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TRR 295 ReTune

Brain-to-gut trafficking of alpha-synuclein by CD11c+ cells in a mouse model of Parkinson's disease.

McFleder RL, Makhotkina A, Groh J, Keber U, Imdahl F, Peña Mosca J, Peteranderl A, Wu J, Tabuchi S, Hoffmann J, Karl AK, Pagenstecher A, Vogel J, Beilhack A, Koprich JB, Brotchie JM, Saliba AE, Volkmann J, Ip CW.

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In addition to the classical motor symptoms that characterize Parkinson's disease (PD), PD patients also suffer from a plethora of non-motor symptoms such as gastrointestinal (GI) dysfunction. This GI dysfunction is associated with accumulation of alpha-Synuclein (αSyn) in the gut similar to that found in the brain of PD patients. We recently described an AAV1/2 A53T-αSyn PD mouse model where pathology is initiated in the brain through the localized expression of the mutated form of αSyn, A53T. Similar to patients, this mouse model exhibits neuroinflammation, neurodegeneration, and motor dysfunction. In this research project, we sought to ask if this "brain-first" mouse model of PD also exhibits pathology in the gut and if we can use this model to study how pathology spreads between the two organs.

Five weeks following disease initiation in the brain, PD mice exhibited both GI dysfunction and αSyn pathology in the ileum. Interestingly, these ileal αSyn accumulations were not contained within neurons but rather CD11c+ immune cells. CD11c+ cells could also be found within the brain of PD mice where they likewise contained αSyn accumulations. By investigating the ileum and SN of PD patients, we could also demonstrate CD11c+ αSyn+ cells indicating the clinical relevance of these findings.

Single-cell sequencing of the CD11c+ cells in the brain and ileum revealed that the brain and ileum share several unique CD11c+ populations that are not present in other immune organs such as the spleen. One of these populations were migratory macrophages which were enriched for the αSyn-receptor, Lrp1. Immunohistochemistry confirmed that these migratory macrophages were the cells containing αSyn in the ileum of PD animals.

To definitively test if CD11c+ macrophages can migrate out of the brain to the ileum, we utilized mice expressing the photo-convertable protein, Dendra2. Dendra2 is a green fluorescent protein, that after exposure to blue light photo-converts to red. By implanting an optic fiber into the SN of mice, we could manipulate this characteristic and specifically photo-convert cells within the SN to red. Red cells could later be found within the ileum, indicating that these cells trafficked from the SN.

This work further characterizes the natural disease progression of the AAV1/2 A53T-αSyn PD mouse model and demonstrates it's ability to recapitulate both motor and non-motor aspects of PD. These findings also identify CD11c+ macrophages as a potential therapeutic target to halt αSyn propagation and PD progression.

Prof. Rhonda McFleder

Rhonda McFleder, is a Junior Professor in Translational Medicine at the Universitätsklinikum Würzburg. Her research is focused on immune dysregulation in PD and utilizing transcriptomics and molecular techniques to develop treatment strategies to target these immune cells.

Prof. Chi Wang Ip

Chi Wang Ip is the Vice Chairman of the Neurology department at the Universitätsklinikum Würzburg. His research is focused on understanding the molecular, cellular and network mechanisms underlying movement disorders and utilizing this understanding to develop novel treatment strategies to improve patient outcomes.

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