ABSTRACT OF THE PHD THESIS BY TOMASZ STĘPKOWSKI

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ENGINEERED LUHMES CELLS FOR THE STUDIES ON MITOCHONDRIAL IMPLICATIONS IN PARKINSON'S DISEASE: ANALYSIS OF MITOCHONDRIA DYNAMICS AND THE EFFECTS OF OVEREXPRESSION OF MITOCHONDRIAL PGAM5 PHOSPHATASE

Parkinson`s disease (PD) is the second most common neurodegenerative disorder affecting mainly elderly people. Till know, the detailed mechanism responsible for its development remains unknown. The research described in three publications constituting this thesis was aimed at searching for the new mitochondrial implications in the etiology of PD. Theoretical part of the thesis, published in Free Radical Biology and Medicine (Elsevier journal) in the article titled ''*Molecular cross-talk between the NRF2/KEAP1 signaling pathway, autophagy, and apoptosis* '', describes the hypothesis explaining the relation between NRF2/KEAP1 antioxidant pathway and pathways regulating autophagy and apoptosis. Special emphasis was put on the hypothetical role of PGAM5, a mitochondrial protein involved in mitophagy and other processes important for PD pathogenesis. The second and third articles constituting the thesis (experimental research) were published in Cellular and Molecular Biology (Springer) and summarize experiments performed on recently established line of immortalized human embryonic mesencephalic cells (LUHMES cells) - a novel in vitro model for studying Parkinson's disease and dopaminergic neuron biology. The article "*6-OHDA-Induced Changes in Parkinson's Disease-Related Gene Expression are not Affected by the Overexpression of PGAM5 in In Vitro Differentiated Embryonic Mesencephalic Cells*'' describes research focused on the effects of PGAM5 overexpression in a cellular model of PD – 6-hydroxydopamine treated LUHMES cells. In the third article titled ''*mitoLUHMES: An Engineered Neuronal Cell Line for the Analysis of the Motility of Mitochondria*'' I present good-quality live-cell recordings of mitochondrial motility in differentiated human neurons and the statistical description of the observed events. The analysis was possible after genetic engineering of human neuronal LUHMES cells to create a new and very convenient model to study various biological processes impacting the morphology and dynamics of mitochondria - the mitoLUHMES cells. For the first time in LUHMES cells I recorded the processes of fusion, fission, and reversal of the motion direction of mitochondria, proving that mitoLUHMES could be an excellent model to study mitochondrial behavior.

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