Antisense therapy for Fukuyama congenital muscular dystrophy (FCMD) and recent advance in dystroglycanopathies, FCMD, ISPD, and LGMD2I

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Fukuyama muscular dystrophy (FCMD) and muscle-eye-brain (MEB) disease are similar disorders characterized by congenital muscular dystrophy, brain and eye anomalies. Hypoglycosylation of α-dystroglycan (α-DG) are common characteristics of these dystroglycanopathies. We identified the genes for FCMD (fukutin) and MEB (POMGnT1). FCMD is the first human disease found to result from ancestral insertion of a SVA retrotransposon. We show that aberrant mRNA splicing, induced by SVA exon-trapping, underlies the molecular pathogenesis of FCMD. Introduction of antisense oligonucleotides (AONs) targeting the splice acceptor, the predicted exonic splicing enhancer and the intronic splicing enhancer prevented pathogenic exon-trapping by SVA in cells of patients with FCMD and model mice, rescuing normal fukutin mRNA expression and protein production. AON treatment also restored fukutin functions, including O-glycosylation of α-DG and laminin binding by α-DG. Thus, we have demonstrated the promise of splicing modulation therapy as the first radical clinical treatment for FCMD.

Recently we identified the previously unknown glycan unit ribitol 5-phosphate (Rbo5P), a phosphoric ester of pentose alcohol, as a tandem repeat that functions as a scaffold for the formation of the ligand-binding moiety of α-DG. We determined the enzyme activities of three major α-DGpathy-causing proteins to be involved in the synthesis of tandem Rbo5P. ISPD is cytidine diphosphate ribitol (CDP-Rbo) synthase. Fukutin and fukutin-related protein are Rbo5P transferases that use CDP-Rbo. Consequently, Rbo5P glycosylation is defective in α-DGpathy models. Supplementation of CDP-Rbo to ISPD-deficient cells restored α-DG glycosylation. These findings expand our knowledge on post-translational modification, and reveal the pathogenesis and therapeutic strategies of α-DG-associated diseases.