Katedry biochémie a genetiky PriF UK
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Vás pozývajú na 112. prednášku v rámci Kuželových seminárov:

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WHAT CAN WE LEARN FROM PARKINSON'S DISEASE-RELATED MUTATIONS?

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v miestnosti CH1-222 Prírodovedeckej fakulty UK

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Lecture annotation:

Mitochondrial dysfunction has been hypothesized to play a central role in the pathobiology of Parkinson's disease (PD). The identification of mutations in genes encoding PINK1 (PTEN-induced kinase 1) and Parkin (E3 ubiquitin ligase) in familial PD and their functional association with mitochondrial quality control provided further support to this hypothesis. We have recently identified a heterozygous missense mutation in PINK1 changing glycine 411 (G411) to serine (S) that increases the risk for PD. Our studies in PD patient's fibroblasts and derived iNeurons carrying heterozygous PINK1 p.G411S mutation revealed aberrant auto-phosphorylation of PINK1 p.G411S and significant reduction of PINK1 kinase activity. We uncovered a partial loss-of-function as well as a dominant-negative effect of the PINK1 p.G411S due to its interaction with WT PINK1. Subsequent impairment in cytoprotective functions of the PINK1/Parkin-mediated mitochondrial quality control then causes later manifestation of the disease in heterozygous p.G411S mutation carriers than homozygous loss-of-function mutations in PD cases.

In order to analyze the molecular mechanisms of p.G411S mutation-mediated pathobiology in greater detail we employed CRISPR/Cas9 technique and introduced p.G411S mutation in HEK293T cells. As a control for our experiments, we introduced in the same genetic background a point mutation which doesn't allow aberrant PINK1 phosphorylation - PINK1 G411 to alanine (A). Our experiments indicate that aberrant phosphorylation of S411, alters substrate binding and reduces the activity of PINK1 towards Ub and Parkin phosphorylation. Surprisingly, introduction of non-phosphorylatable residue A411 dramatically increased the activity of PINK1 towards these substrates. Our findings are supported by structural modeling and dynamics simulations that suggest higher receptivity of PINK1 A411 across different PINK1 substrates. Importantly, the increase of PINK1 A411 activity translates to higher mitochondrial turnover after mitochondrial damage induction with potential cytoprotective impact.

Selected publications:

- Hou X., Fiesel F.C., Truban D., Casey M.C., Lin W., Murray M.E., Soto A.I., Tacik P., Rousseau L.G., Diehl N.N., Heckman M.G., Lorenzo-Betancor O., Ferrer I., Arbelo J.M., Steel J.C., Farrer M.J., Cornejo-Olivas M., Torres L., Mata I.F., Graff-Radford N.R., Wszolek Z.K., Ross O.A., Dickson D.W., Springer W. (2018) Age- and disease-dependent increase of the mitophagy marker phospho-ubiquitin in normal aging and Lewy body disease. *Autophagy* **14**(8): 1404-1418.
- Truban D., Hou X., Caulfield T.R., Fiesel F.C., Springer W. (2017). PINK1, Parkin, and Mitochondrial Quality Control: What can we Learn about Parkinson's Disease Pathobiology? *J. Parkinsons Dis*. **7**(1): 13-29.
- Puschmann A., Fiesel F.C., Caulfield T.R., Hudec R., Ando M., Truban D., Hou X., Ogaki K., Heckman M.G., James E.D., Swanberg M., Jimenez-Ferrer I., Hansson O., Opala G., Siuda J., Boczarska-Jedynak M., Friedman A., Koziorowski D., Aasly J. O., Lynch T., Mellick G.D., Mohan M., Silburn P.A., Sanotsky Y., Vilarin C., Farrer M.J., Chen L., Dawson V., Dawson T. M., Wszolek Z.K., Ross O.A., Springer W. (2016). Heterozygous PINK1 p.G411S increases risk of Parkinson's disease via a dominant negative mechanism. *Brain* **140**(Pt 1): 98-117.