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論 文 名　：**Novel Osteoblast-Lineage Specific Cell-Surface Antigen Possibly Regulating Bone Remodeling and Hard Tissue Regeneration**

（骨改造と硬組織再生を制御する新規骨芽細胞特異的細胞表面抗原に関する研究）

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論 文 内 容 の 要 旨

Bone remodeling is a dynamic lifelong process involving precisely coordinated interactions between various bone cells in distinct multi-cellular units. Osteoclasts, specialized multinucleated bone resorbing cells, play a pivotal role in bone remodeling. Although RANKL/RANK axis is considered to determine the gross number of osteoclasts present in bone tissues, detailed molecular events regulating bone remodeling related to sites of osteoclast appearance to initiate bone remodeling and coupling of bone resorption and bone formation, are still ambiguous. We hypothesized that osteoblast-specific cell-surface molecules could contribute to the fine modulation of bone remodeling.

Therefore, we searched for regulatory cell-surface molecules expressed on osteoblasts by utilizing B-cell hybridoma technology. BALB/c mice were immunized with a clone of the rat osteoblastic cell line ROS17/2.8 and a panel of antibodies was prepared by fusing splenocytes with murine myeloma cell line (P3X63-AG8-U1). After screening and extensive cloning, one hybridoma secreting the monoclonal antibody-A7 (A7 MAb) highly specific to cells in the osteoblast lineage was obtained. Immunoreactivity of A7 MAb was examined using cultures of osteoblasts and bone marrow cultures and by use of bone tissue sections. Bioactivity of this MAb was assessed using *in vitro* calcification system of primary calvarial-

derived osteoblasts and bone marrow cultures for forming osteoclasts. Immunoreactivity of A7 MAb was also examined in mandibles of adult and neonatal rats.

In vitro, A7 antigen was expressed on cell-surface of osteoblasts and osteoblast-like bone marrow stromal cells. *In vivo*, A7 antigen was detected in a subset of bone surface osteoblasts and in osteocytes, with a typical cell membrane expression pattern. Tissue array analysis showed a limited expression of A7 antigen in osteocytes just close to the bone surface. Immunoblotting revealed that A7 antigen was lineage-specific of approximate molecular weight of 45 KDa. Immunoprecipitation of A7 antigen from biotinylated osteoblast cell-surface proteins also gave a single band of 45 KDa protein. Cross-linking of cell-surface A7 antigen in cultures of osteoclastogenesis showed limited stimulation of osteoclast formation. Marked suppression of calcification in primary osteoblast cultures was observed when A7 antigen was cross-linked with A7 MAb. A7 antigen was also expressed in mature odontoblasts. These data collecively suggest that A7 antigen could regulate recruitment of osteoclasts and triggering of calcification. A7 antigen could be an important molecule involved in the fine regulation of bone remodeling. The expression of A7 antigen in odontoblasts also suggests a regulatory role of this antigen in odontoblast differentiation and dentin regeneration.