

Overexpression of branched-chain amino acid aminotransferases rescues the growth defects of cells lacking the Barth Syndrome related gene TAZ1

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The yeast protein Taz1 is the orthologue of human Tafazzin, a phospholipid acyltransferase involved in cardiolipin (CL) remodeling via a monolyso CL (MLCL) intermediate. Mutations in Tafazzin lead to Barth syndrome (BTHS), a metabolic and neuromuscular disorder that primarily affects the heart, muscles, and immune system. Similar to observations in fibroblasts and platelets from patients with BTHS or from animal models, abolishing yeast Taz1 results in decreased total CL amounts, increased levels of MLCL, and mitochondrial dysfunction. However, the biochemical mechanisms underlying the mitochondrial dysfunction in BTHS remain unclear. To better understand the pathomechanism of BTHS, we searched for multi-copy suppressors of the *taz1Δ* growth defect in yeast cells. We identified the branched-chain amino acid transaminases (BCATs) Bat1 and Bat2 as such suppressors [1]. Similarly, overexpression of the mitochondrial isoform BCAT2 in mammalian cells lacking TAZ improves their growth. Elevated levels of Bat1 or Bat2 did not restore the reduced membrane potential, altered stability of respiratory complexes, or the defective accumulation of MLCL species in yeast *taz1Δ* cells. Importantly, supplying yeast or mammalian cells lacking TAZ1 with certain amino acids restored their growth behavior [1]. Hence, our findings suggest that the metabolism of amino acids has an important and disease relevant role in cells lacking Taz1 function.

[1] Antunes D., Chowdhury A., Aich A., Saladi S., Harpaz N., Stahl M., Schuldiner M., Herrmann J.M., Rehling P., Rapaport D. (2019) Overexpression of Branched-Chain Amino Acid Aminotransferases rescues the growth defects of cells lacking the Barth Syndrome related gene TAZ1. *J. Mol. Med.*, 97:269-279.