OSTEOCYTE-SPECIFIC Cas KNOCKOUT MICE EXHIBIT DECREASED BONE MASS THROUGH INCREASED OSTEOCLASTIC BONE RESORPTION

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The skeleton is a metabolically active organ that undergoes continuous remodeling throughout life. Osteoporosis, which is fostered by advancing age, is the most common clinical disorder affecting bones. Although it has been postulated that osteocytes play an important role in sensing mechanical load in bone tissues, detailed molecular mechanisms of how osteocytes regulate bone metabolism remain largely unclear. The adaptor molecule p130Cas (Crk-associated substrate, hereafter referred to as Cas), which is phosphorylated at focal adhesions upon extracellular matrix engagement, is involved in various cellular processes including migration, survival, transformation, and invasion. In addition, we reported that Cas binds to the cytoskeletons in a stretch-dependent manner. This suggests that Cas can function as an initiator of intracellular signaling cascades through force-dependent changes in the cytoskeleton network. To investigate the role of Cas in bone metabolism, we generated osteocyte-specific Cas conditional knockout (cKO) mice by mating Casfloxflox mice with Dentin matrix protein 1 (Dmp1)-Cre transgenic mice, in which the Cre recombinase gene was specifically expressed in osteocytes. The resulting Dmp1-Cre+/–;Casfloxflox mice (referred to herein as Cas cKO mice) exhibited a significant decrease in bone volume, as determined by μCT analysis. Histomorphometric analysis of Cas cKO mice revealed a significant increase in the eroded surface/bone surface ratio, osteoclast surface, and osteoclast number. Furthermore, the expression levels of RANKL genes were significantly increased in the osteocyte fractions derived from Cas cKO mice. Collectively, these findings suggest that the bone loss in Cas cKO mice was caused by increased osteoclastotic bone resorption.

Biography

Tsuyoshi Miyazaki has completed his MD at the age of 24 years and his PhD at the age of 31 years from University of Tokyo and postdoctoral studies from Yale University School of Medicine. He is the director of Department of Orthopaedic Surgery, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology. He has published more than 30 papers in reputed journals.

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