Cellular mechanisms underlying LRRK2-related Parkinson's disease

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Résumé

Autosomal-dominant point mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common cause of familial Parkinson's disease (PD), and variants at the LRRK2 locus are major genetic susceptibility factors for sporadic PD. These findings suggest that LRRK2 plays a key role in the entire PD disease spectrum. Recent mass spectroscopy studies have revealed that LRRK2 phosphorylates a subset of Rab proteins *in vitro* and *in vivo*, with their phosphorylation being enhanced by all pathogenic LRRK2 mutants in a cellular context. Rab8 and Rab10 serve as the most prominent LRRK2 kinase substrates, and their LRRK2-mediated phosphorylation is detectable in various cells and tissues including brain. Therefore, and given the relevance of LRRK2 for PD, it is crucial to determine the cellular processes which are most significantly affected by a LRRK2-mediated increase in Rab8/10 phosphorylation. LRRK2 regulates various vesicular membrane trafficking events, some of which may be of direct relevance to the pathomechanism(s) underlying PD. Rab GTPases are key regulators of intracellular vesicular membrane trafficking events, and LRRK2-mediated phosphorylation interferes with the ability of Rab8 and Rab10 to bind to effectors and regulatory proteins. This is expected to lead to a loss-of-function phenotype for the trafficking steps these Rab proteins are implicated in. Other data indicate that LRRK2-mediated Rab phosphorylation may cause additional, toxic gain-of-function phenotypes possibly underlying LRRK2-related PD. This talk will provide an update on our current cellular understanding of the LRRK2-Rab nexus as relevant for PD.

Mots-Clés: LRRK2, mitochondria, Parkinson's disease

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