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Protein moonlighting in inborn errors of metabolism: the case of the mitochondrial acylglycerol kinase

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Protein moonlighting is a biological phenomenon in which a protein with a canonical function acquired an additional role during evolution. This phenomenon is relevant for inborn errors of metabolism because knowing all molecular functions of a protein is crucial to explain the pathophysiology associated with its deficiency. The discovery of these acquired or novel functions, however, is experimentally challenging as they are often difficult to predict based on domain conservation or protein classification. Many fascinating examples exist such as HSD17B10 that functions as 2-methyl-3-hydroxybutyryl-CoA dehydrogenase in isoleucine degradation and as an essential component of a protein complex involved in mitochondrial tRNA maturation (Ofman et al 2003; Holzmann et al 2008; Deutschmann et al 2014). A defect in the latter function is largely responsible for the disease in patients with mutations in the *HSD17B10*. Two back-to-back published articles in Molecular Cell now report another elegant example of protein moonlighting in an inborn error of metabolism (Kang et al 2017; Vukotic et al 2017). Sengers syndrome is a mitochondrial disorder associated with a deficiency of the mitochondrial carrier ANT1 (SLC25A4; adenine nucleotide translocator). Exome sequencing has identified mutations in the mitochondrial acylglycerol kinase (*AGK*) as the underlying cause (Mayr et al 2012), but a molecular mechanism explaining the ANT1 deficiency remained poorly defined. Domain conservation and experimental evidence suggests that the main function of AGK is as a diacylglycerol and monoacylglycerol kinase. Given the importance of phospholipid metabolism and remodeling for mitochondrial function, Mayr et al speculated that AGK affects ANT1 stability via effects on mitochondrial phospholipid metabolism (Mayr et al 2012). The teams of Stojanovski and Langer now show that a major function of AGK is as a subunit of the TIM22 protein import complex (Kang et al 2017; Vukotic et al 2017). This protein complex is involved in the import of transmembrane proteins such as mitochondrial carrier family members (SLC25A family) from the cytosol into the mitochondrial inner membrane. This finding provides an unambiguous molecular mechanism for the ANT1 deficiency, and as such the protein import defect appears largely responsible for the observed mitochondrial disease phenotype. Importantly, the function of AGK in protein import is independent of its evolutionary conserved kinase activity. The kinase-dependent function of AGK and its role in Sengers syndrome remain poorly defined and require further studies.

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