Trends in Immunology

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Novel insights and recent progress in osteoimmunology

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Osteoimmunology is an interdisciplinary branch of immunology studying bidirectional interactions between the immune and skeletal systems. Bone marrow is vital for the production of immune cells and is implicated in multiple diseases across all immunology disciplines. Here, we briefly discuss recent progress from the past 5 years in the field and how it impacts our current understanding of health and disease.

Osteoimmunology explores the intricate relationship between the skeletal and immune systems, highlighting their interconnected roles in tissue maintenance and disease development. Although researchers have long suspected a link between these systems based on the effects of certain cytokines on bone cells, this connection has only become better understood in the past decade or so [1].Despite the lack of an established society or dedicated journal, osteoimmunology has flourished under the auspices of an international conference (held in Greece every 2 years) which brings together immunologists across all disciplines and scientists interested in the skeletal system. Although osteoimmunology initially attracted bone biologists and immunologists, the field has expanded to include hematology, stem cell biology, and epigenetics, along with a plethora of musculoskeletal diseases with multiple implications in autoimmunity, cancer, and tissue regeneration. Here, we raise awareness about the field by briefly discussing a few of the top findings from the past 5 years and demonstrate how novel concepts have emerged through interdisciplinary research in osteoimmunology.

Trained immunity and inflammatory osteoclasts

One important topic that is relevant to the field is the concept of innate immune memory, or trained immunity. This is the ability of an innate immune cell to acquire characteristics that allow it to mount stronger immune responses to a second exposure of a stimulus due to 'memory' or 'training' by a past event. The bone marrow is central to trained immunity, being the major organ of myelopoiesis and the tissue where any alterations in hematopoietic stem and progenitor cells are detected in mice [2].

Bone marrow alterations, due to immune dysregulation, can lead to hypersensitive myeloid cells that respond to an array of immune signals and are linked to multiple comorbidities, including periodontal disease and arthritis [3]. These changes have long-lasting effects that include the increased expression of specific immunoreceptors such as CLEC5A in osteoclast precursors that act as co-stimulatory molecules in humans and mice and increase osteoclastogenesis *in vitro* [4]. These immunoreceptors are expressed on macrophages and recent work demonstrated that these cells can be reprogrammed by interleukin (IL)-23, transforming growth factor (TGF)β, and tumor necrosis factor (TNF), to drive the process of inflammatory osteoclastogenesis [5]. Specifically, IL-23 can reprogram $CD11c^{+}$ cells to express RANK and therefore act as osteoclast precursors [5]. The concept of trained immunity not only reconciles multiple studies but also sheds new light on osteoclast ontogeny by suggesting a more fluid understanding of osteoclast precursors.

Another recent study demonstrated that excessive osteoclast activation in mice can be inhibited by the action of eosinophil peroxidase, secreted by eosinophils, bringing much-needed balance during inflammatory states [6]. Collectively, the interplay between cytokines and immune cells in the bone marrow can regulate the osteoclast precursor pool in circulation, quantitatively and qualitatively, and modulate their availability and activation states in the bone and joints. It is therefore plausible that different types of inflammatory arthritis and recurring flares of inflammation reflect, to some extent, these qualitative changes [7] (Figure 1).

The circulation, skeletal stem cells, and stromal immunology

Recent advances in imaging techniques and genetic manipulation have provided insights into the heterogeneity of bone vessels, further validating the fundamental role that the vasculature plays in the health and disease of the skeletal system. In particular, the identification of type H vessels that link angiogenesis and osteogenesis is an important finding in the field. Historically, bone and bone marrow were thought to lack lymphatic vessels, but a recent study showed that there are lymphatic vessels in bone and that lymphatic endothelial cells produce chemokine CXCL12, thus contributing to bone regeneration and hematopoiesis [8]; however, it is important to note that there are also articles that report conflicting data [9].In addition, site-specific skeletal stem cells have recently gained significant attention. For instance, there are distinct markers and functional differences among growth plate, periosteal, and bone marrow stem cells. The vertebrate is the common host for bone metastasis and a recent study suggested that vertebral skeletal stem cells are responsible for metastasis [10]. This is interesting work showing that site-specific skeletal stem cells can account for diseases occurring in different regions of the skeleton [10]. It is noteworthy that naïve and stress hematopoiesis in the bone marrow vary significantly across different regions of the skeleton [11]. Fibroblasts, endothelial cells, and periosteal cells are

