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"Recent Progress in Extracellular Matrix Research"

11th Proteoglycan Forum

Luncheon Seminar

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Room B-1

11TH Proteoglycan Forum

[Abstract]

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Title: "Role of Perlecan in Mouse Development and Human Diseases"

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Role of perlecan in mouse development and human diseases

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Perlecan, a heparan sulfate proteoglycan, is present in all basement membranes and in some other tissues such as cartilage. Perlecan consists of a 400-kDa protein core, which can be divided into five distinct domains designated I-V. Perlecan has various biological activities, such as cell growth and differentiation, modulation of growth factor activity, and binding to many molecules, including extracellular matrices, growth factors, and cell surface receptors. Most of these activities were identified in *in vitro* systems. However, recent studies with gene knockout mice and human genetic disorders provide some insights into the role of perlecan in development and tissue functions.

Functional-null mutation of perlecan gene in mice

The perlecan-null mutation in mice showed lethal chondrodysplasia and die perinatally. Cartilage of perlecan -/- mice revealed a disorganized growth plate with reduced chondrocyte proliferation and differentiation. Endochondral ossification was defective and abnormal membrane ossification was increased for compensation. We proposed two functions of perlecan in cartilage development, modulation of growth factor activity, such as FGF/FGFR3c, and matrix formation in the hypertrophic zone.

Two classes of human diseases caused by perlecan mutations

We searched for the human disease caused by perlecan mutation. Two classes of diseases were identified by different approaches. Similarities of the skeletal abnormalities of perlecan knockout mice led us to identify a human disorder, DDSH (dyssegmental dysplasia Silverman-Handmaker type). DDSH is a rare lethal autosomal recessive skeletal dysplasia characterized by anysospondyly and micromelia. We identified two different mutations in the perlecan gene in three DDSH patients. These mutations are predicted to create truncated perlecan molecules. Immunostaining and Western blotting revealed that the protein was not secreted. Thus, DDSH is caused by functional null mutations of the perlecan gene, similar to the gene knockout mice. Another human disorder caused by perlecan gene mutations was Schwartz-Jampel syndrome (SJS). SJS is characterized by a unique combination of myotonia and chondrodysplasia, and patients with SJS survive. SJS mutations result in different forms of perlecan in reduced levels that are secreted to the extracellular matrix and are probably partially functional. These findings indicate an important

role of perlecan in neuromuscular function and cartilage formation. Perlecan is present in muscle basement membranes and is enriched at the neuromuscular junction (NMJ) of wild-type mice. At the NMJ, the nicotinic ACh receptor mediates postsynaptic depolarization and terminates this process by hydrolyzing acetylcholine (ACh). Efficient and accurate synaptic transmission requires proper localization of many signaling proteins in the synaptic membrane such as acetylcholinesterase (AChE), ACh receptors (AChR), agrin, dystroglycans, rapsyn, and utrophin. In the perlecan knockout mice, muscle development and differentiation appear to be normal and normal nerve terminals are formed at birth. Most clustering molecules are present at the NMJ of the mutant mouse muscles. However, AChE is absent at the NMJ of newborn perlecan-null mice, although AChE protein is synthesized normally. These results indicate that perlecan plays an essential role in targeting of AChE to the NMJ and the defect in high-density localization of AChE at the synapse may explain the mechanism of myotonia in SJS.