, but most of them originate from the hematopoietic tissue. At the third week of human embryonic development, stem cell lineages are formed in the yolk sac.1,2 These lineages multiply asymmetrically, maintaining their original population and differentiating to other types of more specialized blood cells.3 The immunological basic steps begin with the primary formation of hematopoietic stem cells lineage, which first appears in the yolk sac, followed by mesodermic of aorta, gonads, and nephrons (mesonephrons), and from there will migrate later to liver, spleen, and lymph nodes. Around the fourth month of fetal life, these hematopoietic stem cells migrate to bone marrow, and at the time of birth, bone marrow is responsible for all hematopoietic function.4,5 Likewise, bone marrow pluripotent stem cells – which are stimulated by growth factors – are divided into two types of multipotent progenitor stem cells: common lymphoid cells and common myeloid cells (Figure 1).
Lymphoid cells

Common lymphoid cells are further divided into three cell types: committed pro-natural killer stem cells, pro-T stem cells, and pro-B stem cells. Pro-natural killer stem cells migrate to peripheral circulation, where they become natural killer cells. Natural killer cells differ from B-cells and T-cells by not having clusters of differentiation 3 (CD3) like T-cells, nor CD19 and CD20 like B-cells. Pro-T stem cells (naïve T-cells) migrate from bone marrow to peripheral circulation, mature in thymus gland, and then some return to peripheral circulation where they become mature T-cells. Some of these mature cells will become T helper (TH) naïve (containing markers CD3, CD4) lymphocytes or T cytotoxic (containing markers CD3, CD8) lymphocytes. TH naïve cells differentiate into TH1 cells and TH2 cells. TH1 cells when activated by interleukin (IL)-4 and IL-5 contribute to convert B-cells to plasma cells called active B-cells producing immunological antibodies. TH2, when activated by interferon-gamma (IFN-γ) and tumor necrosis factor-α (TNF-α), contribute to activate monocytes to be highly active macrophages, epithelioid cells (modified monocytes), and giant cells. IFN-γ receptor knockout mice showed exaggerated bone destruction in inflammatory arthritis in comparison with normal mice. IFN-γ induces TNF receptor-associated factor 6 (TRAF6) ubiquitination and degrades proteolytic TRAF6, ultimately leading to the inhibition of receptor activator of nuclear factor Kappa-B ligand (RANKL)-mediated osteoclastogenesis.6,7 Activities of TH2 cells constitute the humoral immunity, while activities of TH1 cells and T cytotoxic cells create the cellular immunity. Pro-B stem cells differentiate in turn to be mature B-cells in peripheral blood circulation.

Myeloid cells

Common myeloid progenitor cells differentiate into granulocyte/macrophage progenitor and megakaryocyte erythroid progenitor (MKEP) cells (Figure 1). Granulocyte/macrophage progenitor cells are divided into monocytes and granulocytes. Later, monocytes migrate to some tissues, reside there, and change their name depending on the tissue, such as monocytes that migrate to inflammation sites are called macrophages, monocytes that migrate to skin are called Langerhans cells, and monocytes that migrate and reside in bone tissue, which will be differentiated into bone resorbing cells are called osteoclasts.8,9 Osteoclasts work mainly at the bone resorption activity controlling the bone turnover cycle.10 Osteoclasts are large multinucleated cells of hematopoietic origin. They have the capability of removing organic and mineral components of bone. The macrophage

Figure 1 Main osteoimmunological cell differentiations and cell lineages. Abbreviation: NK cell, natural killer cell.
Osteoimmunological cytokines

