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Progetto "New molecular pathways responsible for mitochondrial derangement in Parkinson's Disease"

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Abstract

The main goal of this project is to investigate the functional role played by NCX3, Siah2 and Rhes in the complex regulation of mitochondrial dynamics and "mitochondrial quality control mechanisms" including mitophagy in preclinical models of PD.

Specifically, the project has been developed on two lines of action.

-The first one, focused on in vitro study and preclinical investigations on A53T α-synuclein transgenic mice as model of familial PD and in WT mice chronically treated with the neurotoxin MPTP plus probenecid (MPTP/p) (animal models of sporadic PD) in order to clarify the contribution of NCX3 post-translational modification in the regulation of mitochondrial dynamics and dopaminergic neuronal demise with particular regard to the role played by Siah2 and Rhes in the ubiquitination and sumoylation.

-The second focused in non-human primate Macaca Mulatta treated with MPTP, and in post-mortem brain tissue from PD affected patients, in which has been explored the hypothesis that NCX3, Siah2 and Rhes play a role in mitochondrial dysfunction associated with dopaminergic neuronal degeneration in PD.

Results

The results of this project provide a comprehensive overview of the NCX3-dependent mechanisms underlying mitochondrial dysfunction in PD. A key strength of the study was the comparative analysis across multiple models, which revealed a significant species-specificity in the expression of Siah2 and Rhes. This evidence highlights the complexity of mitochondrial quality control and justified the transition toward a more targeted mechanistic study. Our data

demonstrate that Siah2 acts as a critical checkpoint in mitochondrial quality control under stress conditions. This strategic approach allowed for a degree of molecular precision that confirms the functional impact of Siah2 on mitochondrial integrity. We demonstrated that the reduction of NCX3 is a common hallmark of mitochondrial derangement, and that its pathological effects are modulated by Siah2-mediated mitophagy regulation. These findings significantly advance our understanding of PD pathogenesis and provide a robust scientific basis for future therapeutic interventions aimed at restoring mitochondrial homeostasis.

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