The role of the PHB complex in mitochondrial biogenesis

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Summary

Mitochondria are essential organelles of most eukaryotic cells. Their most prominent function is to supply the cell with energy generated by oxidative phosphorylation (OXPHOS). Oxidation/reduction reactions along the electron transport chain (complexes I, II, III and IV) generate a proton gradient that is used by ATP synthase (complex V) to phosphorylate ADP producing ATP. Impaired OXPHOS can severely affect cellular function and OXPHOS defects are responsible for a wide range of human degenerative diseases. Building up the OXPHOS system requires the coordinate expression of the nuclear and the mitochondrial genome. OXPHOS enzymes are embedded in the inner membrane of mitochondria and incomplete or incorrectly assembled enzymes have a high potential of disturbing the integrity of the membrane. Therefore the correct assembly of the OXPHOS system poses a challenge to the cell.

This thesis focuses on the mitochondrial PHB complex and its role in respiratory complex assembly.

In Chapter 1 of this thesis I have reviewed several aspects of the regulation of mitochondrial biogenesis, from mitochondrial gene expression to the final assembly of OXPHOS complexes. I have particularly focused on the process of assembly and the role of the quality control apparatus in view of the putative role of the PHB complex in the biogenesis and assembly of respiratory chain complexes in cooperation with the quality control system.

I have further presented studies covering several aspects of the mitochondrial PHB complex. In Chapter 2, a review is presented, which critically discusses the many different cellular roles proposed for the prohibitin proteins that were confusing and difficult to reconcile with the localisation of PHB proteins to mitochondria. The review focuses on the proposed function for the PHB complex in mitochondrial respiratory complex assembly by acting as a holdase/chaperone, and assesses its possible role in ageing and degenerative diseases. The review is based on data presented in Chapter 3 where we show that in *Saccharomyces cerevisiae* the PHB complex stabilises newly mitochondrial translation products by (transiently) interacting with them. We further show a short but statistically significant sequence similarity with members of the hsp60 family of proteins. Based on these results, we propose that the PHB complex is a novel type of membrane-bound chaperone/holdase specifically required when there are imbalances between nuclear- and mitochondrial-encoded subunits of the respiratory chain.

In Chapter 4, we used mass spectrometric techniques in combination with chemical cross-linking to gain insight on the structure of the yeast PHB complex. Information on amino acid distances gave us spatial restraints, which in combination with structure prediction algorithms, were used to derive a structural model for the PHB complex.

PHB genes are strongly conserved among eukaryotes suggesting that they probably serve an important role in cell function. However, deletion of PHB genes in *S. cerevisiae* does not result in a clear observable growth phenotype, in either respiratory or fermentable carbon sources. Therefore, in Chapter 5 we investigated the role of PHB proteins in the development of a mul-
tacellular organism, the soil nematode *Caenorhabditis elegans*. We demonstrated that the PHB complex is essential during embryogenesis and gonad differentiation. We further showed that PHB proteins are required for mitochondrial morphology and distribution in body wall muscle cells. This chapter represents an important contribution to our understanding of the importance of the PHB complex during the development of multicellular organisms.

Finally, in Chapter 6 I have discussed the data presented in this thesis together with results from other researchers regarding the proposed role for the PHB complex as an additional component of the quality control system. Further, based on the structural model presented in Chapter 4, I have put forward alternative hypotheses for the functioning of the PHB complex in membrane biology.