講　演　抄　録

国際シンポジウム

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Session 1 ：Molecular and cellular mechanism of bone metabolism and bone diseases

Disorders with excessive loss of jaw bones
－lessons from genetic and clinical studies

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The genetic disorder known as “cherubism”, discovered and named by Dr. W. A. Jones（Brit J Radiol 1938；11：227）, is characterized by severe inflammatory bone loss in the jaws of growing children and young adults. Identification of the responsible gene and research into its regulatory functions has provided substantial insights into mechanisms underlying jaw bone development and growth, maintenance and aging. Using DNA from members of several families with the disorder, mutations were identified in a gene encoding the protein known as SH３BP２－a regulator of intracellular signaling pathways in practically all cells. To investigate the roles of SH３BP２ and the pathogenetic effects of the cherubism mutations on the functions of osteoblasts, osteoclasts, macrophages and T-and B-cells, the most common mutation found in affected families was introduced into the *Sh3bp2* gene of mice. Based on studies of the mutant mice, the lecture will discuss（a）how SH３BP２ serves as a regulator of responses to incoming signals in macrophages, osteoclasts and osteoblasts；（b）how the cherubism mutations prevent degradation of the protein, such that many pathological consequences are the results of increased cellular levels of SH３BP２；（c）jaw bones may be primarily affected in patients with cherubism because specific pathological events, triggered by the innate immune system, occur in these bones at the time of initiation of the anomalies in children with the disease；（d）reasons for why the pathology of cherubism may regress after puberty. Finally, with pathogenetic mechanisms of cherubism as background, the cause of an osteonecrosis and osteomyelitis condition, limited to jaw bones and resulting in severe loss of bone, will be discussed. In this case, genetic factors are unlikely to have a causative role. However, bacterial processes may trigger many of the same mechanisms that are affected by increased levels of mutant SH３BP２ in cherubism.

Biosketch

Bjorn Reino Olsen was born in Skien, Norway, on April 22, 1940. He received his MD and PhD degrees from the University of Oslo in 1967, where he became a faculty member and Associate Professor of Anatomy. In 1971, he moved to the United States to work with Professor D. Prockop and joined the faculty of the Department of Biochemistry at Rutgers Medical School, where he was promoted to Professor in 1976. In 1985 Professor Olsen was appointed Hersey Professor in the Department of Anatomy and Cellular Biology at Harvard Medical School, now the Department of Cell Biology. Since 1996 he has also been Professor of Developmental Biology at Harvard School of Dental Medicine (HSDM), where he was Chair of the new Developmental Biology department until 2005, when he became Dean for research (2005－2017). Professor Olsen has received numerous honors and awards, including the Fell-Muir and Humboldt Research Awards, multiple Honorary Degrees and the 2019 King Faisal Prize in Medicine.

Professor Olsen's discoveries range from identification of "founding" members of novel families of collagenous proteins (FACIT collagens IX, XII and XIV；short chain collagens VIII and X；multiplexin collagen XVIII) with critical functions in skeletal tissues, to identification of mutations in matrix molecules (collagens IX, X, XI), transcription factors (Runx２, HOXD13) and receptors/signaling components (LRP５, SH３BP２, ANK) responsible for inherited osteochondrodysplasias (murine chondrodysplasia, Schmid metaphyseal dysplasia, multiple epiphyseal dysplasia, Stickler syndrome, synpolydactyly, osteoporosis pseudoglioma syndrome, craniometaphyseal dysplasia, and cherubism) in humans and mice. Studies of vascular syndromes identified mutations in a receptor tyrosine kinase (TIE２) causing Venous Malformations, and led to finding that mutations in Anthrax toxin receptor 1 and increased levels of VEGF are associated with rapidly growing Infantile Hemangioma tumors. The discoveries unraveled developmental and disease mechanisms at the intersection between skeletal and vascular biology, as well as highlighting the roles of VEGF in differentiation of mesenchymal stem cells to osteoblasts and bone marrow adipocytes.