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YEAST AS A MODEL SYSTEM TO SHED LIGHT ON THE ROLE OF THE HUMAN DISEASE PROTEIN MPV17

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An intriguing gene necessary for the maintenance of mtDNA is human MPV17, mutation of which leads to a peculiar form of hepatocerebral mtDNA depletion syndrome (MDS). Even though Mpv17 mutations are one of the causes of MDS in humans and the discovery of this protein has been reported more than 20 years ago, its function is not yet understood. Originally considered as a peroxisomal membrane protein, it was later demonstrated that Mpv17 is localized to the inner mitochondrial membrane, as also previously demonstrated for the yeast orthologue Sym1, identified as a heat shock protein with a role in metabolism and/or tolerance to ethanol. With the aim of clarifying the role of MPV17 pathological alleles in MDS, we took advantage of *S. cerevisiae* as a model system. These studies in yeast have shed some light on the function of Sym1. The *sym1* mutant mitochondria are morphologically abnormal, with flattened mitochondrial cristae and accumulation of electron-dense particles, suggesting a role for Sym1 in the structural preservation of the inner mitochondrial membrane. This defect is not a consequence of the mtDNA instability because it has been observed under cultural conditions where no defect of mtDNA was observed, indicating that the morphogenetic effects of Sym1 are likely to precede and possibly determine its effects on mtDNA stability. The phenotypes of double mutants (*cit1 sym1*, *cit2 sym1*) and the nature of multicopy suppressors (*ODC1, YMC1*) suggest for *sym1* null mutant a defect in Krebs cycle confirmed by an enzymatic analysis that clearly indicates a heavy reduction of succinate dehydrogenase activity. Accordingly, *sym1Δ* displays a significant reduction in the amount of glycogen that is dependent on gluconeogenesis, which is in turn regulated by the anaplerotic flux of tricarboxylic acid intermediates from mitochondria to the cytosol. Interestingly, patients with Mpv17 mutations suffer from drastic, often fatal, hypoglycaemic crises, which are likely due to glycogen shortage in liver. Moreover blue-native gel electrophoresis immunovisualization clearly demonstrated that Sym1 is part of a high-molecular weight complex. While further work is necessary to identify the primary role of Sym1, including the molecular dissection and characterization of the Sym1-containing protein complex, these results indicate that Sym1 is involved in the structural and functional stability of the inner mitochondrial membrane, thus

controlling crucial mechanisms related to this compartment, including respiratory chain complexes activity, mitochondria morphology and mtDNA maintenance.