Brevican determines specialization of the hyaluronan-binding nodal matrix assemblies at the large diameter nodes of Ranvier in the CNS

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Objective: Brevican is known to be an abundant extracellular matrix (ECM) component in the adult brain and a structural constituent of perineuronal nets (PNN). It also acknowledged as an extracellular component at the node of Ranvier in the CNS. To explore the role of brevican in the formation of the nodal matrix, immunohistochemical staining was conducted in the facial nerve tract of wild-type and brevican-deficient mice.

Results: We herein show that brevican, tenascin-R (TN-R) and phosphacan are present at the nodes of Ranvier on myelinated axons with a particularly large diameter in the CNS. A brevican deficiency resulted in a reorganization of the nodal matrices, which was characterized by the shift of TN-R, and concomitantly phosphacan, from an axonal diameter-dependent association with nodes to an axonal diameter independent association. Supported by the co-immunoprecipitation results, these observations indicate that the presence of TN-R and phosphacan at nodes is normally brevican-dependent, while in the absence of brevican these molecules can also be recruited by versican V2. The versican V2 and Brall distribution was not affected, thus indicating a brevican-independent role of these two molecules for establishing hyaluronan-binding matrices at the nodes.

Conclusions: Our results revealed that brevican plays a crucial role in determining the specialization of the hyaluronan-binding nodal matrix assemblies in large diameter nodes.

REFERENCE


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Significance of the dystrophin-glycoprotein complex that connects the cytoskeleton to the basal lamina.

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Duchenne muscular dystrophy (DMD) is a lethal muscle disorder caused by mutations of the DMD gene, which codes a 427 kDa spectrin-like cytoskeletal protein, dystrophin. Dystrophin is localized just beneath the sarcolemma, and binds F-actin via its N-terminal domain and beta-dystroglycan via its cysteine-rich domain, forming a vital link between the actin cytoskeleton and extracellular matrix in skeletal and cardiac muscle. The lack of dystrophin, accompanied by loss of dystrophin-binding proteins, weakens the muscle membrane, leading to degeneration of myofibers. There is no effective treatment for the disease at present, but exon skipping by antisense oligonucleotides is a novel method to restore the reading frame of the mutated DMD gene, and rescue dystrophin production.

We recently reported that systemic delivery of Morpholino antisense oligonucleotides targeting exon 6 and 8 of the canine DMD gene, efficiently recovered functional dystrophin proteins at the sarcolemma of dystrophic dogs, and improved performance of affected dogs without serious side effects (Yokota et al, Ann Neurol, in press). To optimize therapeutic antisense Morpholinos for more frequent mutations of the DMD gene, we designed 14 kinds of antisense Morpholinos targeting exon 51 of the mouse DMD gene, and injected them separately or in combination into the muscles of mdx52 mice, in which exon 52 has been deleted by a gene targeting technique. A combination of two Morpholinos showed an excellent restoration of sarcolemmal dystrophin in injected muscle. We, therefore, intravenously injected them into mdx52 mice at 7 times weekly. Two weeks after the final injection, dystrophin was expressed at the sarcolemma throughout the body, with an average of about 10-50% normal levels. This was accompanied by amelioration of dystrophic pathology, and improvement of contractile force of EDL, grip power test, and treadmill performance. This study provides a proof of concept for exon 51 skipping in the DMD animal model and that can be applicable to DMD patients.