ABSTRACT

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Grant Title: Molecular Basis of Ribitol Phosphate Modification and Muscular Dystrophy Therapy

Ribitol phosphate is a novel post-translational moiety identified from dystroglycan (DG), an extracellular matrix receptor. DG plays an important physiological role in muscle and nerve tissues, and its abnormal glycosylation causes muscular dystrophies called dystroglycanopathy (DGpathy). We have revealed that the DGpathy-causing gene products (fukutin, FKRP, and ISPD) are enzymes involved in ribitol phosphate modification. Fukutin and FKRP are transferases that incorporate ribitol phosphate into sugar chains, and ISPD is a synthetase of CDP-ribitol, which is a donor substrate of ribitol phosphate. However, metabolic pathway for CDP-ribitol synthesis is not fully understood. In addition, there are no effective treatments for ribitol phosphate-defective muscular dystrophies. Therefore, the aim of this study was to elucidate the molecular basis of ribitol phosphate modification and to establish a therapeutic strategy for ribitol phosphate-defective muscular dystrophies.

This study provides the molecular pathway necessary for CDP-ribitol biosynthesis. We found that aldo-keto reductase (AKR) family is involved in the synthesis of ribitol-5-phosphate, which is a substrate of ISPD. In addition, we have examined various therapeutic strategies using fukutin-deficient cells and Ispd-deficient mice. In summary, this project has provided a major clue to the full understanding of the molecular basis of the ribitol phosphate modification. Based on the molecular mechanism of ribitol phosphate modification, novel therapeutic strategies, such as substrate replacement therapy, are also under investigation.