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The relevance of autophagy in the dopaminergic effects of PTEN-induced kinase I (PINK-I)

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Autophagy is a main cellular mechanism to remove misfolded proteins and aggregates as well as damaged and dysfunctional organelles, which recently emerged as critical for neuroprotection. In fact, in several disease models suppression of autophagy produces cell death *in vitro* and *in vivo*, while autophagy inducers reduce protein aggregates and apoptotic cell death. Recently, PINK1, a kinase mutated in autosomal recessive Parkinson's disease, was shown to be neuroprotective. Distinct PINK1 isoforms are known to be active outside and within mitochondria to prevent mitochondrial damage and apoptosis and to regulate mitochondria dynamics. Moreover PINK1 also interacts with the pro-autophagic protein Beclin1 and positively regulates basal and starvation-induced autophagy, a key protective mechanism against neuronal cell loss.

The aims of this study was to characterize the multiple roles of PINK1 in protecting dopaminergic cells from neurodegeneration. For this reasons this study is articulated in the following steps, to define: (i) whether PINK1 interacts with the pro-autophagic proteins Beclin1and parkin to modulate autophagy; (ii) how PINK1 modulates autophagy/mitophagy

The effect of PINK1 wt, mutant and siRNA on autophagy and apoptotic pathways and on mitochondria dynamics is characterized through a range of complementary techniques using *in vitro* models of neurodegeneration. Using in vitro models, we showed that PINK1 wild type (wt), but not mutants, strongly interacts with Beclin1. We also found that PINK1wt positively modulates autophagy in baseline conditions through a fairly specific promotion of mitochondrial turn over which keeps mitochondrial function and morphology despite neurotoxic insults. These results highlight a novel role of PINK1 acting as a strategic cellular sensor of mitochondrial damage. This study helps understand the interconnection between mitochondrial dysfunction and DA cell death.

Key words
Mitochondria, autophagy, Parkinson's disease, neurodegeneration