Osteoclasts are bone resorbing cells that play a pivotal role in remodeling of mineralization, connective tissues and extracellular matrix proteins in bone. Since bone volume is tightly regulated by an interaction between osteoclasts and osteoblasts, imbalance of the activity of these cells causes bone disease such as osteoporosis. Osteoclasts are also implicated in the bone destructive diseases such as bone metastasis and rheumatoid arthritis, and that regulation of osteoclast activity is crucial to control these diseases. On the other hand, macrophage giant cells such as foreign body giant cells are formed in response to foreign body reaction, and are considered to play a role in matrix and tissue destruction under inflammatory condition.

Osteoclasts and macrophage giant cells are both derived from hematopoietic stem cells and form large multinuclear giant cells by cell-cell fusion of mononuclear osteoclasts or macrophages, respectively. Several cell fusion mediating factors have been reported in osteoclasts and macrophage giant cells, however, what molecules are required for cell-cell fusion, and the role of multinucleation remain uncharacterized. Here we identify the dendritic cell-specific transmembrane protein (DC-STAMP), a putative seven transmembrane protein, by a DNA subtraction screen between multinuclear osteoclasts and mononuclear macrophages.

To analyze the role of DC-STAMP in vivo, we generated DC-STAMP deficient mice. We interestingly found that cell-cell fusion of osteoclasts was completely abrogated in DC-STAMP deficient, despite normal expression of osteoclast markers and cytoskeletal structure. The cell-cell fusion in osteoclasts was effectively rescued by forced expression of DC-STAMP in DC-STAMP null cells by an infection of retrovirus expressing DC-STAMP. Thus DC-STAMP specifically regulates cell-cell fusion in osteoclasts. Defects in osteoclast multinucleation reduce bone-resorbing activity, and that DC-STAMP deficient mice show increased bone mass. Thus DC-STAMP regulates physiological bone volume by regulating osteoclast function through cell-cell fusion. Similar to osteoclasts, foreign body giant cell formation by macrophage cell fusion was also completely abrogated in DC-STAMP deficient mice. We have thus identified an essential regulator of osteoclast and macrophage cell fusion, DC-STAMP. Interestingly, regulation of DC-STAMP expression in osteoclasts and macrophage giant cells is different. This may explain a physiological role of DC-STAMP in osteoclasts whereas an inflammatory role of DC-STAMP in macrophage giant cells. I will discuss about the role of DC-STAMP and the regulation of DC-STAMP expression in osteoclasts and macrophage giant cells.