



Role of perlecan as a modulator in neuromuscular signaling

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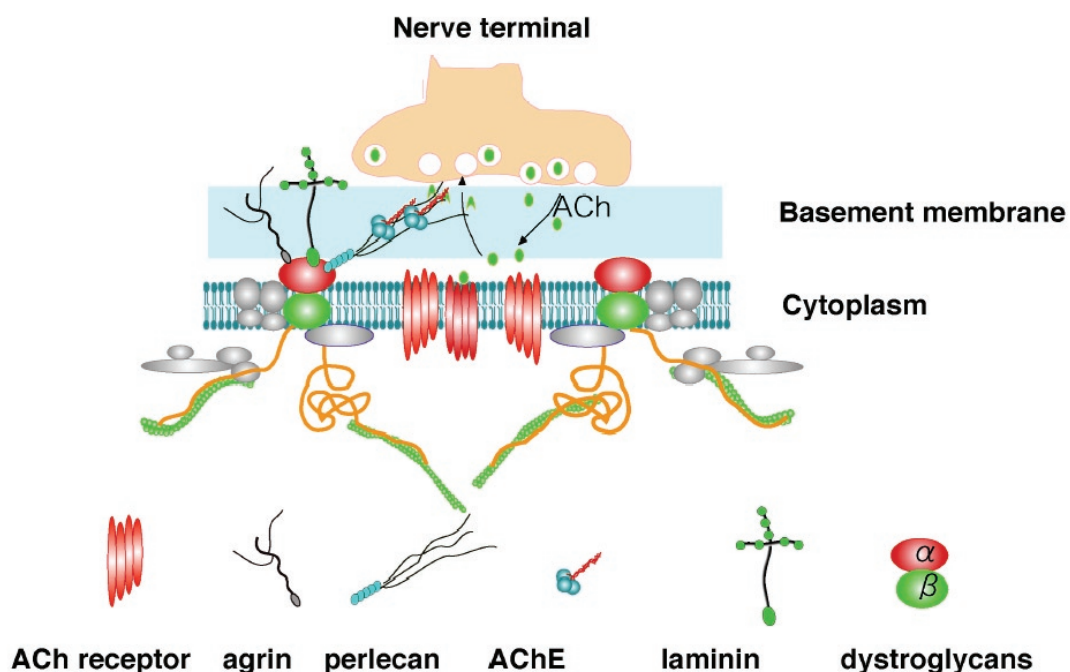
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I am a neurologist who received my M.D. and Ph.D. from Juntendo University School of Medicine. I worked at the National Institute of Dental and Craniofacial Research, National Institutes of Health (NIH) for 5 years (1996-2001), where I studied the functions of perlecan and laminin-1 in development and diseases. I discovered the essential role of perlecan in cartilage development and neuromuscular junction function by creating gene knockout mice. I also identified

mutations in the perlecan gene of patients with Dyssegmental dysplasia, Silverman-Handmaker type (DDSH), which is a rare lethal autosomal recessive skeletal dysplasia characterized by ankylospondyly and micromelia. In addition, I identified several mutations in patients with Schwartz-Jampel syndrome (SJS), characterized by myotonia and mild chondrodysplasia. She returned to Juntendo University in 2001, where I am currently a Lecturer at the Research Institute for Diseases of Old Age. My major research interest has been in the extracellular matrix in development and diseases with a special focus on muscular disorders.

Figure. Molecules clustered at the neuromuscular junction



Perlecan, a large heparan sulfate proteoglycan, is a structural and functional molecule present in all basement membranes and at the periphery of cells in some tissues such as cartilage. The core protein of perlecan consists of five domains with 2-3 heparan sulfate (HS) side chains at the N-terminus and one or two HS/chondroitin sulfate (CS) chains at the C-terminus. Perlecan binds many matrix molecules, growth factors, and cell surface receptors. In muscle, perlecan is enriched at the neuromuscular junction (NMJ) and is required for maintaining NMJ function by providing mechanical support and by modulating signals such as growth factor activity. Gene mutation studies in mice and humans revealed critical roles of perlecan in neuromuscular function. Functional mutations in the perlecan gene, which result in truncation of perlecan molecules, have been identified in patients with Schwartz-Jampel syndrome (SJS), characterized by myotonia (muscle stiffness) with mild chondrodysplasia. We also previously demonstrated that perlecan is essential for localizing acetylcholinesterase (AChE) to the NMJ in perlecan-null mice. However, the molecular mechanism of myotonia of SJS and the role of perlecan in neuromuscular signaling are unclear. To investigate the function of perlecan in adult tissues, we created a new mouse model by rescuing the perinatal lethality of perlecan-null mice by expressing recombinant perlecan in cartilage but

not other tissues under the control of a cartilage-specific promoter. Muscles of the mutant mice show a continuous discharge on the electromyography (EMG), characteristic to myotonia, similar to SJS patients. We analyzed the diaphragm of mutant mice using a microelectrode technique for the resting potential and end-plate potential (EPP) of muscle membrane. We found that the decay of the EPP was significantly prolonged in perlecan-null muscle, indicating a deficiency of AChE activity at the NMJ. We also observed an increased acetylcholine (ACh) release from nerve terminals in response to an action potential. These results suggest that combinations of these presynaptic abnormalities and postsynaptic muscle defects cause a continuous contraction of perlecan-null muscle.

Next we examined the effect of the loss of perlecan on vascular tension development in arteries of mutant mice. Thoracic aorta contraction by phenylephrine, an α 1-adrenergic receptor agonist, was significantly increased in perlecan-null mice. ACh-induced, endothelium-dependent vascular relaxation was significantly reduced in the perlecan-null artery, whereas sodium nitroprusside-elicited, endothelium-independent relaxation was not affected by perlecan deficiency. In addition, mutant mice often had aortic dissection (25%). These findings suggest that perlecan deficiency results in vascular smooth muscle and endothelial dysfunction.

References:

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