ROLE OF LRRK2 IN INFLAMMATORY BOWEL DISEASE

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Background:

Variants of the leucine-rich repeat kinase 2 (LRRK2) are associated with an increased susceptibility to Parkinson disease but also Crohn's disease (CD).

Aims: The present research is designed to develop a comprehensive understanding of the role of LRRK2 in immune system modulation, and how dysfunction of this pathway may lead to the development of CD.

Methods: WT and LRRK2-deficient neutrophil were infected with Gram-positive Bacteria (Listeria monocytogenes-LM) in a gentamicin protection assays and colony-forming unit assessment will determine the competence of LRRK2 deficient cells for bacterial phagocytosis as well as killing capacity. To examine how LRRK2 is involved in the generation of ROS during the respiratory burst, we will first examine if neutrophil from LRRK2-KO mice have altered ROS generation upon infection with LM and addition of PMA. We evaluate in vitro the ability of neutrophils from LRRK2-KO versus WT mice to transmigrate in vitro in a transwell assay using fMLP as a chemoattractant. Also, we investigate the peritoneal cells (by FACS analysis) after injection of different microbial stimuli including FK105 (NOD1 ligand), MDP (NOD2 ligand) and LPS (TLR4 ligand) and anti-cd3 model of ileitis.

Results: We found that LRRK2 KO mice have a defect in migration of neutrophils to the peritoneal cavity after injection of different microbial stimuli including FK10565 (NOD1 ligand), MDP (NOD2 ligand) and LPS (TLR4 ligand). Neutrophils from LRRK2 mice were compromised in their ability to transmigrate in vitro in a transwell assay using fMLP as a chemoattractant. Chemotaxis was also compromised. In parallel, we designed experiments to examine reactive oxygen species (ROS) produced in response to infection of myeloid cells with bacteria. Neutrophils from LRRK2 KO mice infected with Listeria monocytogenes were less able to restrict bacteria growth compared to WT cells. Consistent with these findings, cells from LRRK2 KO mice produced lower levels of ROS following bacterial infection. In order to determine whether myeloid cell migration is compromised in vivo during inflammation, we performed experiments in WT and KO mice looking at different models of ileitis/colitis.

Conclusions: With this work we will further characterize the role of LRRK2 in intestinal homeostasis and mucosal barrier maintenance, including how its deficiency may predispose an individual to developing CD.

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