IL-1 is a very essential cytokine in osteoimmunological processes. The analysis of supernatants from phytohemagglutinin-stimulated peripheral blood monocytes in healthy humans suggested that IL-1 acts as the main stimulus of osteoclast-activating factor, which has a central role in osteoclastogenic activity. Subsequently, the same bone resorbing stimulating activity was found in TNF-α and IL-6. Indeed, IL-1, IL-6, and TNF-α increase the osteoclast response to RANKL and consequently osteolysis (Table 1). Estrogen withdrawal after menopause has the same stimulating effect, increasing osteoclastic activity through IL-1, IL-6, and TNF-α effects. Proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-17 (Table 1) are also elevated in patients with rheumatoid arthritis, contributing to increased RANKL expression and subsequent osteolysis. Schett et al have reviewed the important relation between autoimmunity and joint erosion in rheumatoid arthritis, revealing the presence of anti-citrullinated protein antibodies and anti-carbamylated protein antibodies in serum of the patients with rheumatoid arthritis. Molecular interaction between anti-citrullinated protein antibodies and the surface of osteoclast precursor cells via citrullinated vimentin induces differentiation and production of bone-resorbing osteoclasts, resulting in excessive bone resorption. Vitamin D₃, prostaglandin E₂, parathyroid hormone, in addition to IL-1, IL-6, IL-11, and TNF-α, can also induce RANKL expression, leading to excessive osteoclastogenesis (Figure 2). Activated T-cells were also reported to regulate bone loss and activation of osteoclastogenesis in vitro through RANKL. Contrariwise, TNF-stimulated gene 6 protein is an inflammation-induced protein that can inhibit osteoblastogenesis and osteoclast activation. In addition, immunoreceptor tyrosine-based activation motif (ITAM) pathway may contribute to the relationship between immune system and bone as a co-stimulatory pathway in osteoclasts. ITAM-dependent receptors regulate myeloid-derived cells functions. Furthermore, ITAM-containing adapter proteins such as DNAX activation protein-12 and the Fc epsilon receptor I gamma chain (FCER1G) play an essential role in osteoclast differentiation. Suppression of calcineurin–nuclear factor of activated T-cells signaling can reduce the activity of ITAM pathway in the late stage of osteoclast differentiation, leading to the reduction of osteoclast differentiation and activity. Calcium signaling induces the calmodulin-dependent kinase pathway role in osteoclast formation and plays a crucial role in the autoamplification of the transcription factor nuclear factor of activated T-cells cytoplasmic-1. Further, activation of TRAF6 and c-Fos pathways by RANKL leads to autoamplification of nuclear factor of activated T-cells cytoplasmic-1 and enhances osteoclastogenesis.

Most frequent rheumatic osteoimmunological disorders and their related serum biomarkers

