LRRK2 interacts with a subset of endosomal vesicular SNAREs: potential role in the physiopathology of Parkinson Disease

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Résumé

Membrane trafficking is an essential process in a highly compartmentalized in eukaryotic cells because it allows both for cell homestasis and communication with the environment.Membrane trafficking relies on membrane fusion events mediated by vesicular and target SNAREs.
Preview studies performed in the lab showed that the v-SNARE, vesicle associated protein (VAMP) 7, VAMP7, interacts with LRRK1, establishing a so called tug of war between VARP, a protein interacting with kinesin 1 hence mediating anterograde transport to the cell periphery, and LRRK1, a protein interacting with dynein retrograde motor hence mediating transport to the cell center. VAMP7 mediates the fusion of vesicles that are derived from the Golgi, late endosomal and lysosomal compartments with the plasma membrane, during neurite growth, phagocytosis, and plasma membrane repair. VAMP7 is also involved in autophagosome biosynthesis and degradation of autophagosomal cargoes and autophagosomal secretion.

LRRK1 is an homologous protein of LRRK2 and missense mutations in this protein are one of the major disease factor involved in both familial and sporadic late-onset Parkinson's Disease.

This protein is involved in several cellular processes, including autophagy, cytoskeletal dynamics, intracellular membrane trafficking, synaptic vesicle cycling/neurotransmission and inflammatory response.

LRRK2 is a large multi-domain protein kinase encompassing a kinase domain and a GTPase domain. The most spread mutations are localized within the kinase domain and the GTPase domain: the G2019S and the R1441C. The kinase mutation in LRRK2 increases twofold its kinase activity whereas the one located in the ROC domain leads to a diminished GTPase activity.

Interestingly VARP, LRRK1 and LRRK2 show a conserved Ankyrin domain repeat, with

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highly conserved aminoacids.

Here we tested the interaction of LRRK2 with virtually all VAMPs: VAMP2, 3, 4, 7, 8, Sec22b and YKT6. We found that VAMP4/LRRK2 interaction was the strongest and we found a hierarchy VAMP4> VAMP7> VAMP8 and residual interactions with VAMP2 and VAMP3. The G2019s and R1441C still inetarcted with VAMP4. We found the same hierarchy of interaction with LRRK1

Furthermore, we did not find significant co-localization between wtLRRK2 and VAMP4 and VAMP7 using confocal microscope in HEK cells. Interestingly, the GFP tagged forms of LRRK2 showed a very peculiar phenotype, characterized by aggregates in the case of both mutations G2019S and R1441C, and these mutants were able to impair VAMP4 localization. These results led us to the hypothesis that LRRK2 interacts mainly with VAMP 4 and 7, potentially impairing endosomal trafficking in Parkinson's Disease and that this mechanism could be responsible of early symptoms of PD.

Mots-Clés: Parkinson, LRRK2, membrane trafficking, SNARE proteins