Alpha-synuclein and LRRK2's cooperation in Parkinson's Disease : a focus on autophagy

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Résumé

Parkinson's Disease (PD), the second most frequent neurodegenerative disease is characterized by a loss of dopaminergic (DA) neurons in the substantia nigra (SN) and the formation of Lewy bodies containing α-synuclein (α-syn). Nowadays, the pathogenic mechanisms underlying PD are still misunderstood. They may involve a complex interaction between environmental and genetic factors. Among genetic factors, mutations of the α-syn gene such as the A53T mutation can accelerate its aggregation. Another gene involved is the one encoding Leucine-Rich Repeat Kinase 2 (LRRK2). Its G2019S mutation is the most frequent one leading to PD familial forms. Moreover, it has been suggested that α-syn and LRRK2 can act jointly in PD pathogenesis. This idea is supported by one of our previous *in vivo* study, using AAV as expression vectors, which has shown that LRRK2-G2019S potentiates the dopaminergic cell death induced by α-syn-A53T in the SN of rats. Furthermore, our team recently showed that LRRK2-G2019S induces a significant increase in the number of neurons expressing a pathological form of α-syn (phospho-Ser129) without inducing any cell loss *in vitro*. Thus, the aim of our project is to determine how α-syn and LRRK2 act together on neuronal stress. We particularly focus on autophagy since this process has been described to be altered in PD, and individually α-syn and LRRK2 have both been found to modulate autophagy. We use a model of rat primary neuronal culture infected with lentiviral to express the WT or mutant forms of α-syn and LRRK2. To induce autophagy in these cultures, we starve them in EBSS. We analyze the basal and induced-autophagic flux by treating them with BafilomycinA1. Analyzes are subsequently done by western blot (conversion of LC3-I to autophagosome-associated LC3-II and p62 expression) and immunofluorescence (expression and localization of LC3 and p62). We showed that α-syn can block neuronal basal autophagy flux. Now, we have to determine if LRRK2 modulate this blockade and what happens for the induced-autophagy flux. In conclusion, our objective is to find which autophagic step is impacted by α-syn and LRRK2 to identify new molecular targets and thereafter develop new therapeutic strategies for PD.

Mots-Clés: Parkinson's disease, alpha, synuclein, LRRK2, autophagy

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