Hiroshi Takayanagi

1 .Topic in Research Achievements in the Year 2006

Our main results are as follows; (1) Identification of the osteoclastogenic helper T cell subset: In autoimmune arthritis, traditionally classifi ed as a T helper (Th) type 1 disease, the activation of T cells results in bone destruction mediated by osteoclasts, but how T cells enhance osteoclastogenesis despite the anti-osteoclastogenic effect of interferon (IFN)-γ remained to be elucidated. So, we examined the effect of various Th cell subsets on osteoclastogenesis and identify Th17, a specialized infl ammatory subset, as an osteoclastogenic Th cell subset that links T cell activation and bone resorption. The interleukin (IL)-23–IL-17 axis, rather than the IL-12–IFN-γ axis, is critical not only for the onset phase, but also for the bone destruction phase of autoimmune arthritis (J Exp Med 203: 2673, 2006). (2) Regulation of osteoclast differentiation and function by the CaMK-CREB pathway: Ca2+/calmodulindependent kinases (CaMKs) and the phosphatase calcineurin activate distinct downstream pathways that are mediated by the transcription factors CREB and NFAT, respectively1. The importance of the calcineurin-NFAT pathway in bone metabolism has been demonstrated in osteoclasts, osteoblasts and chondrocytes. However, the contribution of the CaMK-CREB pathway is poorly understood, partly because of the difficulty of dissecting the functions of homologous family members. So, we showed that the CaMKIV-CREB pathway is crucial for osteoclast differentiation and function. Pharmacological inhibition of CaMKs as well as the genetic ablation of Camk4 reduced CREB phosphorylation and downregulated the expression of c-Fos, which is required for the induction of NFATc1 (the master transcription factor for osteoclastogenesis) that is activated by receptor activator of NF-κB ligand (RANKL). Furthermore, CREB together with NFATc1 induced the expression of specific genes expressed by differentiated osteoclasts. Thus, the CaMK-CREB pathway biphasically functions to regulate the transcriptional program of osteoclastic bone resorption, not only by enhancing induction of NFATc1 but also by facilitating NFATc1-dependent gene regulation once its expression is induced (Nat Med 12: 1410, 2006). These results may provide a cellular and a molecular therapeutic target(s) for bone diseases.

2 .Publications in the year 2006

○ Asagiri, M., Takayanagi, H. The molecular understanding of osteoclast differentiation. Bone 40, 251-264 (2007)

○ Sato, K.*, Suematsu, A. (QSS)*, Nakashima, T., Takemoto-Kimura, S., Aoki, K., Morishita, Y., Asahara, H., Ohya, K., Yamaguchi, A., Takai, T., Kodama, T., Chatila, T. A., Bito, H., & Takayanagi, H. Regulation of osteoclast differentiation and function by the CaMK-CREB pathway. Nat Med 12, 1410-1416 (2006)
* equal contributor

○ Suematsu, A., Tajiri, Y., Nakashima, T., Taka, J., Ochi, S., Oda, H., Nakamura, K., Tanaka S., and Takayanagi H. Scientific basis for the efficacy of combined use of antirheumatic drugs against bone destruction in rheumatoid arthritis. Mod Rheumatol, in press

○ Sato, K., Suematsu, A., Okamoto, K., Yamaguchi, A., Morishita, Y., Kadono, Y., Tanaka, S., Kodama, T., Akira, S., Iwakura, Y., Cua, D. J., & Takayanagi, H. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med 203, 2673-2682(2006)

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Commentary on: Winslow MM, et al. Calcineurin/NFAT signaling in osteoblasts regulates bone mass. Dev Cell 10, 771-82 (2006)

○ Ochi S (SS), Harigai M, Mizoguchi F, Iwai H, Hagiyama H, Oka T, Miyasaka N. Leflunomide-related acute interstitial pneumonia in two patients with rheumatoid arthritis: autopsy findings with a mosaic pattern of acute and organizing diffuse alveolar damage. Mod Rheumatol. 16, 316-20 (2006)

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○ Sato, K., Takayanagi, H. Osteoclasts, rheumatoid arthritis, and osteoimmunology. Curr Opin Rheumatol 18, 419-426(2006)

3 . Abstracts in the year 2006

Asagiri M, Koga T, Sato K, Takatsuna H, Umezawa K. & Takayanagi H.
Keystone symposia: NF-κB: 20 Years on the Road from Biochemistry to Pathology (Banff, Canada).
Regulation of bone metabolism by NF-κB and NFAT
2006

Sae Ochi, Masahiro Shinohara, Kojiro Sato and Hiroshi Takayanagi
12th Asia Pacific League of Associations for Rheumatology (APLAR) Congress 2006 (Malaysia)
Immunoreceptor signaling and TNFa-induced acceleration of osteoclastogenesis
2006

Suematsu A., Sato K. & Takayanagi H.
1st international conference on osteoimmunology: Interactions of the immune and skeltal systems (Crete, Greece)
Regulation of osteoclast differentiation and function by CaMK and CREB pathway
2006