Format: Abstract

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Metabolomics Analysis of Skeletal Muscles from FKRP-Deficient Mice Indicates Improvement After Gene Replacement Therapy.

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Abstract

Muscular dystrophy-dystroglycanopathies comprise a heterogeneous and complex group of disorders caused by loss-of-function mutations in a multitude of genes that disrupt the glycobiology of α-dystroglycan, thereby affecting its ability to function as a receptor for extracellular matrix proteins. Of the various genes involved, FKRP codes for a protein that plays a critical role in the maturation of a novel glycan found only on α-dystroglycan. Yet despite knowing the genetic cause of FKRP-related dystroglycanopathies, the molecular pathogenesis of disease and metabolic response to therapeutic intervention has not been fully elucidated. To address these challenges, we utilized mass spectrometry-based metabolomics to generate comprehensive metabolite profiles of skeletal muscle across diseased, treated, and normal states. Notably, FKRP-deficient mice elicit diverse metabolic abnormalities in biomarkers of extracellular matrix remodeling and/or aging, pentoses/pentitols, glycolytic intermediates, and lipid metabolism. More importantly, the restoration of FKRP protein activity following AAV-mediated gene therapy induced a substantial correction of these metabolic impairments. While interconnections of the affected molecular mechanisms remain unclear, our datasets support the notion that global metabolic profiling can be valuable for determining the involvement of previously unsuspected regulatory or pathological pathways as well as identifying potential targets for drug discovery and diagnostics.

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