mTOR Inhibition Alleviates Mitochondrial Disease in a Mouse Model of Leigh Syndrome

Mitochondrial dysfunction contributes to numerous health problems, including neurological and muscular degeneration, cardiomyopathies, cancer, diabetes, and pathologies of aging. Severe mitochondrial defects can result in childhood disorders such as Leigh syndrome, for which there are no effective therapies. We found that rapamycin, a specific inhibitor of the mechanistic target of rapamycin (mTOR) signaling pathway, robustly enhances survival and attenuates disease progression in a mouse model of Leigh syndrome. Administration of rapamycin to these mice, which are deficient in the mitochondrial respiratory chain subunit Ndufs4 [NADH dehydrogenase (ubiquinone) FE-S protein 4], delays onset of neurological symptoms, reduces neuroinflammation, and prevents brain lesions. Although the precise mechanism of rescue remains to be determined, rapamycin induces a metabolic shift toward amino acid catabolism and away from glycolysis, alleviating the buildup of glycolytic intermediates. This therapeutic strategy may prove relevant for a broad range of mitochondrial diseases.