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Abstract

O-Mannosyl glycan is a type of *O*-glycan in which the reducing terminal mannose is attached to proteins via serine and threonine residues. We previously reported that a defect in *O*-mannosyl glycan is the primary cause of α-dystroglycanopathy (α-DGpathy), a group of congenital muscular dystrophies caused by aberrant α-dystroglycan (α-DG) glycosylation. Recent studies have revealed the various structures of *O*-mannosyl glycan, and these structures can be classified into three types: coreM1, GlcNAcβ1-2Man; coreM2, GlcNAcβ1-2 (GlcNAcβ1-6)Man; and coreM3, GalNAcβ1-3GlcNAcβ1-4(phospho-6)Man. Several genes have been shown to cause α-DGpathy. In addition, the products of these genes are also involved in *O*-mannosyl glycan biosynthesis. The defective coreM3 structure is associated with α-DGpathy. However, the glycan structure and biosynthetic pathway of coreM3 are not fully understood.

Here, we determined the entire structure of coreM3, and it contained a previously unknown tandem structure consisting of two molecules of ribitol 5-phosphate (Rbo5P), which is a phosphoric ester of pentose alcohol.[1] From MS and NMR analyses, we determined that the coreM3 structure was "$[GlcA\text{-}Xyl]_n$-Rbo5P-1Rbo5P-3GalNAcβ1-3GlcNAcβ1-4(phospho-6)Man". Furthermore, we showed that the three proteins responsible for α-DGpathy act as enzymes in the synthesis of tandem Rbo5P. Isoprenoid synthase domain-containing protein (ISPD) is a cytidine diphosphate ribitol (CDP-Rbo) synthase. Fukutin and fukutin-related protein are Rbo5P transferases that act sequentially and use CDP-Rbo.

Additionally, we showed that mutation of *POMGNT1*, one of the genes responsible for α-DGpathy, also causes retinitis pigmentosa (RP).[2] The total loss of POMGnT1 activity underlies characteristic α-DGpathy phenotypes, while mutations of POMGnT1 that induce subnormal activity are associated with RP.

References

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