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## 7P5

### Rosiglitazone protects differentiated SH-SY5Y cells against damage induced by rotenone through mitochondrial biogenesis and by anti-oxidative mechanisms

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While the pathogenic mechanisms of Parkinson's disease (PD) remain elusive, increasing evidence suggests that neurodegeneration in PD is associated with impaired mitochondrial 'quality control' — an imbalance between biogenesis and removal by autophagy. PD has also been associated with impaired mitochondrial complex I activity and complex I inhibitors like the neurotoxin rotenone cause pathological and neurochemical changes with a remarkable similarity to PD [1]. Rosiglitazone is a member of thiazolidinediones (TZDs), used clinically as insulin-sensitizing drugs. These compounds selectively bind to peroxisome proliferator-activated receptor gamma (PPARg) a nuclear receptor and ligand-dependent transcription factor that regulates the expression of several genes involved in lipid and carbohydrate metabolism, upregulates antioxidant defences and promotes mitochondrial biogenesis and has anti-inflammatory properties [2]. PPARg agonists provide protection in several *in vitro* and *in vivo* models of neurodegenerative disorders [3,4], but the mechanism of protection is not clear. We have studied whether rosiglitazone prevents mitochondrial damage of differentiated human neuroblastoma SH-SY5Y cells exposed to rotenone and have explored the interaction of biogenesis, autophagy and oxidative stress pathways in neuroprotection. Our data show that chronic partial inhibition of complex I in differentiated SH-SY5Y cells by rotenone decreases mitochondrial mass and membrane potential, while increasing autophagy and free radical generation. All these changes were reversed by co-treatment of the cells with rosiglitazone, which increased mitochondrial biogenesis and decreased autophagy and free radical generation. Our data indicate that rosiglitazone is potentially neuroprotective, acting directly on mitochondrial function in neurons, and not indirectly by suppressing inflammation, and might provide a valuable therapeutic strategy for the treatment of progressive neurodegenerative disease such as Parkinson's disease.

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## 7P6

### The membrane potential is a key regulator for oxidation-dependent protein import into the mitochondrial inter membrane space (IMS)

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The respiratory chain of mitochondria produces the main amount of the cellular ATP. To maintain the function of this machinery most of its proteins have to be imported into mitochondria after their synthesis in the cytosol. Although most soluble mitochondrial proteins contain a mitochondrial targeting signal (MTS), many of the proteins of the IMS do not contain a MTS but instead are imported by an oxidative folding mechanism [1,2]. Examples of such proteins are the so called twin-$CX_9C$ proteins that contain four conserved cysteines. After translocation into the IMS two intramolecular disulfide bonds are formed which contribute to the correct folding and the retention of the proteins [3]. The machinery that facilitates oxidation is composed of two main components, the essential disease-related proteins Mia40 and ALR. Mia40 is an oxidoreductase that interacts with the reduced and unfolded substrate proteins and oxidizes them. Mia40 is reduced after this reaction, and it is subsequently regenerated by ALR [4]. This pathway has so far been almost exclusively characterized in yeast cells and on isolated mitochondria. We aim to characterize the pathway and its regulation in intact mammalian cells. In our experiments we could verify the importance of Mia40 and ALR for import and assembly of proteins of the twin-$CX_9C$-family in intact cells. Surprisingly the import machinery of Mia40 and ALR is quite robust and unaffected by several mitochondrial stress conditions like the inhibition of respiratory chain complexes and limited oxygen availability. However, contrary to *in vitro* data, the oxidative protein import depends on the membrane potential; exhibiting similarities to the MTS-dependent protein import. Despite the dependence on the proton gradient, both import pathways exhibit significant differences in the kinetics of import. Import and processing of MTS-containing proteins is a fast process that occurs co-translationally or in a very fast posttranslational manner. Conversely, the substrates of Mia40 remain soluble in the cytosol after synthesis, and are imported in a slow process that is limited by the rate of Mia40-mediated oxidation.

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## 7P7

### Biogenesis of mitochondria connects to the cell cycle

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