

Osteoimmunology: An Evolving Discipline

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Osteoimmunology is an emerging interdisciplinary field that focuses on the cellular and molecular events underlying the interplay between bone and immune system. The term “osteoimmunology” was first employed in 2000 to describe the interactions between cells from the immune and skeletal systems [1]. The discovery of the receptor activator NF- κ B (RANK) ligand (RANKL), the RANKL/RANK/osteoprotegerin (OPG) pathway and the identification of their pivotal role in osteoclast activation, have been crucial in the development of this discipline [2,3].

Given that immune cells and haematopoietic cells originate in the bone marrow, it is perhaps not surprising that there is a cross-talk between these two systems [4-6]. Some of the molecular pathways involved in bone remodelling are also involved in regulating hematopoiesis. Moreover, multiple cytokines from lymphocytes, macrophages and Dendritic Cells (DC), influence bone remodelling and there are actually several regulatory molecules common to osteoclasts and immune cells, such as cytokines, chemokines, receptors, signalling molecules and transcription factors, all of which influence each other mutually [4]. Thus, the activity of the immune and skeletal systems should now be reconsidered in the more holistic context of the autoimmune system. In recent years, our understanding of the relationships between the cells and molecules that act in the osteoimmune system has advanced, not only those at play in normal physiological conditions but also, in diseases as far as arthritis, osteoporosis, periodontal disease or cancer. In fact, by studying the interaction of osteoclasts and T lymphocytes, we now better understand the mechanism of bone destruction in several diseases such as Rheumatoid Arthritis (RA), spondyloarthritis or osteoporosis.

RANKL is one of the most important cytokines for bone cells and for several lineages in the immune system, being essential for osteoclast differentiation/activation and for immune regulation. RANKL was originally identified as a product of T cells [2,7], but we now know that it is also expressed by osteoblasts, osteocytes, B cells, activated T lymphocytes, synovial fibroblasts and DC. In RA, RANKL is expressed strongly in the synovium and inflammation-mediated bone damage can be largely attributed to abnormally high expression of RANKL [4,6]. By contrast, OPG is a soluble decoy receptor for RANKL that inhibits the interaction of RANKL with its specific receptor, and this represents a negative feedback loop during osteoclastogenesis [8]. In addition to its effects on osteoclast precursors, RANKL also fulfils important roles in regulating immune events, such as lymph node organogenesis and self tolerance [9].

Osteoclast precursor cells also express different kinds of receptors for proinflammatory and osteoclastogenic cytokines mainly produced by macrophages and synoviocytes, such as IL-1, TNF- α and IL-6. IL-1 indirectly stimulates osteoclastogenesis by acting on osteoblasts [10], whereas TNF- α exerts a direct effect on osteoclastogenesis by acting on osteoclast precursors, and indirectly by upregulating the production of M-CSF and RANKL by mesenchymal cells [11,12]. Similarly, IL-6 induces osteoclastogenesis by increasing RANKL expression in mesenchymal cells [13]. Overall, pro-inflammatory cytokines stimulate osteoclastic bone resorption in RA, both directly by acting on osteoclast

precursor cells and indirectly by upregulating RANKL expression in synovial fibroblasts.

There are also several co-stimulatory molecules that act in these processes, although their role remains unclear. One of these molecules is OSCAR, an orphan IgG-like receptor that transmits an intracellular signal complementary to that of RANK, and which acts through the nuclear factor of activated T cells c1 (NFATc1) to modulate the activation and maturation of cells of the monocyte-macrophage lineage. This receptor could be relevant in the pathogenesis and severity of diseases that causes osteoclast activation. Co-stimulatory molecules use membrane adapters that contain ITAM motifs, such as DAP12 or FcR- γ . The deficiency of transmembrane signal adapters containing ITAM motifs provokes a failure in osteoclast activation and when this defect involves both molecules, it produces severe osteopetrosis [14]. Interestingly, many of the transcription factors that are important for osteoclast differentiation are key regulators of immune responses, such as NF- κ B and NFATc1. This finding was an early clue to the close relationship between skeletal biology and immunology. In summary, experimental evidence is accumulating that skeletal and immune systems share the same signalling systems and transcriptional mediators [15].

One of the main features of the rheumatoid synovium is T cell infiltration. When activated, T cells express RANKL, but depending on their profile they also secrete other cytokines like IFN- γ and IL-4, which have potent anti-osteoclastogenic effects even at very low concentrations. In an exhaustive study, Th1 and Th2 cells were both shown to inhibit osteoclast formation through their canonical cytokines, IFN- γ and IL-4, respectively [16]. In contrast, Th17 cells are potent stimulators of osteoclastogenesis through the secretion of IL-17. This effect appears to be dependent on the presence of osteoblasts, leading to the conclusion that T cell-derived RANKL alone is not sufficient for osteoclast differentiation. Nowadays, there is evidence that Th17 lymphocytes play an important role not only in the inflammation but also, in the bone destruction that occurs in arthritis [16-18]. Importantly, synovial fibroblasts produce pro-inflammatory cytokines, like TNF- α and IL-1, promoting bone destruction by direct and indirect mechanisms. Likewise, synovial fibroblasts stimulate the migration of Th17 cells into the joint with a concomitant increase in IL-17 production, promoting osteoclastogenesis through the upregulation of RANKL expression [19,20].

