Mini Review

DC-STAMP and Osteoimmunology

Takeshi Miyamoto[1-4,*], and Yoshiaki Toyama[1]

[1]Department of Orthopedic Surgery, [2]Department of Musculoskeletal Reconstruction and Regeneration Surgery, [3]Division of Orthopedic Research, Keio University School of Medicine and [4]Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency

The investigations from the aspect of "osteoimmunology" provided a recent advance on bone cell biology[1]. Various molecules identified to play a crucial role in immune system also play a role in bone system. For example, RANK-RANKL system was originally identified in dendritic cells and T cells[2], but these molecules are both essential for osteoclast differentiation and skeletal development[3,4]. Nuclear factor of activated T cells (NFATc1) was also originally identified in T cells, but plays an essential role in osteoclast differentiation[5]. Thus bone and immune systems share common molecules. Here we introduce a seven transmembrane receptor protein, dendritic cell specific transmembarne protein (DC-STAMP) as an "osteoimmunology" molecule, which plays a role in both bone and immune systems.

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* Correspondence should be addressed to:
T Miyamoto, M.D., Department of Orthopedic Surgery, Keio University School of Medicine, 35 Shinano-machi, Shinjuku-ku, Tokyo 160-8582, Japan. Phone: +81-3-5363-3812, Fax: +81-3-3353-6597, e-mail: miyamoto@sc.itc.keio.ac.jp

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DC-STAMP and Bone system

Osteoclasts are bone-resorbing giant cells derived from hematopoietic stem cells or monocyte/macrophage lineage cells[6]. The most characteristic feature of osteoclasts is multi-nucleation induced by a cell-cell fusion of mono-nuclear osteoclasts. Various molecules such as macrophage fusion receptor, E-Cadherin and meltrin-α had been reported involved in osteoclast or macrophage cell-cell fusion[7-9], however, defects in cell-cell fusion of osteoclasts and macrophages had not been shown by using knockout mice of these genes.

To isolate an osteoclast cell-cell fusion molecule, we undertook DNA subtraction screen between multi-nuclear osteoclasts and mono-nuclear macrophages, and we identified dendritic cell specific transmembrane protein (DC-STAMP) as an osteoclast specific molecule[10]. DC-STAMP was originally isolated from dendritic cells or IL-4 stimulated macrophages[11,12], and was reportedly involved in osteoclast differentiation[13]. We generated DC-STAMP-deficient mice and found that DC-STAMP was essential for cell-cell fusion of osteoclasts and macrophages[10]. Cathepsin K, a terminal differentiation marker of osteoclasts, or c-Fos and NFATc1, both of which are essential transcription factors, were equally expressed in DC-STAMP-deficient and wild-type osteoclasts. The defect of cell-cell fusion in DC-STAMP-deficient osteoclasts was rescued by a forced expression of DC-STAMP. Thus DC-STAMP was considered specifically required for cell-cell fusion of osteoclasts rather than differentiation.

Although the multi-nucleation of osteoclasts is well known phenomena, the role of cell-cell fusion on bone system had not

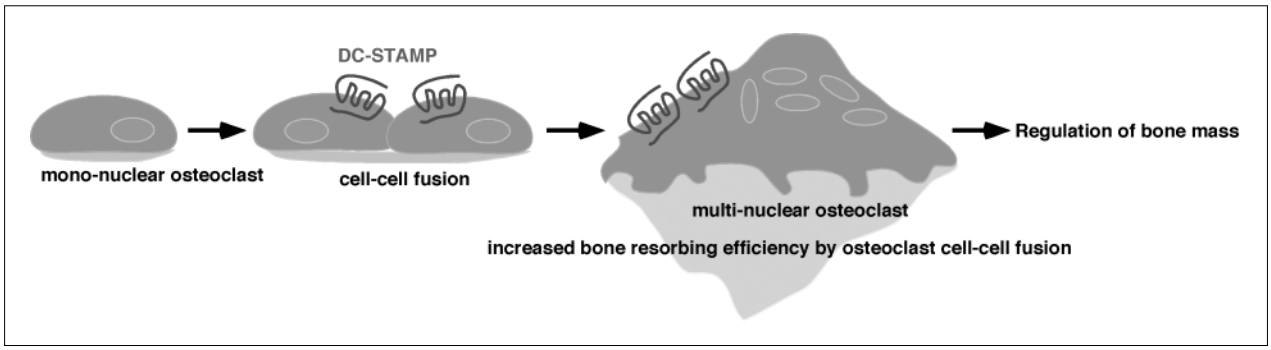

Fig.1 Osteoclast multi-nucleation and function

been characterized. We found that cell-cell fusion of osteoclasts upregulated the efficiency of bone resorption, and therefore, DC-STAMP-deficient mono-nuclear osteoclasts were less efficient to resorb bone compared with wild-type multi-nuclear osteoclasts. This leads DC-STAMP-deficient mice to increased bone mass than wild-type mice. Thus DC-STAMP regulates osteoclast cell-cell fusion, efficiency of osteoclast bone-resorption and physiological bone mass (Fig.1). Since DC-STAMP expression is directly regulated by c-Fos and NFATc1 in osteoclasts[14], DC-STAMP plays a critical role in regulating bone homeostasis through osteoclasts. Recently, v-ATPase V0 subunit d2 (ATPv0d2) was reportedly involved in osteoclast cell-cell fusion[15], and its expression was promoted by NFATc1[16]. The expression of ATPv0d2 was not different between DC-STAMP-deficient and wild-type osteoclasts[15], suggesting that DC-STAMP and ATPv0d2 regulate osteoclast cell-cell fusion independently. Further studies are required to elucidate the mechanisms of osteoclast cell-cell fusion.

