



# Osteoimmunology

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Interactions between the immune system and bone were initially recognised more than 35 years ago with the discovery by Horton that activated peripheral blood leukocytes release a soluble activity that stimulates osteoclastic bone resorption [1]. With advances in cell and molecular biology, several molecules have since been discovered that play roles both in the regulation of bone remodelling and immune responses, most notably receptor activator of nuclear factor kappa B (RANK) and RANK Ligand (RANKL) which were initially identified as mediators of T-cell activation and dendritic cell function [2] but which then were found to be crucial regulators of osteoclastogenesis [3].

The term “osteoimmunology” was first coined about 18 years ago by Arron and Choi [4] to describe the process whereby bone cells and immune cells interact when commenting on a seminal paper by Takayanagi which showed that RANKL-induced activation of osteoclasts by T-cells was counterbalanced by interferon gamma produced by the same cells [5]. Since these beginnings, interest in the discipline of osteoimmunology has evolved rapidly (Fig. 1). It is for this reason that we have devoted the current issue of *Calcified Tissue International* to the topic of osteoimmunology.

The issue begins with an authoritative and beautifully illustrated overview of the field by Terashima and Takayanagi [6]. This review, from one of the leading laboratories in the field, details the signalling pathways used by RANKL to regulate osteoclastogenesis and considers the role of the RANK–RANKL pathway as a mediator of both systemic bone loss and the local bone loss that accompanies T-cell

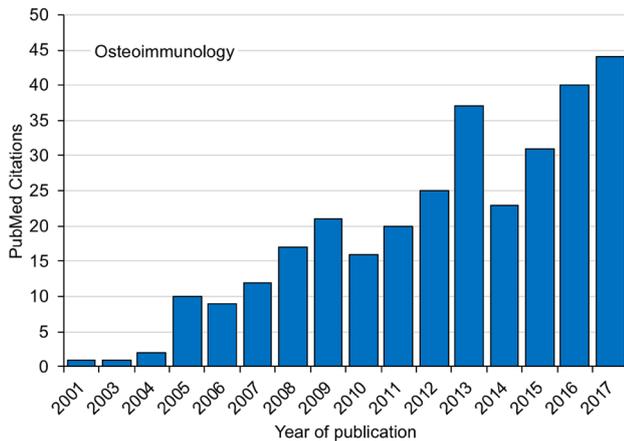
activation in rheumatoid arthritis. The authors then go on to discuss the importance of immune cells in fracture healing and the contribution of bone cells to the development and maturation of hematopoietic stem cells. Finally, the many paracrine factors that regulate cell–cell communication in the bone marrow are discussed. The second article by Hsu and Pacifici [7] provides a state-of-the-art review on the related disciplines of osteoimmunology and osteomicrobiology which links nicely with the recent special issue of *Calcified Tissue International* which focussed on the relation between the microbiota and bone health [8]. The osteoimmunology special issue continues with an article by Hauser and Harre who review the role that autoantibodies play in regulating bone metabolism through their interactions with Fc receptors and effects on the RANK–RANKL–OPG system [9].

The next series of articles deal with the abnormalities of bone metabolism that occur in different rheumatic diseases. Shim et al. discuss the cytokines and signalling pathways implicated in the pathogenesis rheumatoid arthritis, the mechanisms of bone erosions and current therapeutic approaches as well as discussing future prospects for repairing erosive damage [10]. The next article by Van Mechelen et al. [11] reviews the pathophysiology of ankylosing spondylitis with particular emphasis on the molecular mechanisms responsible for the florid skeletal abnormalities that are characteristic of this disease. Paine and Ritchlin [12] review the alterations in bone remodelling that occur in psoriatic arthritis. In a comprehensive article, the authors discuss the mediators of abnormal bone resorption and formation; the role of environmental factors such as trauma, the intestinal microbiome, obesity and smoking; and the effects of currently available treatments on radiographic progression. The disease-specific section concludes with a review by Bultink [13] who discusses recent advances in understanding the mechanisms of bone loss in systemic lupus erythematosus and other connective tissue diseases as well as giving details of the clinical features, epidemiology and treatment of osteoporosis in these conditions.

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The vertical axis shows the number of citations in PubMed which included the term “osteoimmunology” and the horizontal axis the year of publication.

**Fig. 1** The rise of osteoimmunology

The special issue closes with two articles which evaluate the effects of anti-rheumatic drug treatments on the skeleton. The review by Guler-Yuksel et al. deals with the effects of glucocorticoids on bone [14]. The authors draw attention to the fact that while glucocorticoids may have negative effects on the skeleton, bone sparing effects can also be observed in the context of inflammatory diseases as the result of their anti-inflammatory and immunosuppressive properties. These and other aspects of glucocorticoid use are reviewed along with recent developments and the latest guidance on management of glucocorticoid induced osteoporosis by pharmacological and non-pharmacological means. The final article by Dubrovsky et al. [15] deals with the effects of anti-rheumatic drugs on the skeleton, covering the effects of traditional disease modifying anti-rheumatic drugs as well as biological therapies. The article also reviews current knowledge with regard to the effects of anti-osteoporosis medications in patients with rheumatic disease.

It has been our great pleasure in working with this talented group of authors to bring this special issue together for our readers. We hope that you will enjoy reading the articles as much as we have.

## Compliance with Ethical Standards

**Conflict of interest** Stuart H. Ralston and Georg Schett declare that they have no conflict of interest.

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