The Parkinson’s disease associated Pink1-Parkin-RhoT1 pathway in pathology and development

https://www.neurodegenerationresearch.eu/survey/the-parkinsons-disease-associated-pink1-parkin-rhot1-pathway-in-pathology-and-development/

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Luxembourg

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The Parkinson's disease associated Pink1-Parkin-RhoT1 pathway in pathology and development

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Research Abstract
Parkinson?s disease (PD) has an aetiology not completely understood. One of the hypothesis in the field is that many neurodegenerative diseases, including PD, are influenced by developmental disorders. The underlying concept is that already during brain development some processes are deregulated producing a higher degree of susceptibility for neurodegeneration during aging. Two hereditary early onset forms of PD are caused by recessive mutations in Pink1 and Parkin proteins that interact with RhoT1 to regulate

mitochondria function and morphology quarantining damaged mitochondria before their degradation. In the here described project we will investigate the contribution of Pink1-Parkin-RhoT1 (expressed in neural stem cells) to Parkinson?s disease associated cellular phenotypes as well as the impact of these mutations in mitochondria physiology. Additionally, we will address whether the protein RhoT1 could be a new modifier of these phenotypes. As starting material we will use two human induced pluripotent stem cells (hiPSCs) lines and the CRISPR/Cas9 system together with homologous recombination to introduce the RhoT1-S156D (phosphomimic mutation) in them. Additionally, two lines with Pink1-G309D and Parkin-V324A mutations (currently being generated in Schwamborn lab) are going to be evaluated in this project. Finally, we plan to introduce the RhoT1-S156D mutation in lines with the Pink1-G309D mutation to create double-mutants.Cells that are mutant for Pink1 and Parkin are expected to show severe cellular phenotypes similar to those present in PD. Since RhoT1 is a target of Pink1/Parkin we will see if the RhoT1-S156D mutation shows cellular phenotypes opposite to the once observed for mutant Pink1 and Parkin. Finally, because of this relation of Pink1 and RhoT1 we expect that the phosphomimic mutation will be able to rescue cellular defects that are caused by mutant Pink1 (addressed by the double mutant). Thereby RhoT1 would be established as novel, interesting and druggable modifier of PD associated cellular phenotypes.

Further information available at:

https://www.fnr.lu/projects/the-parkinsons-disease-associated-pink1-parkin-rhot1-pathway-in-pathology-and-development-2/

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