The most frequent rheumatic osteoimmunological disorders regroup bone metabolic diseases, such as osteoporosis and Paget’s disease of bone, systemic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis, and other rheumatic diseases including osteoarthritis and spondyloarthritis, whereas periodontitis is frequently associated with systemic rheumatic conditions (Table 2). In almost all these disorders, serum levels of osteoimmunological biomarkers have been characterized in the literature (Table 2), and they can be combined to define a
<table>
<thead>
<tr>
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<th>Cells or sites of production</th>
<th>Roles in osteoimmunology</th>
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<td>Increases osteoclasts formation and bone resorption</td>
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<td>Fibroblast growth factor (acidic)</td>
<td>Bone matrix, osteoblasts</td>
<td>Increases bone formation</td>
<td>51</td>
</tr>
<tr>
<td>Fibroblast growth factor (basic)</td>
<td>Bone matrix, osteoblasts</td>
<td>Increases bone formation</td>
<td>51</td>
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<tr>
<td>GM-CSF</td>
<td>Stromal cells, Paneth’s cells, macrophages, dendritic cell, mast cells, endothelial cells, smooth muscle cells, fibroblasts, chondrocytes, as well as IL-23-stimulated TH17 cells, IL-1b-stimulated TH1 and TH17 cells</td>
<td>Induces stem cells to produce granulocytes (neutrophils, eosinophils, basophils) and monocytes, RANKL signaling and osteoclastogenesis inhibition</td>
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<td>Insulin growth factor-1</td>
<td>Osteoblasts, bone matrix</td>
<td>Increases bone formation</td>
<td>53</td>
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<td>Interferon-γ</td>
<td>TH1 cells, natural-killer cells</td>
<td>Immunological natural antiviral and antitumor</td>
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<td>Interleukin-1 β</td>
<td>Leukocytes, osteoblasts, tumors</td>
<td>Increases osteoclasts, formation, and bone resorption</td>
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<tr>
<td>Interleukin-4</td>
<td>TH2 cells, NKT cells, and unclear but possible other sites are mast cells and basophils</td>
<td>Helps in bone formation</td>
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<td>Interleukin-5</td>
<td>Lymphocytes T Helper 2 (TH2)</td>
<td>Plays essential role for thymic stromal lymphopoietin in TH2-mediated immunity (lymphocyte development)</td>
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<td>TH2 cells, dendritic cells, leukocytes, osteoblasts, tumors</td>
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<tr>
<td>Interleukin-10</td>
<td>TH2 cells</td>
<td>Induces eosinophil to proliferate, to differentiate, to be mature, and to migrate then to survive</td>
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<tr>
<td>Interleukin-17</td>
<td>TH17 cells, memory T-cells</td>
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<td>M-CSF (CSF-1)</td>
<td>Osteoblasts/stromal cells</td>
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<td>Osteoblasts/stromal cells</td>
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<tr>
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<td>Platelets, osteoblasts, bone matrix, tumors</td>
<td>Increases osteoclasts formation, and bone resorption, and increases bone formation</td>
<td>51</td>
</tr>
<tr>
<td>RANKL</td>
<td>Osteoblasts/stromal cells, osteocytes, T-cells</td>
<td>Increases differentiation and maturation of osteoclasts, and bone resorption</td>
<td>26</td>
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<tr>
<td>Transforming growth factor-β</td>
<td>Osteoblasts, bone matrix, leukocytes</td>
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<td>Tumor necrosis factor-alpha (TNF-α)</td>
<td>Monocytes/macrophages, TH1 cells</td>
<td>Involved in lipid metabolism, coagulation, insulin resistance, and endothelial function</td>
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<tr>
<td>Tumor Necrosis Factor-beta (TNF-β)</td>
<td>Leukocytes, tumors</td>
<td>Helps in bone formation</td>
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**Abbreviations:** GM-CSF, Granulocyte-macrophage colony-stimulating factor; IL, Interleukin; TH, T helper; RANKL, Receptor Activator of Nuclear factor Kappa-B Ligand; NKT, natural-killer T; M-CSF, macrophage-colony stimulating factor.
specific osteoimmunological pattern associated with a given rheumatic disease. For example, bone formation markers are usually increased in all these diseases, except in osteoporosis and rheumatoid arthritis (decreased level) and in systemic lupus erythematosus and systemic sclerosis (normal level). Bone resorption markers are also usually increased except for osteoarthritis and systemic lupus erythematosus (normal level). In addition, some proinflammatory cytokines may be of paramount importance at differentiating different rheumatic disorders. IL-17 and IL-6 levels are usually simultaneously increased in the same disorders, except for Paget’s disease of bone and systemic sclerosis; in both diseases, IL-6 is elevated but not IL-17. Finally, the pattern of IFN-γ serum levels in rheumatic diseases is very interesting: it is increased in almost all diseases, with the exception of osteoporosis and psoriatic arthritis (decreased level), and rheumatoid arthritis and ankylosing spondylitis (normal level). Overall, a combination of one serum biomarker of bone formation, one bone resorption biomarker, two proinflammatory cytokines such as IL-17 and IL-6 in addition to IFN-γ serum levels would be able to classify with a good sensitivity the most frequent rheumatic osteoimmunological disorders. Adding other already available biomarkers in clinical practice, such as autoantibodies, would increase the specificity of such a combination, and its clinical utility (ie, combination of markers for outcome/prognosis prediction and/or a pharmacogenomic test to guide the choice of any targeted biotherapy) may further be validated in prospective cohorts.

