

S1.P13**Evaluation of mitochondrial ATP distribution using theoretical description of FoF1-ATP synthase catalytic cycle**

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Theoretical description of FoF1-ATP synthase can be very useful in evaluation of mitochondrial ATP synthesis and consumption. Distribution of the enzymes on the membrane became known in recent years [1]. A theoretical description of FoF1-ATP synthase catalytic cycle using combined mathematical approaches was provided and realized in a computer simulation Program of ATP Synthesis and Hydrolysis (PASH) [2]. Flexibility of parameter settings in synthesis and hydrolysis of active enzymes and their regulation allows universal application of this approach in the evaluation of ATP production both for one enzyme and for different types of organelles and cells [3]. This model describes both ATP synthesis and hydrolysis and the switching between these processes automatically depending on external medium parameters and substrate concentration that is very applicable in case of small volumes like mitochondria. Due to its low computational demands, the algorithm can be easily and widely applied. Spatial distribution of ATP synthesized and consumed in time is obtained applying results of modeling on numerical data of ATP synthase coordinates on cristae. Possibility to pre-set a number of parameters, such as enzyme modifiers, the precise mechanism of action, the viscosity of the membrane near the protein and its characteristics, such as pKa or elasticity of protein parts allows getting the precisely calculated values of ATP molecules near the crista surface. Energetic status of the cell and/or organelle is one of the most important factors of its normal physiological functioning. Meanwhile its experimental evaluation is not always possible and reasonable due to high costs and invasiveness. Theoretical description of ATP distribution can help in profound evaluation of mitochondrial, physiological and pathological conditions of cell functioning.

References

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doi: [10.1016/j.bbabbio.2014.05.206](https://doi.org/10.1016/j.bbabbio.2014.05.206)

S1.P14**Loss of LRPPRC causes ATP synthase deficiency**

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Defects of the oxidative phosphorylation system, in particular of cytochrome-c oxidase, are common causes of Leigh syndrome (LS), which is a rare neurodegenerative disorder with severe progressive neurological symptoms that usually present during infancy or early childhood. The

COX-deficient form of LS is commonly caused by mutations in genes encoding COX assembly factors, e.g. SURF1, SCO1, SCO2 or COX10. However, other mutations affecting genes that encode proteins not directly involved in COX assembly can also cause LS. The leucine-rich pentatricopeptide repeat containing protein (LRPPRC) regulates mRNA stability and polyadenylation and coordinates mitochondrial translation. In humans, mutations in LRPPRC cause the French Canadian type of LS. Despite the finding that LRPPRC deficiency affects the stability of most mitochondrial mRNAs, its pathophysiological effect has mainly been attributed to COX deficiency. Surprisingly, we show here that the impaired mitochondrial respiration and reduced ATP production observed in LRPPRC conditional knockout mouse hearts are caused by an ATP synthase deficiency. Furthermore, the appearance of inactive subassembled ATP synthase complexes causes hyperpolarization and increases mitochondrial reactive oxygen species production. Interestingly, the endogenous inhibitor protein of mitochondrial ATPase (IF1) is stabilized and found associated with these oligomycin resistant sub-complexes. Our findings shed important new light on the bioenergetic consequences of the loss of LRPPRC in cardiac mitochondria.

doi: [10.1016/j.bbabbio.2014.05.207](https://doi.org/10.1016/j.bbabbio.2014.05.207)

S1.P15**Defining the impact on yeast ATP synthase of five mutations in mitochondrial ATP6 gene found in human cancer cells**

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Saccharomyces cerevisiae has played an important role as a model system to understand the biochemistry and molecular biology of mammalian cells. The genetic tools available and the petite positive phenotype have also made yeast a powerful system to study mitochondrial dysfunctions. Due to its ability to conduct glucose fermentation, yeast can survive mutations that impair mitochondrial respiration. Furthermore, mutagenesis of yeast mtDNA is possible. Using a biolistic transformation, the mutations can be introduced into the yeast mtDNA allowing obtaining a homoplasmic population. In previous studies, we were able to better define how several mutations in mitochondrial ATP6 gene leading to mitochondrial disorders impact the ATP synthase. Mutations in this gene (more than 50) have been also found in various cancer cells. Because no technology to manipulate mtDNA in cell lines exists, it has been difficult to study the effects of mtDNA mutations and their role for cancer cells. We have analyzed the conservation described in the literature of mutated amino acids in Atp6 protein of human cancer cells in comparison to yeast Atp6p. Five mutations were chosen for introduction into corresponding positions of the yeast Atp6p. The positions of mutations in ATP6 gene of cancer cells (thyroid, parathyroid, prostate and breast) are: A8716>G, C8914>A, C8932>T, A8953>G and T9131>C. In human Atp6 protein these mutations change the following amino acids: K64>E, P130>T, P136>S, I143>V and L202>P. To characterize the impact of these mutations on ATP synthase and mitochondrial functions, we have created yeast strains bearing the equivalents of these mutations and analyzed their properties. We found that all but one mutation do not impair the functioning of yeast ATP synthase, with no or minor deficit in mitochondrial ATP production.

doi: [10.1016/j.bbabbio.2014.05.208](https://doi.org/10.1016/j.bbabbio.2014.05.208)