Lysosomal dysfunction in PD (SNCA, ATP13A2, GBA)

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Résumé

Parkinson's disease is a common neurodegenerative disorder of unknown origin mainly characterized by the loss of neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta and the presence of intraneuronal proteinaceous inclusions called Lewy bodies. For a long time, lysosomes were widely known as terminal catabolic stations that rid cells of waste products taken up by endocytosis from the external milieu or from the cytosol by autophagy and scavenge metabolic building blocks that sustain essential biosynthetic reactions during starvation. But, in recent years, this classical view has been dramatically expanded by the discovery of new roles of the lysosome in nutrient sensing, transcriptional regulation, and metabolic homeostasis. These discoveries have elevated the lysosome to a decision-making centre involved in the control of cellular growth and survival, while communicating the overall metabolic state of the cell to nutrient-sensing modules. To date, increasing amounts of evidence suggest a central role of lysosomal impairment in PD aetiology, and it is commonly accepted that lysosomal impairment is increasingly regarded as a major pathogenic event in PD.
This talk provides an update on how genetic evidence (*SNCA*, *ATP13A2*, *GBA* and sidekicks) support this connection and highlights how the neuropathologic and mechanistic evidence might relate to the disease process in sporadic forms of Parkinson's disease. Then, we discuss the influence of ageing on lysosomal impairment and PD aetiology.

Finally, according to these new findings, primary lysosomal defects could potentially account for aggregates formation and neurodegeneration in PD, laying the groundwork for the prospective development of new disease-modifying therapeutic strategies aimed at restoring lysosomal levels and function.

Mots-Clés: Parkinson's disease, lysosomes

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