Tissue- and species-specific differences in cytochrome c oxidase assembly induced by SURF1 defects

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Mitochondrial protein SURF1 is specific assembly factor of cytochrome c oxidase (COX), but its function is poorly understood. SURF1 gene mutations cause a severe COX deficiency manifesting as the Leigh syndrome in humans, whereas in mice SURF1$^{-/-}$ knockout leads only to a mild COX defect. We used SURF1$^{-/-}$ mouse model for detailed analysis of disturbed COX assembly and COX ability to incorporate into respiratory supercomplexes (SCs) in different tissues and fibroblasts. Furthermore, we compared fibroblasts from SURF1$^{-/-}$ mouse and SURF1 patients to reveal interspecies differences in kinetics of COX biogenesis using 2D electrophoresis, immunodetection, arrest of mitochondrial proteosynthesis and pulse-chase metabolic labeling.

The crucial differences observed are accumulation of abundant COX1 assembly intermediates, low content of COX monomer and preferential recruitment of COX into I-III_2-IV_n SCs in SURF1 patient fibroblasts, whereas SURF1$^{-/-}$ mouse fibroblasts were characterized by low content of COX1 assembly intermediates and milder decrease in COX monomer, which appeared more stable. This pattern was even less pronounced in SURF1$^{-/-}$ mouse liver and brain. Both the control and SURF1$^{-/-}$ mice revealed only negligible formation of the I-III_2-IV_n SCs and marked tissue differences in the contents of COX dimer and III_2-IV SCs, again less noticeable in liver and brain than in heart and muscle.

Our studies support the view that COX assembly is much more dependent on SURF1 in humans than in mice. We also demonstrate markedly lower ability of mouse COX to form I-III_2-IV_n supercomplexes, pointing to tissue-specific and species-specific differences in COX biogenesis.

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