**Paget’s disease of bone as a potential osteoimmunological disorder**

**Paget’s disease of bone**

Paget’s disease of bone is the second most frequent metabolic bone disorder after osteoporosis, where more than 3% of Caucasians older than 55 years are affected. This disorder is characterized by an excessive increased bone resorption by osteoclasts accompanied by aberrant osteoblastic bone formation. This aberrant bone remodeling causes fragile and weaker bones. To date, about 30 mutations in SQSTM1/p62 gene have been reported in familial forms and unrelated patients with Paget’s disease of bone. Furthermore, several common single nucleotide polymorphisms have been associated with Paget’s disease of bone, in genome-wide association study, in particular in CSF1, OPTN, TNFRSF11A, PML, RIN3, and NUP205 genes. The consequences of these polymorphisms on osteoclast phenotype and activity are yet unknown.

**SQSTM1/p62 role and importance of osteoclastogenesis in Paget’s disease**

The SQSTM1/p62 protein anatomical structure has some important domains that regulate their essential functions such as Phox and Bem1p (PB1), ZZ, TRAF6 binding domain, LIR, KIR, and ubiquitin-associated (UBA) domains. PB1 plays a role in adipogenesis by inhibiting ERK1, and it also activates NF-κB pathway through interaction with PKCζ. ZZ domain activates NF-κB through the interaction with receptor interacting protein.
<table>
<thead>
<tr>
<th>Bone metabolic diseases</th>
<th>Systemic autoimmune rheumatic diseases</th>
<th>Other rheumatic diseases</th>
<th>Periodontitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>References</strong></td>
<td><strong>OP</strong></td>
<td><strong>PDB</strong></td>
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<tr>
<td></td>
<td><strong>RA</strong></td>
<td><strong>SLE</strong></td>
<td><strong>SSc</strong></td>
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<tr>
<td></td>
<td><strong>OA</strong></td>
<td><strong>PsA</strong></td>
<td><strong>AS</strong></td>
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<tr>
<td><strong>Bone formation markers</strong></td>
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<tr>
<td>Total alkaline phosphatase</td>
<td>++</td>
<td>=</td>
<td></td>
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<tr>
<td>Bone alkaline phosphatase</td>
<td>++</td>
<td>=</td>
<td></td>
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<tr>
<td>Osteocalcin</td>
<td>–</td>
<td>+ or =</td>
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<tr>
<td>P1NP</td>
<td>++</td>
<td>=</td>
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<tr>
<td>P1CP</td>
<td>+</td>
<td>=</td>
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<tr>
<td>SPARC</td>
<td></td>
<td></td>
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<tr>
<td>Sclerostin</td>
<td>+</td>
<td>=</td>
<td></td>
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<tr>
<td>Dickkopf-related protein 1</td>
<td>+</td>
<td>=</td>
<td></td>
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<tr>
<td><strong>Bone resorption markers</strong></td>
<td></td>
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<tr>
<td>CTX-1</td>
<td>++</td>
<td>++</td>
<td></td>
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<tr>
<td>ICTP</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Urinary pyridinoline</td>
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<td>Osteoprotegerin</td>
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<td>+</td>
<td></td>
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<td>TRAP5b</td>
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<tr>
<td>RANKL</td>
<td>++</td>
<td>=</td>
<td></td>
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<tr>
<td>uNTX</td>
<td>++</td>
<td>=</td>
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<tr>
<td>Matrix metalloproteinases</td>
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<td></td>
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<tr>
<td>Osteopontin</td>
<td>+</td>
<td>++</td>
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<td><strong>Cytokines</strong></td>
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<tr>
<td>Interleukin-17</td>
<td>+</td>
<td>–</td>
<td></td>
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<tr>
<td>Interleukin-6</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Tumor necrosis factor-α</td>
<td>+</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>+</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>–</td>
<td>=</td>
<td></td>
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<tr>
<td>Interleukin-4</td>
<td>–</td>
<td>=</td>
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</tr>
</tbody>
</table>

**Notes:** ++, elevated levels; +++, very elevated levels; =, normal levels; –, decreased levels; ––, very decreased levels.

