Abstract

Mitochondria are essential organelles for most eukaryotic cells, containing intricate networks of numerous proteins. These include, among others, complexes I–IV of the electron transport chain. Being at the crossroads of the tricarboxylic acid cycle and the respiratory chain, mitochondrial complex II plays a key role in cellular metabolism. The protein complex, also known as succinate dehydrogenase, is capable of not only succinate oxidation and electron transfer but also contributes to the production of reactive oxygen species. Mitochondrial complex II consists of four subunits, SDHA-D, and four dedicated protein assembly factors SDHAF1-4 that participate in complex II biogenesis. Mutations and epigenetic modulations of genes coding for succinate dehydrogenase subunits or assembly factors are associated with pathological conditions such as neurodegenerative diseases, or may result in tumor formation. However, inborn complex-II-linked mitochondrial pathologies are rather understudied, compared to diseases with causative errors of other mitochondrial complexes, presumably due to the fact that none of complex II subunits is encoded in the mitochondrial genome. Recent studies have shown that impairment of mitochondrial complex II function or assembly leads to accumulation of alternative assembly forms of the complex, comprising subunit SDHA and assembly factors SDHAF2 and SDHAF4, with potential signaling function in mitochondria. The overall aim of this thesis is to study the role of succinate dehydrogenase in cancer, primarily in tumors exhibiting mutations in genes encoding complex II subunits, which may result in the complex alternative assembly forms. The alternative forms are then studied in cells lacking SDHAF2 and SDHAF4, with particular emphasis on the SDHAF4 protein, whose role within complex II assembly has not been fully elucidated.

Keywords: mitochondria, electron transport chain, mitochondrial complex II, succinate dehydrogenase, succinate, cancer