ABSTRACT

This thesis was prepared in the Laboratory for study of mitochondrial disorders at the Department of Pediatrics, First Faculty of Medicine, Charles University in Prague.

The study of human mitochondrial biogenesis, particularly of the oxidative phosphorylation system (OXPHOS), and its pathologies has seen remarkable progress in past two decades. The knowledge of the complete sequence of the human genome, together with the results of elegant yeast studies aimed at the identification of respiratory important gene products, enabled us to identify and study the molecular and biochemical bases of numerous human mitochondrial pathologies. These studies not only continue to reveal the underlying disease mechanisms but shed completely new light on the various processes of mitochondrial biogenesis and function in humans.

The work presented in this thesis was aimed mainly at the understanding of the various roles of nuclear-encoded mitochondrial inner membrane proteins Sco1, Sco2, Surf1 and Oxa1l in the assembly and/or maintenance of the five multimeric complexes of the human OXPHOS system.

The presented data demonstrate that human Sco1 and Sco2 are involved, in a highly tissue-specific manner, in distinct posttranslational steps of maturation of the cytochrome c oxidase (CcO) subunit 2 (Cox2). Furthermore, both SCO proteins, together with the assembly factor Surf1, are implicated herein in the regulation of cellular copper homeostasis. The human homologue of the yeast Oxa1 translocase, OXA1L is shown to be required for the assembly/stability of the respiratory complex I and the F_1F_O-ATP synthase (complex V). Finally, the dissection of the assembly patterns of CcO in the various CcO deficient backgrounds suggests novel important addition to the current model of human CcO assembly.