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Session 5 "Special Lecture"

From proteoglycans to enzymes:

Koji Kimata

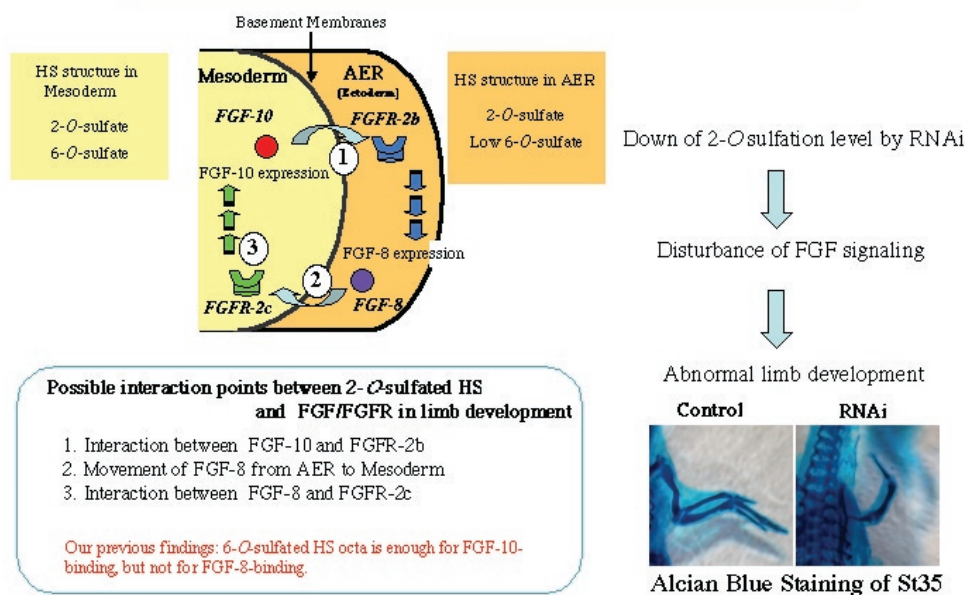
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Dr. Kimata received his Ph.D. from the Department of Chemistry, Faculty of Science, Nagoya University under the guidance of Prof. Suzuki in 1975 while he was working as Assistant Professor there. His work revealed the occurrence of three different types of proteoglycans in 12-day chick embryonic cartilage which function as the microenvironment for cartilage cyto-differentiation as well as as cartilage structural element. He also found that chondroitin sulfate chains of those proteoglycans were changing in their structures spacio-temporally. Those results led to an interest in the mechanisms of cartilage differentiation. His lecture today will

cover the details of this project including recent findings. He had chance to study abroad as visiting scientist at the National Institute of Dental Research, National Institutes of Health, Bethesda in 1978 and collaborate with many extracellular matrix scientists there such as Drs. Hascall and Yamada. In 1993 he was appointed as a Fogarty International Center Scholar-in-Residence at the National Institutes of Health by this contribution. He moved to the Institute for Molecular Science of Medicine, Aichi Medical University as Associate Professor in 1987 and now Professor there. His recent work focuses on enzymes involved in biosynthesis of heparan sulfate, chondroitin sulfate, and hyaluronan, which help understand not only the biosynthetic mechanisms of those glycosaminoglycans but also their functions *in vivo*.

FGF/FGFR signaling loop in limb development



Chick limb is a good system to learn mechanisms of cartilage differentiation and the tissue-formation as well as molecules involved in such events, because any developmental stages of chick limbs can easily be obtained and handled under microscope.

Our experiment started to identify molecules in 12-day embryonic chick cartilage. This brought us to characterize PG-H (aggrecan), PG-Lt (type IX collagen), and PG-Lb (epiphykan). Then, we have been interested in how the cartilage with a spatio-temporally regulated pattern is formed from the mesenchyme anlagen in the limb buds. The analysis for the molecules in the limb buds revealed the presence of a large chondroitin sulfate proteoglycan, versican/PG-M, hyaluronan and heparan sulfate proteoglycans. Versican/PG-M was found to play an important role in the mesenchymal condensation, which is an event essential for cartilage differentiation. Heparan sulfate proteoglycans

regulate the activities and locations of cell growth factors and morphogens in the limb bud the way that interactions between heparan sulfate chains and the factors are controlled spatio-temporally. *O*-sulfation at various residues of heparan sulfate are key reactions to make the interactions specific to individual factors. Therefore, it is worth looking at what would happen if *O*-sulfation enzymes are modified in their expressions. We have recently found that siRNA inhibition of heparan sulfate 2-*O*-sulfotransferase expression resulted in truncation of the limb bud, which appeared to be caused by disruption of the FGF-signaling loop. Taken together with the observation that 2-*O*-sulfation is important for interactions of many of FGF isoforms, how GAG chain structures are modified by enzymes and how altered structures are involved in cell growth factor and morphogen signaling are becoming important issues to be studied as our next subject.

Keywords : Limb bud, Cartilage, Heparan sulfate proteoglycans, Cell growth factors, Heparan sulfate *O*-sulfotransferases