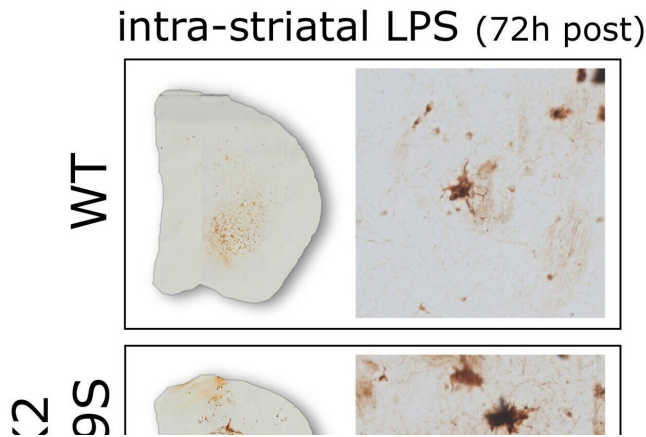


Parkinson's disease mutation misdirects iron in the brain

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G2019S LRRK2 induces iron accumulation in inflammatory microglia in vivo. Credit: Mamais A et al., 2021, *PLoS Biology*, CC-BY 4.0 (creativecommons.org/licenses/by/4.0/)

A common gene mutation for Parkinson's disease drives mislocalization of iron in activated microglia, according to a new study publishing December 16th in the open-access journal *PLoS Biology*, by Mark Cookson of the National Institute on Aging and colleagues. The results may help explain the accumulation of toxic iron in affected brain areas in the disease and provide a basis for the development of therapies designed to correct the iron trafficking defect.

Mutations in the LRRK2 gene account for about 5% of all cases of familial Parkinson's disease, and about 1% of non-familial disease cases. LRRK2 is a kinase, an enzyme that regulates other proteins through addition of a phosphate group, and disease-causing [mutations](#) are known to increase the kinase activity of the enzyme. One of the targets that LRRK2 regulates is called Rab8a, a protein which, along with many others of the Rab family, helps control the movement or "trafficking" of a wide variety of cellular vesicles (membrane-

bound subcellular compartments). One of Rab8a's jobs is to regulate the import of iron into the cell via the transferrin receptor, and to help recycle that receptor back to the membrane after it releases the transferrin and the iron it carries.

To understand how the LRRK2 mutations found in Parkinson's disease might affect this process, the authors first visualized Rab8a movements in mouse astrocytes containing LRRK2 with a pathogenic mutation. They found that the [mutant protein](#) was responsible for redirecting Rab8a away from its normal location at the endocytic recycling compartment and sequestering it at damaged lysosomes.

This mislocalization of Rab8a had a clear effect on the transferrin receptor: in cells containing normal LRRK2, the transferrin receptor was distributed among multiple vesicle types. However, in cells containing the Parkinson's mutant LRRK2, the transferrin receptor and its iron instead clustered at the same damaged lysosomes where Rab8a and mutant LRRK2 were found. That same mislocalization of Rab8a and transferrin receptors was observed in activated microglia derived from [human cells](#) carrying a pathogenic LRRK2 mutation. Microglia are key drivers of inflammation in the brain. Finally, when mice carrying the same Parkinson's mutation were exposed to a proinflammatory trigger, iron accumulated in microglia in the striatum, a region of the brain that controls movement and is one of the most prominent parts of the brain affected in Parkinson's disease.

"Our data suggest that a key step in the pathogenesis of LRRK2 Parkinson's disease is the interaction of the protein with Rab8a and its subsequent effect on mislocalization of iron in activated microglia," Cookson said. Iron deposition in the brain is a feature of Parkinson's disease and other [neurodegenerative diseases](#), and its accumulation may drive free radical production and

damage to mitochondria, both thought to be critical steps in the disease cascade. "These results should help us understand the implications of blocking LRRK2 as a potential therapeutic for Parkinson's disease."

"Our study demonstrates altered regulation of iron in Parkinson's disease models based on the gene LRRK2," Cookson adds. "Previous data has shown that [iron](#) can be deposited in the brain, which we now link to a known genetic cause of Parkinson's [disease](#) that may be relevant to novel treatments."

More information: Mamais A, Kluss JH, Bonet-Ponce L, Landeck N, Langston RG, Smith N, et al. (2021) Mutations in LRRK2 linked to Parkinson disease sequester Rab8a to damaged lysosomes and regulate transferrin-mediated iron uptake in microglia. *PLoS Biol* 19(12): e3001480. doi.org/10.1371/journal.pbio.3001480

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