**NEUROSCIENCE**

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We study basic mechanisms underlying neurodegenerative diseases and nerve cell damage in the brain. Our specific areas of focus are protein ubiquitination and the role of mitochondrial and endoplasmic reticulum (ER) stress pathways as well as autophagy in the pathogenesis and models of brain diseases. Furthermore, we examine neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and their tyrosine kinase receptors, Trk and p75, in regulation of cell-specific events. We employ various proteomic and gene expression methods, cell culture and animal models of disease and genetically modified mice. Although the majority of the group is housed in the Institute of Biomedicine, Faculty of Medicine, the group is actively engaged in research at Minerva.

**Molecular Mechanisms Underlying Neurodegenerative Diseases**

**Role of Usp14 in protein aggregation diseases**

Mitochondria dysfunction and ER stress play a role in human degenerative diseases affecting the brain. Using a cellular model, we have previously shown that Sigma-1 receptors present in mitochondria-associated ER membrane structures (MAMs) play a role in Huntington’s disease (HD) by counteracting ER stress. We have now shown that aggregates of mutant huntingtin (Htt) protein are decreased by expression of the deubiquitinating enzyme (DUB) Usp14. Usp14 is widely expressed in brain neurons and had been linked previously to nerve cell signaling as shown in an ataxia (axJ) mouse model lacking Usp14. We found that Usp-14 plays a role in clearing of mutant Htt protein aggregates by binding to the ER protein, IRE1alpha (Hyrskyluoto et al, 2014). Using a mouse model for HD, we further showed that the Usp14-IRE1alpha interaction is specifically reduced in striatum of an animal model of HD suggesting a functional role of Usp14 in HD pathogenesis (Hyrskyluoto et al, 2014). Recently we observed that Usp14 expression increases autophagy flux in neuronal cells via the autophagy-associated protein LC3B in autophagosomes. Our further studies are focused on understanding the molecular mechanisms of the Usp14-mediated autophagy flux and the role that Usp14 may play in other neurological diseases including Parkinson’s disease (PD).

**Role of PGC-1 in neuroprotection and control of mitochondria functions in neurons**

With regard to PD, we also study the transcriptional coactivator protein, peroxisome proliferator activated receptor-gamma (PPAR-gamma) coactivator 1-alpha (PGC-1) that is a master regulator of mitochondrial and oxidative stress in cells. Previously, using transgenic mice overexpressing PGC1 in the brain, we showed that dopaminergic neurons in the substantia nigra are resistant to the neurotoxin MPTP (Mudo et al 2012). In addition, we recently showed that brain neurons in the PGC-1 transgenic mice are partially protected against excitotoxic injury induced by the glutamate agonist kainic acid. Gene profiling and proteomic studies of brain tissue from control and PGC-1 transgenic mice revealed an interesting pattern of changes. These changes were most prominent in mitochondria-associated proteins that contribute to increased nerve cell viability in the PGC-1 transgenic mice. These genes and proteins will be the objectives of future studies.

PGC-1 acts by binding the PPAR-gamma receptor in cell nuclei to regulate various genes. We have therefore analyzed the effects of chemical compounds and drugs that are known to influence PPAR-gamma signaling. These drugs are usually employed for treatment of metabolic disorders such as type-2 diabetes, and we are studying whether they may also have beneficial effects in brain disorders (Patrone et al., 2014). For many of these studies we are using the Seahorse XF Analyzer that permits testing of mitochondrial functions living neurons in real-time. As a result, we have obtained evidence that some growth factors (Mäkelä et al., 2014) as well as bona fide neurotrophic factors (unpublished) regulate the levels and activity of PGC-1 in neuronal cells. We are currently exploring these mechanisms in more detail.

**Selected publications**


Mäkelä J, Tselykh TV, Maiorana F, Eriksson O, Do HT, Mudo G, Korhonen LT, Belluardo N, Lindholm D.


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