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

Tatsushi Toda

Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

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.