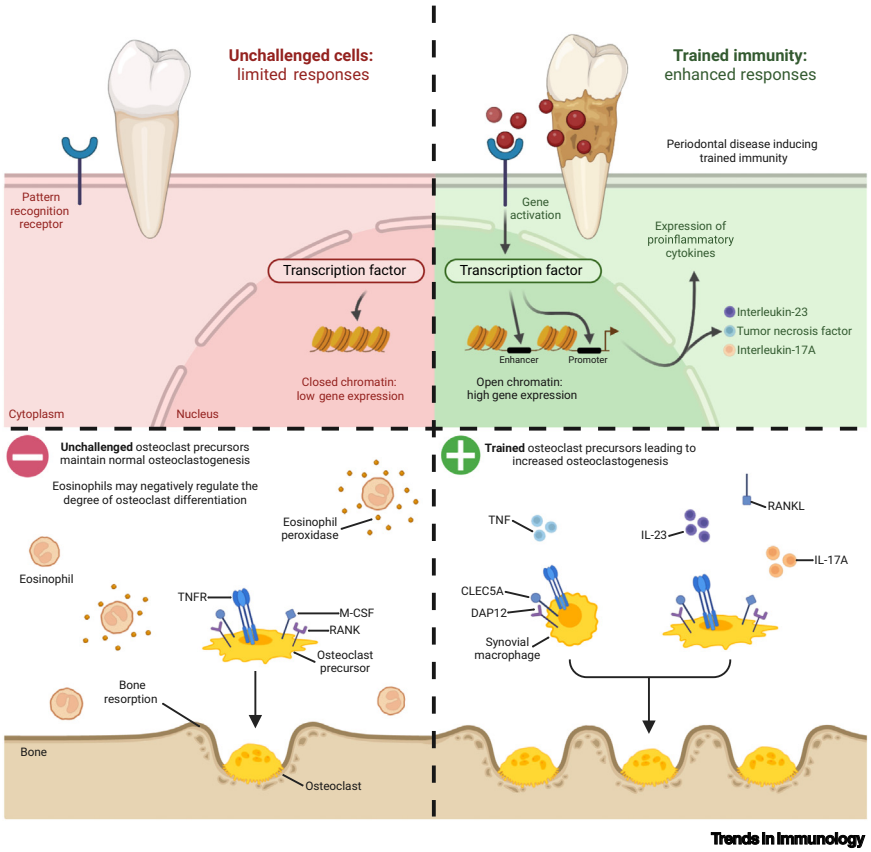

Figure 1. Newfound interactions between the immune and skeletal systems. Mammalian immune-mediated responses resulting from periodontal disease can instigate trained immunity. Trained immunity results in an increased production of proinflammatory cytokines and expression of co-stimulatory receptors on osteoclast precursors, leading to increased bone resorption [4,5]. By contrast, eosinophils can inhibit osteoclast precursor differentiation through eosinophil peroxidase, thus restoring balance in bone remodeling [6]. (–) indicating reduced and or (+) increased bone resorption. Abbreviations: CLEC5A, c type lectin superfamily member 5; DNAX, activating protein of 12 kDa; IL, interleukin; M-CSF, macrophage colony stimulating factor; RANKL, receptor activator of nuclear factor kappa beta; TNF, tumor necrosis factor. Figure created using BioRender.com.

stromal cells, which constitute a part of our body structure. Emerging evidence indicates that they are more than structural cells. For instance, it was previously thought that the immune system exclusively protects against neoplastic diseases, but a recent report showed that periosteal cells can also protect against cancer invasion. When a tumor proliferates and comes close to the periosteum, periosteal cells start to express a high amount of tissue inhibitor of metalloproteinases (Timp)1, which inhibits various metalloproteinases, resulting in the thickening of the periosteum. Thus, Timp1 knockout mice (*Timp1*$^{-/-}$) are susceptible to cancer invasion in the bone, as shown in a mouse model of squamous cell carcinoma. Indeed, the periosteal reaction (thickening of the periosteum) is a well-known X-ray finding in bone cancer, osteomyelitis, and fracture, but it can serve as a barrier to protect against cancer invasion [12]. In autoimmune arthritis, the immune system stimulates resident cells such as fibroblasts to play important roles in inflammation and bone destruction. Moreover, RANKL-expressing fibroblasts contribute to accelerated osteoclastogenesis, as evidenced from human/mouse single cell RNAseq and mouse fibroblast transplantation models in mice. Indeed, ETS1 is a key transcription factor that serves to guide tissue-destructive fibroblasts by inducing RANKL as well as metalloproteinases [13]. These findings have further suggested that stromal cells can play a protective role in the host. Similarly to the identification of certain pathways in the immune system, these findings could pioneer a new frontier in stromal immunology.

Concluding remarks

Overall, despite the occurrence of the coronavirus disease 2019 (COVID-19) pandemic, there has been considerable progress in the field of osteoimmunology that clearly illustrates the importance of interdisciplinary research in connecting signaling pathways, tissues, and functions. This research has increased our understanding of the role of the immune system and advanced our goal to combat not only musculoskeletal diseases, but also autoimmunity, and cancers. We advocate for further and more frequent interdisciplinary interactions among scientists, which can only facilitate unbiased research and open new frontiers for discovery in osteoimmunology.

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Declaration of interests

The authors have no conflicts of interest to declare.

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