LRRK2 and deficits of membrane trafficking in Parkinson Disease

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Résumé

Introduction: Parkinson's disease (PD) is the most common neurodegenerative motor disease. Mutations in the leucine rich repeat kinase 2 (*LRRK2*) gene are linked to autosomal dominant parkinsonism, and genomic variation at the *LRRK2* locus is associated with increased risk for sporadic PD. LRRK2 is a multiphosphorylated protein and reduced phosphorylation is associated to disease. Biologically, dephosphorylation leads to alterations in LRRK2 complex formation and subcellular localization. PD is characterized by impaired intracellular trafficking, however the link between LRRK2 phosphorylation and membrane trafficking is not fully understood. Interestingly, LRRK1, the closest homolog of LRRK2, interacts with VAMP7 (Vesicule Associated Membrane Protein 7) and blocks synaptic vesicule fusion. Furthermore, several vesicular Rab-GTPases are LRRK2 substrates including Rab8, Rab10, Rab29. Here we have studied how LRRK2 phosphostatus affects its Rab substrates as well as the mutual regulation of LRRK2 phosphorylation sites.
Methods: We used LRRK2 phosphomimick and phosphodead mutants in a cluster of phosphorylation sites including S860-S910-S935-S955-S973-S976 to assess the phosphorylation changes on non-mutated sites induced by individual or combined phosphosite mutations as well as the phosphorylation of the known LRRK2 substrates Rab8 and Rab10 *in cellulo*. In addition, phosphomutant LRRK2 was purified to assess *in vitro* kinase activity.

Results: With analysis ongoing, our results demonstrate that the phosphoregulation of the tested phosphosites is interdependent and that LRRK2's phosphostatus affects the intensity of LRRK2's kinase activity on its Rab vesicular substrates *in cellulo*. This presents a direct link between LRRK2 phosphorylation and Rabs phosphorylation state. The results suggest that LRRK2 phosphorylation leads to the modification of its kinase activity and change in the phosphorylation state of LRRK2.
Conclusions: This study will contribute to improving our understanding of LRRK2's role in membrane perturbation in PD. We hypothesize that phosphorylation may alter LRRK2's subcellular localization thereby regulating its cellular role. The central role of LRRK2 phosphorylation and it localization is crucial to understand the regulation of vesicular trafficking.

Mots-Clés: LRRK2 Lysosome Membrane Vesicular Trafficking

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