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Invited Plenary Abstract
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Immune mechanisms in osteoclastogenesis

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Signaling through receptor activator of NF-κB ligand (RANKL) induces osteoclast differentiation in the presence of M-CSF. To explore the molecular mechanism of osteoclast differentiation, we performed a genome-wide screening of genes induced by RANKL. We identified that the transcription factor nuclear factor of activated T cells c1 (NFATc1) is specifically induced by RANKL and it plays a central role in RANKL-mediated osteoclast differentiation.

Induction and activation of NFATc1 is regulated by calcium-dependent phosphatase calcineurin. Immunoreceptor tyrosine-based activation motif (ITAM) signaling mediated by dual membrane adaptors, Fc receptor (FcR) common γ subunit (FcRγ) and DNAX activating protein (DAP12) is essential for RANKL induction of osteoclast differentiation. FcRγ and DAP12 associate with multiple immunoreceptors such as OSCAR and TREM-2 and activate calcium signals leading to the induction of NFATc1. The importance of ITAM-mediated signaling in the skeletal system is underscored by the observation that the combined deficiency of FcRγ and DAP12 results in severe osteopetrosis due to impaired osteoclast differentiation. RANKL-induced osteoclast differentiation is finely regulated through costimulatory signals provided by multiple immunoreceptors. Thus, RANKL and M-CSF are not sufficient to activate the signals required for osteoclast differentiation. Recent advances in the understanding of osteoclastogenic signal transduction will also be discussed in the context of osteoimmunology.

References
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