Description for the general public

The main aim of research project is to describe the impact of mitochondrial mutations encoding cytochrome *b* on structure and function of complex III (cytochrome bc_1). Understanding the molecular effects of these mutations allows for a more complete description of catalytic and side reactions occurring within the cytochrome bc_1. Cytochrome *b* is one of 11 subunits composing a monomer of mitochondrial complex III. Cytochrome *b* together with two other subunits, cytochrome c_1 and iron-sulfur protein (ISP), form a catalytic core, in which all stages of reaction catalyzed by cytochrome bc_1 occur. Cytochrome bc_1 is involved in the acquisition of metabolically useful form of energy by a cell in oxidative phosphorylation.

Due to the fact that cytochrome *b* is encoded by mitochondrial DNA, the probability of point mutations in cytochrome *b* gene is higher than for nuclear DNA genes encoding other subunits of complex III. Therefore, the probability of amino acid substitution in cytochrome *b* is higher than in other subunits. Such a strategy is evolutionarily advantageous because it allows a better fit of organisms to changing environment Examples of such adaptation to the environment are adaptive mutations that occur in a population living in a northern climate. There is also the risk of the occurrence of mutations which impede the enzyme action. These mutations were found to be related to diseases (mitochondrial disease-related mutations in cytochrome *b*): exercise intolerance, myopathy, cardiomyopathy and other. As a result of side reactions, cytochrome bc_1 may produce free radical that could cause damage to certain cellular macromolecules. Accumulation of this damage can lead to further development of symptoms of mitochondrial diseases and contribute to aging of the organism.

In the research project, bacterial equivalents of human mitochondrial disease-related mutations in cytochrome *b* will be introduced into *Rhodobacter capsulatus* cytochrome *b*. Due the fact that *Rb capsulatus* cytochrome bc_1 consists of only the catalytic core and has a high homology to the catalytic core of a human complex III, the molecular effects of mutations in the bacterial cytochrome *b* can be related to the molecular effects of equivalent mutations in human cytochrome *b*. Moreover, one adaptive mutation (adaptation to the cold climate) and one mutation associated with longevity will be also examined in the research project.

The basic research which will be performed in the project include both experimental and theoretical studies. Experimental studies include: testing of functionality of cytochrome bc_1 *in vivo*, measurements of kinetics and free radical production, potentiometric titration of cofactors, studying of interactions between quinone pool and cofactor of ISP subunit and between this cofactor and cytochrome *b* cofactors. The results of experimental studies of molecular effects of bacterial equivalents of human mitochondrial mutations can provide detailed information concerning the mechanism of cytochrome bc_1 action. This is particularly important to understand the molecular effects of mitochondrial disease-related mutations in cytochrome *b*, because these information may help to understand causes and effects of mitochondrial diseases. The results of the experimental work will be tested in a theoretical model consisted of a set of differential equations.

Based on the mechanism of production of free radical by complex III and the role of coenzyme Q which acts as a substrate for generation of free radical, the question arises whether, despite its antioxidant properties, coenzyme Q is always beneficial for the organism. Some studies have shown that organisms with coenzyme Q_{10} deficiency live longer. Coenzyme Q_{10} and its analogues (e.g. idebenone) are used in the treatment of mitochondrial diseases but they do not always improve the state of health. In the project we will try to find the answer if coenzyme Q_{10}, in spite of its dual role in generation of free radical (as an antioxidant and as a substrate for the formation of free radicals), should always be used as a drug against mitochondrial diseases.