**Abbreviations:** OP, osteoporosis; PDB, Paget's disease of bone; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSC, systemic sclerosis; OA, osteoarthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis; P1NP, serum procollagen N-propeptide of type I collagen; P1CP, carboxy-terminal propeptide of type I procollagen; SPARC, Serum protein acidic and rich in cysteine; CTX-1, serum cross-linked C-telopeptide of type I collagen; ICTP, cross-linked carboxyterminal telopeptide of type I collagen; TRAP-5b, Tartrate-resistant acid phosphatase 5b; RANKL, Receptor activator of nuclear factor-κB ligand; uNTX, Urinary cross-linked N-telopeptide of type I collagen.
Interaction of TRAF6 with the TRAF6 binding domain can activate NF-kB pathway. SQSTM1/p62 can activate autophagy by interaction of LC3 with LIR domain, and autophagy can be inhibited by mTOR. The UBA domain of SQSTM1/p62 has a very important role for this protein function; it interacts non-covalently with ubiquitin protein to perform post-transcriptional modifications and degradation by 26S multi-subunit protease or by autophagy. The UBA domain also has an important role in induction and activation of some transcription factors such as NF-kB. In osteoclasts, NF-kB–RANK signaling pathway is very important for osteoclastogenesis. With impairment of UBA functions, ubiquitin protein cannot interact with its domain in SQSTM1/p62 disrupting the autophagy and NF-kB signaling pathways, and consequently, osteoclastogenesis.26,30,31 The KIR domain of SQSTM1/p62 plays a role in oxidative stress with Keap1 (cysteine-rich protein) that has antioxidant effect. Several studies have found a relationship between viral infections and excessive enhanced osteoclasts activity.42 Inclusion bodies contained in osteoclasts were reported to be similar to Paramyxoviral nucleocapsids. Measles virus, respiratory syncytial virus, and canine distemper virus may play a role in Paget’s disease of bone.43 The expression of measles virus nucleocapsid protein (MVNP) in osteoclasts was reported to lead to the formation of pagetic-like osteoclasts. MVNP is known to increase the production of IL-6 that in turn leads to increase the production of TAFII-17 and increase the sensitivity of osteoclasts to 1,25-(OH)2D3. The pagetic phenotype of osteoclast is characterized by hypermultinucleation and hypersensitivity to 1,25-(OH)2D3. NF-kB signaling can be increased in cells by increasing the production of IL-6 and IL-1.44

Environmental factors
Environmental factors may also contribute to Paget’s disease of bone.26 Although controversial in the literature, several studies have found a relationship between viral infections and excessive enhanced osteoclasts activity.42 Inclusion bodies contained in osteoclasts were reported to be similar to Paramyxoviral nucleocapsids. Measles virus, respiratory syncytial virus, and canine distemper virus may play a role in Paget’s disease of bone.43 The expression of measles virus nucleocapsid protein (MVNP) in osteoclasts was reported to lead to the formation of pagetic-like osteoclasts. MVNP is known to increase the production of IL-6 that in turn leads to increase the production of TAFII-17 and increase the sensitivity of osteoclasts to 1,25-(OH)2D3. The pagetic phenotype of osteoclast is characterized by hypermultinucleation and hypersensitivity to 1,25-(OH)2D3. NF-kB signaling can be increased in cells by increasing the production of IL-6 and IL-1.44

Paget’s disease as a potential osteoimmunological disorder
Paget’s disease of bone should be considered as a potential osteoimmunological disorder for several reasons. First, the RANKL-NF-kB signaling has a major role in pagetic osteoclast differentiation and activation, and the cytokine profile observed in this disease is very similar to those observed in other osteoimmunological diseases (Table 1). However, the exact role of the immune system in Paget’s disease of bone is not very well understood, except for cellular responses to...
MNVP. Second, dendritic cells may also play a role in the pathogenesis of Paget’s disease of bone. Immature myeloid dendritic cells express CDw150, a signaling lymphocyte activation molecule acting as a receptor for measles virus. Dendritic cells matured by stimulation of Toll-like receptors 2 and 4 will overexpress CDw150 up to fivefold. Then, human dendritic cells may increase the expression of measles virus. However, the latter contributing to Paget’s disease of bone

