AL09 **Elucidation of pathology and drug development for muscular dystrophy through the comprehension of novel glycosylation mechanisms**

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O-Mannosyl glycan is a type of *O*-glycan for which the reducing terminal mannose is attached to serine and threonine residues of proteins. In 1997, mammalian *O*-mannosyl glycan was originally identified in α-dystroglycan (α-DG) from peripheral nerve, skeletal muscle, and brain tissues. The *O*-mannosyl glycan mainly consists of four sugars: Sia α 2-3Gal β 1-4GlcNAc β 1-2Man-Ser/Thr. In initial studies of the biosynthesis of *O*-mannosyl glycan, we identified protein *O*-mannosyltransferase 1 (POMT1), POMT2, and protein *O*-linked mannose β1,2-*N*-acetylglucosaminyltransferase 1 (POMGNT1). Then, the genes encoding POMT1/2 and POMGNT1 were identified as causative for autosomal recessive disorders characterized by congenital muscular dystrophies with neuronal migration disorders. Based on these pioneering findings, the aberrant *O*-mannosylation of α-DG is causative for some forms of congenital muscular dystrophy, which are referred to as α-dystroglycanopathy. *O*-Mannosyl glycan on α-DG is required for its binding to extracellular matrix components such as laminin, and the defective laminin-binding is associated with α-dystroglycanopathy. To date, 18 genes have been identified as causative in α-dystroglycanopathies.

The development of sensitive methods for analyzing glycan structures has revealed many novel sugar structures. After the first identification of the *O*-mannosyl glycan, numerous studies have been performed and revealed various structures of *O*-mannosyl glycans, which can be classified into three types: core M1, GlcNAc β1-2Man; core M2, GlcNAcβ1-2(GlcNAc β1-6)Man; and core M3, GalNAc β 1-3GlcNAc β 1-4(phosphor-6)Man. Actually, the defective core M3 structure has been suggested to be associated with α-dystroglycanopathy, but not the first identified core M1 structure, because the laminin-binding epitope has been identified from core M3 structure.

Recently, we revealed the entire structure of *O*-mannosyl glycan containing ribitol-phosphate (RboP), which has not been identified in a glycan component in mammals. In addition, its unique biosynthetic pathway was elucidated by identifying the functions of four causative gene products for α-dystroglycanopathy to be involved in the synthesis of tandem RboP. In this seminar, I would like to review the new insights about the mammalian *O*-mannosyl glycans biosynthesis obtained from our research.

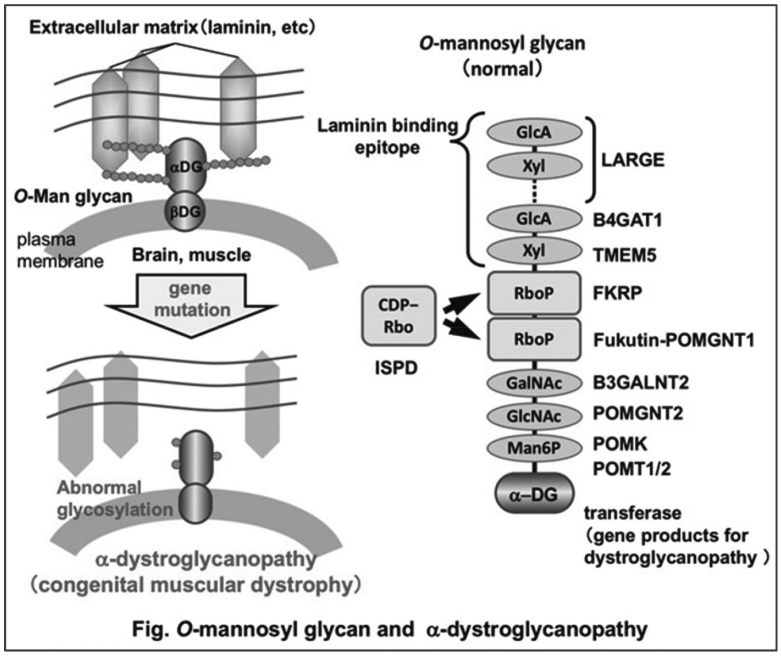

Fig. *O*-mannosyl glycan and α-dystroglycanopathy