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NOVEL MECHANISM UNDERLYING MITOCHONDRIAL DISEASES

Mitochondrial diseases usually manifest themselves in disorders of the nervous system and muscles. They are caused by genetic changes in cells. Dr. Karthik Mohanraj and Dr. Michał Wasilewski from the UW Centre of New Technologies are members of the scientific team that has discovered a novel mechanism underlying many mitochondrial diseases. The discovery may yield new strategies in the treatment of mitochondrial diseases. The results of the scientific research were published in a magazine entitled 'EMBO Molecular Medicine'.

Mitochondria represent the cellular organelles that are responsible for energy conversion. Mitochondrial diseases caused by genetic impairment of mitochondrial functions lead to acute deficiencies of nervous and muscular systems, which often manifest early in the childhood. Some of these mutations occur in the nucleus, in which the majority of mitochondrial proteins are encoded. These proteins are produced outside of mitochondria and require specialized import machineries to reach their final destination in the mitochondria.

Dr. Karthik Mohanraj and Dr. Michał Wasilewski from the Laboratory of Mitochondrial Biogenesis led by Prof. Agnieszka Chacińska studied the import of mutant forms of COA7 found in patients. COA7 plays an important role in the formation the respiratory chain, which is the molecular machinery responsible for energy production. The project was accomplished in collaboration with scientists from the Institute of Biochemistry and Biophysics PAS, the University of Cambridge and the University Medical Center of Göttingen.

"The import of the mutant forms of COA7 is much slower than the wild-type protein. As a consequence, the mutant forms of COA7 are exposed to degradation by the proteasome – a proteostatic mechanism responsible for utilization of damaged or improperly localized proteins. The premature degradation of the mutant forms of COA7 leads to almost complete absence of this protein in patient cells. The attenuation of proteasome activity by specific inhibitors not only increased the levels of COA7 protein but also led to partial restoration of mitochondrial functions", explains Dr. Michał Wasilewski.

Inhibitors of proteasome such as bortezomib are currently used in the treatment of certain types of cancer. The scientists propose that many mitochondrial diseases connected to partial or complete loss of mutated variants of mitochondrial proteins may in fact result from their

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improper localization and excessive degradation outside of mitochondria. The discovery by the group led by Prof. Agnieszka Chacińska indicates that the class of drugs that inhibit the proteasome may offer new prospects for more efficient treatment of patients with mitochondrial diseases. This discovery also yielded a patent application.

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