Linking glucocorticoid-induced osteoporosis to osteoimmunology

Stephan von Gunten and Hans-Uwe Simon

Over millions of years, the skeletal and the immune systems have coevolved in the development from bony fish to terrestrial animals to form a symbiotic and highly interactive relationship. It has been suggested that environmental pressures, such as higher levels of UV light and oxygen, or lower levels of calcium in the terrestrial environment, promoted the establishment of the protective endosteal niche for haematopoietic stem cells (HSCs) in the bone marrow. Besides other aspects, the tight connection between the immune and the skeletal systems is reflected by the following facts: (1) origination of osteoclasts from haematopoietic progenitor cells, (2) colocalization of ostearth and osteoclast progenitor cells with immune cell progenitor and memory cells in the bone marrow, (3) immunomodulatory effects of the major pro-osteoclastogenic cytokine receptor activator of NF-κB ligand (RANKL) and its expression by both osteoblast lineage cells and lymphocytes, (4) reciprocal effects of immune and bone remodelling cells in cell differentiation and bone remodelling, and (5) reduction of bone mass in inflammatory disorders, eventually as a consequence of excessive bone resorption.

In the last two decades, significant new insights into the complex interaction between the immune and skeletal systems brought light to the relationship. It has been suggested that environmental pressures in the terrestrial environment, promoted the establishment of the protective endosteal niche for haematopoietic stem cells (HSCs) in the bone marrow. Besides other aspects, the tight connection between the immune and the skeletal systems is reflected by the following facts: (1) origination of osteoclasts from haematopoietic progenitor cells, (2) colocalization of osteoblast and osteoclast progenitor cells with immune cell progenitor and memory cells in the bone marrow, (3) immunomodulatory effects of the major pro-osteoclastogenic cytokine receptor activator of NF-κB ligand (RANKL) and its expression by both osteoblast lineage cells and lymphocytes, (4) reciprocal effects of immune and bone remodelling cells in cell differentiation and bone remodelling, and (5) reduction of bone mass in inflammatory disorders, eventually as a consequence of excessive bone resorption.

In this issue of Cell Death and Disease, Song et al. report a central role of T cells for GIOI (Fig. 1). Using models with T-cell-deficient SCID or nude mice, they demonstrated that T cells are indispensable for the establishment of GIOI. SCID mice develop osteoporosis upon adoptive transfer of T cells, which was paralleled by an increase of RANKL in serum. T cells homing in the bone marrow were found to express RANKL and were able to stimulate ex vivo the differentiation of osteoclasts in co-culture experiments with myeloid RAW264.7 cells. Given that in other types of osteoporosis T-cell-derived cytokines have been shown to enhance RANKL expression in osteoblasts and other cells, it is possible that such indirect effects also contribute mechanistically to the development of GIOI.

Peripheral lymphopenia can result from impaired lymphopoiesis in the endosteal niche due to diminished IL-7 production by osteoblasts, as observed under septic conditions. In contrast, while dexamethasone treatment resulted in the reduction of circulating T-cell numbers and an increase of apoptotic T cells in the spleen, Song et al. observed an accumulation of viable T cells in the bone marrow, suggesting a protective influence of the endosteal niche. The increased T-cell homing to the bone marrow was found to be dependent on chemokine ligand receptor interactions with significant involvement of the CXCL10-CXCR3 axis. CXCL10 and CXCR3 receptor signalling have previously been linked to bone loss related to increased osteoclast differentiation and activity in various models of disease, including conditions with an established pathogenic role of T cells.
The study by Song et al. highlights the importance of T cells in the pathogenesis of GIOP and may support the consideration of osteoimmunological approaches in the prevention of GIOP. However, while the existing literature documents distinct contributions of T-cell subsets, cytokines, and chemokines in the development of osteoporosis1,10,11, their relevance to GIOP remain to be explored. Furthermore, it will be important to consider that significant differences in immune responses exist not only between species13,14, but also among human individuals15,16. Future pharmacotherapeutic strategies are expected to be inspired by a better understanding of molecular networks17, and the mutual interactions between the bone and immune systems in GIOP, eventually resulting in more personalized approaches to steroid therapy.

Conflict of interest
The authors declare that they have no conflict of interest.

Publisher’s note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 3 November 2020 Revised: 5 November 2020 Accepted: 13 November 2020

Published online: 14 December 2020

References
1. Tsukasaki, M. & Takayanagi, H. Osteoimmunology: evolving concepts in bone-immune interactions in health and disease. Nat. Rev. Immunol. 19, 626–642 (2019).
2. Brylka, L. J. & Schinke, T. Chemokines in physiological and pathological bone remodeling. Front. Immunol. 10, 2182 (2019).
3. Amon, J. R. & Choi, Y. Bone versus immune system. Nature 408, 535–536 (2000).
4. von Gunten, S. et al. Mechanisms and potential therapeutic targets in allergic inflammation: recent insights. Allergy 68, 1487–1498 (2013).
5. Ahmad, M. et al. A jack of all trades: impact of glucocorticoids on cellular cross-talk in osteoimmunology. Front. Immunol. 10, 2460 (2019).
6. Boutros, C. et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat. Rev. Clin. Oncol. 13, 473–486 (2016).
7. Hofbauer, L. C. et al. Prevention of glucocorticoid-induced bone loss in mice by inhibition of RANKL. Arthritis Rheum. 60, 1427–1437 (2009).
8. Piemontese, M., Xiong, J., Fujiwara, Y., Thostenson, J. D. & Obrien, C. A. Cortical bone loss caused by glucocorticoid excess requires RANKL production by osteocytes and is associated with reduced OPG expression in mice. Am. J. Physiol. Endocrinol. Metab. 311, E587–E593 (2016).
9. Song, L. et al. The critical role of T cells in glucocorticoid-induced osteoporosis. Cell Death Dis. 10. Walsh, M. C., Takeghara, N., Kim, H. & Choi, Y. Updating osteoimmunology: regulation of bone cells by innate and adaptive immunity. Nat. Rev. Rheumatol. 14, 146–156 (2018).
10. Weitzmann, M. N. & Ofotokun, I. Physiological and pathophysiological bone turnover—role of the immune system. Nat. Rev. Endocrinol. 12, 518–532 (2016).
11. Terashima, A. et al. Septic-induced osteoblast ablation causes immunodeficiency. Immunity 44, 1434–1443 (2016).
12. D’Amelio, P. & Sass, F. Osteoimmunology: from mice to humans. Bonekey Rep. 5, 802 (2016).
13. Schneider, C. et al. MG regulates the survival of human but not mouse neutrophils. Sci. Rep. 7, 1296 (2017).
14. von Gunten, S. et al. Siglec-9 transduces apoptotic and nonapoptotic death signals into neutrophils depending on the proinflammatory cytokine environment. Blood 106, 1423–1431 (2005).
15. Luetcher, R. N. D. et al. Unique repertoire of anti-carbohydrate antibodies in individual human serum. Sci. Rep. 10, 15436 (2020).
16. von Gunten, S. The future of pharmacology: towards more personalized pharmacotherapy and reverse translational research. Pharmacology 105, 1–2 (2020).