DC-STAMP and Immune system

Dendritic cells (DCs) are professional antigen presenting cells that present processed antigens to T cells. DC-STAMP was originally identified in dendritic cells[11], however, its specific role in DCs was not demonstrated. Since DCs do not fuse, it was speculated that DC-STAMP has a role other than cell-cell fusion in dendritic cells. We found that DC-STAMP regulated antigen presentation activity in DCs and maintenance of immune self-tolerance[17].

DCs take up and process antigens, and present them to T cells in the context of MHC class I and II molecules. We found that antigen presentation activity of DC-STAMP-deficient DCs was higher than that of wild-type DCs in both class I and II pathways[17]. The lack of DC-STAMP did not inhibit differentiation or proliferation of DCs, suggesting that DC-STAMP specifically regulates antigen presentation activity of DCs. Since the activation of T cells by DCs in both class I and II pathways is high in DC-STAMP-deficient DCs than wild-type DCs, a general mechanism, such as phagocytotic activity, may underlie high antigen presentation to class I and II pathways in DCs from DC-STAMP deficient mice. Indeed, DC-STAMP-deficient DCs showed higher phagocytotic activity than wild-type DCs.

Interestingly, aged DC-STAMP-deficient mice showed several systemic autoimmune symptoms including spontaneous lymphoproliferation, splenomegaly associated with infiltration of T-cells in several organs and increased serum anti-double stranded DNA antibody production[17]. Excessive immunization with activated DCs induces autoimmune disease[18,19], whereas, prolonged DC survival by inhibiting apoptosis of DCs induces autoimmunity[20], suggesting that over or prolonged antigen presentation by DCs induces autoimmune symptoms. DC-STAMP plays a role in regulating maintenance of immune self-tolerance through controlling antigen presentation of DCs.

Discussion

To date, various molecules have been identified to play a role in regulating both bone and immune systems. We previously demonstrated that osteoclasts and DCs share common precursor cells[21]. From common precursor cells, osteoclasts and DCs differentiate into professional bone resorbing and antigen presenting cells, respectively. DC-STAMP is highly expressed in both cells, and plays an essential role in regulating cell-cell fusion and bone resorbing efficiency in osteoclasts or phagocytosis and antigen presentation activity in DCs, respectively (Fig.2). Thus DC-STAMP plays a critical role in regulating both bone and immune system as an “osteoimmunology” molecule.

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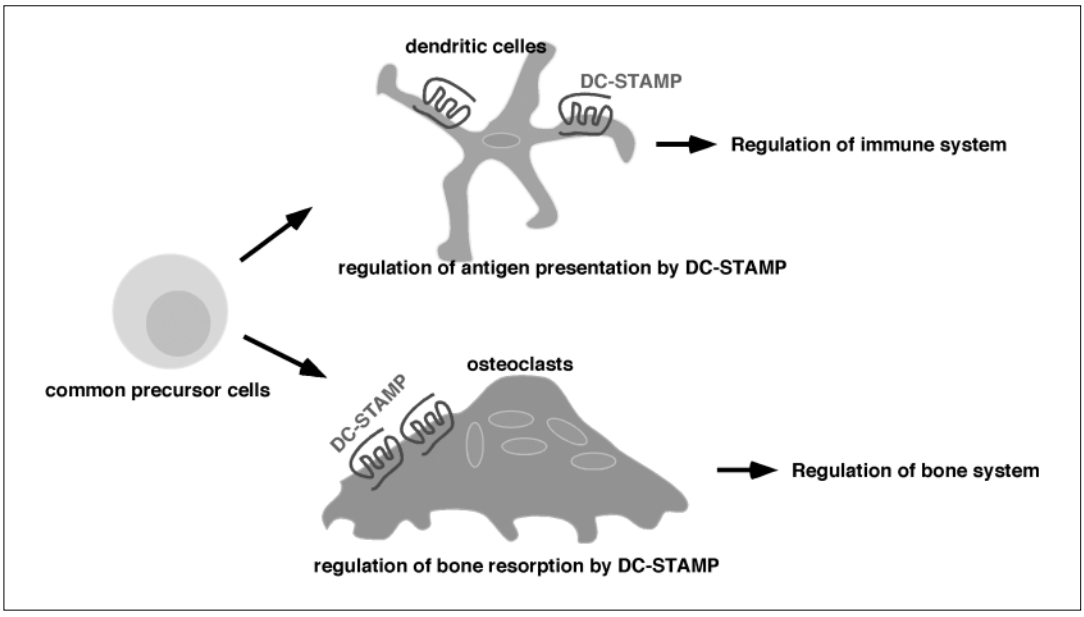

Fig.2 Role of DC-STAMP in bone and immune systems

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