Does the stress protein TP53INP1 limit dopamine neuron death associated with normal ageing and Parkinson's disease ?

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Résumé

Parkinson's disease (PD) is characterized by the progressive degeneration of nigrostriatal dopaminergic (DA) neurons. These neurons are also more prone to degeneration during normal ageing, which remains the biggest risk factor for developing idiopathic PD. The mechanisms underlying neuron death include neuroinflammation, oxidative stress and mitochondrial dysfunction. Interestingly, recent works pointed to TP53INP1 as a molecular nexus at the crossroad of metabolic pathways essential for reversing stress-induced alterations in cellular homeostasis: it interacts with the PD-linked proteins PINK1 and Parkin, and its deficiency has been linked with metabolic syndrome via altered mitophagy, oxidative stress and chronic inflammation. This study aims at investigating the unexplored role of TP53INP1 in the maintenance of neuron homeostasis by examining the consequences of its deficiency in the context of ageing and PD-related stress conditions, using behavioral tests and regional analysis of nigra DA neurons in WT and Trp53inp1-KO mice. First, we show that age-related DA neuron loss predominates in the rostral part of the nigra in WT mice and is worsened specifically in the caudal part in KO mice. Second, TP53INP1 deficiency leads to worsened motor deficits and neurodegeneration in a PD model based on viral vector-mediated overexpression of human α-synuclein. Again, DA neuron loss predominates in the rostral nigra in this model and is exacerbated mostly in the caudal part on KO mice. These data provide the first evidence for a neuroprotective role for TP53INP1 and give insights into differential vulnerability among nigral DA neurons. Supported by Fédération pour la Recherche sur le Cerveau.

Mots-Clés: dopamine neurons, neurodegeneration, ageing, Parkinson's disease, stress, induced protein

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