



Title of Project : The osteoimmune network

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【Purpose and Background of the Research】

Bone functions as a locomotor organ and a mineral reservoir as well as a primary lymphoid organ where hematopoietic stem cells and immune progenitors are maintained. The history of modern bone research began with endocrinology, but recently the regulatory network governed by the bone has attracted much attention. In response to various environmental stimuli, bone remotely interacts with other organs to regulate systemic biological functions. We have explored the interdisciplinary field “osteimmunology” by elucidating the interplays between the bone and the immune system. Osteoimmunology started with the concept of bone destruction by the immune cells in rheumatoid arthritis. However, it has become clear that osteoimmune interactions exert various physiological and pathological functions throughout the life. Bone and immune cells share the same micro-environment and interact with each other to cooperatively carry out the functions of the “osteoimmune system”. Thus, it can be interpreted that the multi-functionality of bone is controlled by the “osteoimmune system”. In this project, we propose the novel concept of the osteoimmune system-centered systemic regulatory network (called the osteoimmune network), and aim to reformulate the understanding of the regulatory mechanism of the higher functions of the vertebrates.

【Research Methods】

[1] Elucidation of the molecular mechanism of the function and development of the osteoimmune system:

We try to understand how the osteoimmune system is established and maintained, by elucidating the function and differentiation of all cell types that make up the osteoimmune system, and elucidate how their interactions regulate the multi-functionality of bone (bone metabolism, mineral metabolism, hematopoiesis, etc.).

[2] Understanding the pathogenesis of osteoimmune diseases to develop new therapeutic approaches (osteoimmune pathology):

There are still lots of intractable skeletal or immune diseases afflicting the people. Until now, most of these osteoimmune diseases have been studied mainly in orthopedics and rheumatology. In the project, we propose the importance of “osteoimmune pathology” to understand the pathogenesis of the osteoimmune diseases, and try to elucidate the mechanisms underlying the pathogenesis of these osteoimmune diseases, to develop future pharmacological intervention. As the osteoimmune diseases, we will focus on autoimmune

diseases, joint diseases and rare genetic diseases that involve both bone and immune cells.

[3] Development of novel cancer strategies based on osteoimmune oncology: In cancer diseases affecting the bone marrow, such as multiple myeloma, myeloproliferative disorders and bone metastases, bone marrow environment can be greatly altered by unregulated tumor progression. Focusing on effects of tumor on the osteoimmune system, we aim to elucidate the mechanisms underlying the pathogenesis of multiple myeloma, bone metastasis, and hematopoietic tumors.

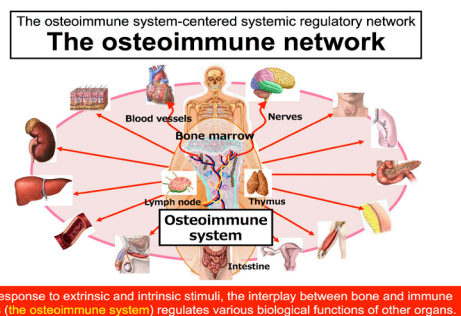


Figure: whole concept of the study

【Expected Research Achievements and Scientific Significance】

We aim to establish the novel concept of the osteoimmune network and revolutionize the traditional framework of modern medical biology. This project will enable a better understanding of the regulatory system of higher biological functions of the vertebrates, and provide a molecular basis for developing new therapeutic strategies for various diseases related to the osteoimmune network. The achievements will contribute significantly to maintaining the health and life expectancy of the people.

【Publications Relevant to the Project】

- Tsukasaki M, Huynh NC, Okamoto K, et al, Stepwise cell fate decision pathways during osteoclastogenesis at single-cell resolution. *Nat Metab.* 2:1382–1390 (2020)
- Asano T, Okamoto K, Nakai Y, et al, Soluble RANKL is physiologically dispensable but accelerates tumour metastasis to bone. *Nat Metab.* 1:868–875 (2019)
- Tsukasaki M and Takayanagi H. Osteoimmunology: evolving concepts in bone-immune interactions in health and disease. *Nat Rev Immunol.* 19(10):626-642 (2019)

【Homepage Address and Other Contact Information】

<http://www.osteimmunology.com>