CDB SEMINAR

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16:00~17:00 A7F Seminar Room

Chemokine-mediated migration control of osteoclast precursors visualized by *in vivo* bone marrow imaging: A novel point of regulation for osteoimmunology

Summary

Osteoclasts (OCs) are bone-resorbing multinuclear giant cells that differentiate from mononuclear macrophage/monocyte-lineage hematopoietic precursors. They play critical roles not only in normal bone homeostasis (called "bone remodeling"), but also in the pathogenesis of bone destructive disorders such rheumatoid arthritis and osteoporosis. Although many molecules are known to contribute to OC differentiation, RANKL chief among them, the mechanisms controlling the recruitment and homing of OC precursors (OPs) to the bone surface have not been elucidated.

Using intravital imaging of the *in situ* behavior of OCs and their precursors within bone tissues, I found that sphingosine-1-phosphate (S1P), a lipid mediator enriched in blood, controls the movement of osteoclast precursors between the blood and the bone surface [their site of final differentiation]. OP monocytes express functional S1P receptors ($S1P_1$ and $S1P_2$), and exhibit positive chemotaxis toward an S1P gradient *in vitro* within a certain ligand concentration range. Intravital imaging of mouse calvaria bone tissues revealed that a potent $S1P_1$ agonist stimulated motility of OP monocytes *in vivo*. Because the concentration of S1P in blood is higher than that in tissues, S1P-mediated chemotaxis of OPs contributes to their recirculation from bone tissues to systemic blood flow. Treatment with FTY720, a clinically used S1P agonist, relieved ovariectomy-induced murine osteoporosis by facilitating recirculation of OPs and thus by reducing the number of mature OCs attached to bone surface.

Further examinations are revealing the possible role of other chemokines, such as CXCL12/SDF-1 and CX_3CR1/fractalkine, on the control of OP migration and thus osteoclastogenesis *in vivo* bone tissues. The bulk of these results support the hypothesis that fine regulation of OP migration mediated by various chemokines dynamically modulates bone homeostasis, suggesting a unique point of action on osteoclastogenesis that may be promising as a future therapeutic target.

In this seminar I will present the latest data on the new concept, i.e., chemokine-mediated migration control of OPs as a novel point of regulation for 'osteoimmunology'. I will also show, with plenty of movies, the detailed methodology of intravital bone marrow imaging and discuss its future application to broader research field, including stem cell biology.

Host:
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