2019 International Symposium
Tokyo Dental College Research Branding Project

What is a real function of osteocalcin ?

Toshihisa Komori, MD, PhD

Director and Professor
Basic and Translational Research Center for Hard Tissue Disease,
Nagasaki University Graduate School of Biomedical Sciences

Osteocalcin is the most abundant non-collagenous protein in bone, and its expression is regulated by Runx 2. Three Glu residues of pro-osteocalcin are carboxylated to γ-carboxyglutamic acid (Gla) residues, and carboxylated osteocalcin (Gla osteocalcin) exhibits high affinity to Ca^{2+} and adopts an α-helical conformation by binding to Ca^{2+}, whereas uncarboxylated osteocalcin (Glu osteocalcin) has no affinity to Ca^{2+}. Osteocalcin has been shown to inhibit bone formation, because the bone mass is increased in osteocalcin-deficient ($Ocn^{-/-}$) mice due to the enhanced bone formation. Further, Glu osteocalcin has been shown to function as a hormone that regulates glucose metabolism, testosterone synthesis, and muscle mass. We generated $Ocn^{-/-}$ mice, in which *Bglap* and *Bglap 2* were deleted, to reveal the essential functions of osteocalcin. Our $Ocn^{-/-}$ mice showed a similar bone mass and BMD in trabecular and cortical bone to those in wild-type mice. Further, glucose metabolism, testosterone synthesis, and muscle mass were normal in $Ocn^{-/-}$ mice. In normal mineralization, the *c*-axis of apatite, which is the predominant direction of crystal growth, aligns almost parallel to the direction of collagen fibrils, which preferentially run along the longitudinal axis of long bones. The orientation degree of collagen and the crystallite size of biological apatite (BAp) in the *c*-axis were normal. However, the crystallographic orientation of the BAp *c*-axis was severely disrupted, and bone strength was significantly reduced in $Ocn^{-/-}$ mice due to the disrupted BAp *c*-axis orientation. Therefore, our results indicate that osteocalcin is required for the alignment of the BAp crystallites and maintaining bone strength but not for the regulation of bone quantity, glucose metabolism, testosterone synthesis, and muscle mass.

Curriculum Vitae

1980 MD Osaka University Medical School, Japan Medical science
1989 PhD Osaka University Medical School, Japan Immunology
1983－1990 Dep.of Medicine III, Osaka University Medical School, Japan Medical staff
1991－1991 Columbia University College of Physicians and Surgeons, Postdoctoral Research Fellow
1991－1993 Harvard University Medical School, Postdoctoral Research Fellow
1993－2004 Dep. of Molecular Medicine, Osaka University Graduate School of Medicine, Japan Assistant Professor
2004－2019 Dep. of Cell Biology, Nagasaki University Graduate School of Biomedical Sciences, Professor
2014－2019 Vice President of Nagasaki University, Director of Life Science Support Center, Director of The Center for Innovative Drug Discovery
2019－ Basic and Translational Research Center for Hard Tissue Disease, Nagasaki University Graduate School of Biomedical Sciences, Director and Professor

Honors

1997；Berz prize
2002；Japanese Society for Bone and Mineral Research Academic Award
2006：Novartis Medical Prize for Rheumatoid Disease

Research Fields of Interest

Molecular mechanism of skeletal development, especially osteoblast and chondrocyte differentiation.

Selected Publications

1. Qin X, Jiang Q, Miyazaki T, Komori T： Runx 2 regulates cranial suture closure by inducing hedgehog, Fgf, Wnt, and Pthlh signaling pathway gene expression in suture mesenchymal cells. ***Hum Mol Genet.*** 28(6)：896－911, 2019.
2. Kawane T, Qin X, Jiang Q, Miyazaki T, Komori H, Yoshida CA, Matsuura-Kawata VKDS, Sakane C, Matsuo Y, Nagai K, Maeno T, Date Y, Nishimura R, Komori T： Runx 2 is required for the proliferation of osteoblast progenitors and induces proliferation by regulating Fgfr 2 and Fgfr 3. ***Sci Rep.*** 10；8(1)：13551, 2018.
3. Kawane T, Komori H, Liu W, Moriishi T, Miyazaki T, Mori M, Matsuo Y, Takada Y, Izumi S, Jiang Q, Nishimura R, Kawai Y, Komori T：Dlx 5 and Mef 2 Regulate a novel Runx 2 enhancer for osteoblast-specific expression. ***J Bone Miner Res.*** 29(9)：1960－1969, 2014.
4. Yoshida CA, Yamamoto H, Fujita T, Furuichi T, Ito K, Inoue K, Yamana K, Zanma A, Takada K, Ito Y, Komori T：Runx 2 and Runx 3 are essential for chondrocyte maturation, and Runx 2 regulates limb growth through induction of Indian hedgehog. ***Genes Dev.*** 18：952－963, 2004.
5. Yoshida CA, Furuichi T, Fujita T, Fukuyama R, Kanatani N, Kobayashi S, Satake M, Takada K, Komori T：Core-binding factor interacts with Runx 2 and is required for skeletal development. ***Nat Genet.*** 32：633－638, 2002.
6. Ueta C, Iwamoto M, Kanatani N, Yoshida C, Liu Y, Enomoto-Iwamoto M, Ohmori T, Enomoto H, Nakata K, Takada K, Kurisu K, Komori T：Skeletal malformations caused by overexpression of Cbfa 1 or its dominant negative form in chondrocytes. ***J Cell Biol.*** 153：87－100, 2001.
7. Liu W, Toyosawa S, Furuichi T, Kanatani N, Yoshida C, Liu Y, Himeno M, Narai S, Yamaguchi A, Komori T：Overexpression of Cbfa 1 in osteoblasts inhibits osteoblast maturation and causes osteopenia with multiple fractures. ***J Cell Biol.*** 155(1)：157－166, 2001.
8. Komori T, Yagi H, Nomura S, Yamaguchi A, Sakaki K, Deguchi K, Shimizu Y, Bronson RT, Gao Y, Inada M, Sato M, Okamoto R, Kitamura Y, Yoshiki S, and Kishimoto T：Targeted disruption of Cbfa 1 results in a complete lack of bone formation owing to maturational arrest of osteoblasts. ***Cell.*** 89：755－764, 1997.