### Table 3 Overview of the main clinical trials or case reports in which a cytokine or its receptor, involved in osteoimmunological process related to a rheumatic or musculoskeletal disorder, was targeted

<table>
<thead>
<tr>
<th>Targeted signalling</th>
<th>Molecule name</th>
<th>Molecule description</th>
<th>Main rheumatic diseases treated</th>
<th>Level of evidence</th>
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<tr>
<td>IL-1</td>
<td>Anakinra</td>
<td>Human recombinant IL-1ra</td>
<td>Rheumatoid arthritis, NOMID syndrome, Still’s disease, Periodic fever syndromes, Acute gout, Behçet’s disease, CAPS syndromes, Periodic fever syndromes, Acute gout</td>
<td>Randomized-controlled trials</td>
<td>40, 128–133</td>
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<tr>
<td>Riloncept</td>
<td>IL-1 trap, IL-1 inhibitor</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Canakinumab</td>
<td>IL-17 receptor inhibitor</td>
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<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor inhibitor</td>
<td></td>
<td>Rheumatoid arthritis, Juvenile idiopathic arthritis, Psoriatic arthritis, Juvenile Paget’s disease, Paget’s disease of bone</td>
<td>Randomized-controlled trials</td>
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<tr>
<td>Secukinumab</td>
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<td>Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis</td>
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<td>Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis</td>
<td>Randomized-controlled trials</td>
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<tr>
<td>Brodalumab</td>
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<tr>
<td>Ustekinumab</td>
<td>Recombinant osteoprotegerin</td>
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<tr>
<td>OPG</td>
<td>Denosumab</td>
<td>RANKL inhibition</td>
<td>Osteoporosis, Treatment-induced bone loss, Bone metastases, Multiple myeloma, Hypercalcemia of malignancy, Giant cell tumor of the bone, Rheumatoid arthritis, Juvenile Paget’s disease, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Behçet’s disease, Rheumatoid arthritis, Juvenile Paget’s disease, Paget’s disease of bone</td>
<td>Randomized-controlled trials</td>
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<tr>
<td>TNF-α</td>
<td>Etanercept</td>
<td>TNF inhibitor (decoy receptor)</td>
<td>Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Juvenile idiopathic arthritis, Rheumatoid arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Ankylosing spondylitis, Behçet’s disease, Rheumatoid arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Behçet’s disease</td>
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<td>Infliximab</td>
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<tr>
<td>Adalimumab</td>
<td>TNF-α inhibition</td>
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<td>Rheumatoid arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Ankylosing spondylitis, Behçet’s disease, Rheumatoid arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Psoriatic arthritis, Behçet’s disease</td>
<td>Randomized-controlled trials</td>
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<td>Golimumab</td>
<td>TNF-α inhibition</td>
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<td>Certolizumab</td>
<td>TNF-α inhibition</td>
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**Abbreviations:** IL, Interleukin; NOMID, Neonatal-onset multisystem inflammatory disease; CAPS, Cryopyrin-associated autoinflammatory syndrome; OPG, osteoprotegerin; RANKL, Receptor Activator of Nuclear factor Kappa-B Ligand; TNF-α, Tumor Necrosis Factor-α.
In conclusion, Paget’s disease of bone should be considered as a new addition to the large family of osteoimmunological disorders. The cytokine profiles observed in this disease are also very similar to those observed in other osteoimmunological disorders that should probably be classified accordingly. The treatment of Paget’s disease of bone may also benefit from progresses in osteoimmunology-targeted therapies, in particular, RANKL and IL-6 signaling inhibition.

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