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Other important cell subsets in the field of the osteoimmunology are regulatory T lymphocytes (Treg lymphocytes), B cells and osteomas. Regulatory T cells play a pivotal role in the prevention of autoimmune diseases, and *in vivo* and *in vitro* data suggest that Treg cells inhibit osteoclastogenesis. However, while Treg cells can suppress osteoclastogenesis *in vitro*, the exact mechanism by which Treg cells affect osteoclastogenesis in physiological and pathological conditions remains to be elucidated. B cells are also a crucial element when studying immune mediated diseases and they play a pivotal role in humoral immunity. Data from animal models suggest a direct role of RANKL expression by B cells in the regulation of bone metabolism [21], although the final role of B cells in promoting osteoclastogenesis is still to be fully analyzed. "Osteomacs" are another interesting cellular subset that participates in the osteoimmune network. Osteomacs are resident tissue macrophages present on the periosteal and endosteal surfaces that regulate osteoblast mineralisation, playing an intriguing role in bone homeostasis [22].

A fascinating issue that has emerged in recent years is related to bone formation. Here we must highlight the enormous advances that have occurred since the definition of the Wnt pathway. Wnt's are glycoprotein ligands that trigger multiple signal cascades involved in key processes during embryogenesis, tumourigenesis and tissue regeneration. So far, 19 different Wnt proteins have been described in mammals, acting in a variety of important signalling pathways [23,24]. The canonical Wnt pathway or that involving Wnt and beta-catenin, is the best known signalling cascade and it plays a key role in osteoblastogenesis. There are also a number of natural antagonists of these Wnt pathways, of which sclerostin, Dickkopf (DKK) and sFRP are currently among those best known, especially DKK-1 and DKK-4 [25-27]. The activity of endogenous inhibitors of the Wnt pathway is tightly regulated due to their extraordinarily important role in many developmental processes and in the activation of several cell systems. In RA, serum levels of these inhibitors are elevated and treatment with a DKK-1 neutralizing monoclonal antibodies improves local erosions in RA hTNF. Tg mice, a model over-expressing TNF that develops an erosive arthritis resembling human RA. An exciting hypothesis would be that these inhibitors are responsible for the poor repair of erosion characteristic of RA, contrary to what occurs in other inflammatory diseases like psoriatic arthritis or ankylosing spondylitis [28].

Another interesting area of research in the field of the osteoimmunology is related to Postmenopausal (PM) osteoporosis. Oestrogen has long been known to have an impact on lymphocyte physiology and there is evidence of RANKL upregulation after ovariectomy [21]. RANKL expression in early PM women triples the number of mononuclear cells in bone marrow, both in terms of preosteoblasts or T and B lymphocytes, compared with premenopausal or PM women treated with oestrogen replacement therapy [29,30]. Several studies have demonstrated that oestrogen therapy modifies cytokine production by T cells and that of the growth factors that promote bone resorption, including the pro-osteoclastic cytokines RANKL and TNF- α [31,32]. Thus, the physiology of T cells may be altered following oestrogen depletion, contributing to the elevated bone resorption observed in PM women [33].

Intercellular communication is another area that is providing novel and fascinating therapeutic targets. For example, Ephrin-B2 and Ephrin B4 are known to mediate the transition of bone resorption to bone formation [34]. In addition to the ephrin family and their Eph receptors, a new group of molecules has attracted great interest in recent years in the dialogue between osteoclasts and osteoblasts. These

are the semaphorins, initially identified as axonal guidance molecules but subsequently involved in numerous physiological functions, including the immune and skeletal system. Indeed, osteoclast semaphorin 4D maintains the resorptive phase of bone remodelling by inhibiting bone formation in mice [35]. By contrast, semaphorin 3A (Sema 3A) binds to neuropilin 1 (NRP-1) blocking RANKL-induced osteoclast differentiation pathways, thereby inhibiting proximal ITAM signal and RhoA while simultaneously stimulating osteoblasts through the canonical Wnt pathway. Sema3A^{-/-} mice develop an osteopenic phenotype that can be reproduced by shifting Sema 3A/NRP-1 signalling, while the intravenous infusion of this semaphorin increases bone volume and accelerates bone regeneration [36].

In conclusion, osteoimmunology is a new and rapidly evolving scientific discipline that involves the study of the interplay between the skeleton and the immune system, both in health and disease. Osteoimmunology has identified a wide range of molecular and cellular interactions, the detailed knowledge of which is providing a solid scientific basis for a paradigm shift in the field of inflammatory and immune diseases. The development of this discipline should enable more exciting, effective and specific therapeutic approaches to be developed for quite different diseases in a near future.

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