

Understanding the role of the Parkinson's associated kinase **LRRK2** in inflammation and infection

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i Karl Isaksson, Medicinaregatan 16, Göteborg, torsdagen den 8e februari, klockan 09.00

av **Maria Öberg**

Fakultetsopponent:

Professor Geert Van Loo
Ghent University, Belgium

Avhandlingen baseras på följande delarbeten

- I. **Öberg M**, Maric I, Strömberg A, Myers C, Saffarzadeh N, Fabrikova D, Fabrik I, Rivas-Galvez L, Skibicka K, Akanbi-Kurzawa M, Paul G, Gekara NO, Härtlova A. *Parkinson's disease kinase LRRK2 accelerates aging, associated inflammation, and neurodegeneration through the STING-IFN-I axis*. Submitted manuscript
- II. Fabrik I, Bilkei-Gorzo O, **Öberg M**, Fabrikova D, Fuchs J, Sihlbom C, Göransson M, Härtlova A. *Lung macrophages utilize unique cathepsin K-dependent phagosomal machinery to degrade intracellular collagen*. Life Sci Alliance. 2023 Jan 25;6(4):e202201535.
- III. Kurzawa-Akanbi M, Whitfield P, Burté F, Bertelli PM, Pathak V, Doherty M, Hilgen B, Gliaudelyté L, Platt M, Queen R, Coxhead J, Porter A, **Öberg M**, Fabrikova D, Davey T, Beh CS, Georgiou M, Collin J, Boczonadi V, Härtlova A, Taggart M, Al-Aama J, Korolchuk VI, Morris CM, Guduric-Fuchs J, Steel DH, Medina RJ, Armstrong L, Lako M. *Retinal pigment epithelium extracellular vesicles are potent inducers of age-related macular degeneration disease phenotype in the outer retina*. J Extracell Vesicles. 2022 Dec;11(12):e12295.

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Maria Öberg

Avdelningen för Mikrobiologi och Immunologi, Institutionen för Biomedicin, Sahlgrenska akademien, Göteborgs universitet, Sverige, 2024.

Abstract

The innate immune system, which mediates pathogen clearance and tissue healing, requires tight regulation to avert self-destruction. The endo-lysosomal system is best known as a network of vesicles that targets particles for degradation and recycling. However, accumulating evidence demonstrates that the endo-lysosomal system is also a hub for innate immune signaling regulation. Defects in this system lie at the core of many pathologies with an inflammatory component including age-associated diseases such as the neurodegenerative disorder Parkinson's disease (PD). Several genetic risk factors for PD have been linked to endo-lysosomal function, one of them being mutations in the kinase Leucine Rich Repeat Kinase 2 (LRRK2). However, the roles of LRRK2 in PD development had not been completely clear.

In my thesis, I demonstrated that the Parkinson's associated kinase LRRK2 is a negative regulator of the endo/auto-phagolysosome system, and that in humans and mice, gain-of-function mutations in this kinase results in a spontaneous antiviral innate immune response, increased release of inflammatory exosomes, accelerated inflammaging via cGAS-STING-IFN signaling axis and cognitive decline.

In summary, this thesis covers both fundamental and translational research aspects centered around the new discovery of LRRK2 as a key regulatory molecule linking the endo/auto-phagolysosome and innate immune system. Furthermore, the results of this thesis contributes to better understanding of the molecular aspect of inflammaging and neurodegeneration which offers a new possibility for treatment strategies.

Keywords: Innate immunity, Endo-lysosomal system, Inflammaging, Neurodegeneration, Parkinson's disease, LRRK2, Extracellular vesicles, STING-IFN axis.