A ROLE FOR PARKINSON DISEASE-LINKED LRRK2 IN THE INNATE IMMUNE SYSTEM

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Introduction: Mutations in leucine-rich-repeat-kinase-2 (LRRK2) are a common cause of sporadic Parkinson disease (PD). LRRK2 was also identified as a susceptibility locus for Crohn's disease which suggested to us a possible role for LRRK2 in the immune system.

Aim: To characterize Lrrk2 in leukocytes and downstream signalling as a model to elucidate its function.

Methods: LRRK2 expression analysis in peripheral blood mononucleated cells (PBMC) by FACS sorting, immunoblotting, rt-PCR and immunocyto/histochemistry.

Results: We detected robust expression levels of LRRK2 in CD14+ monocytes, CD19+ B-cells, and moderate levels in CD4+ and CD8+ T-cells. Leukocyte subtypes were isolated by affinity purification and FACS sorting from human PBMCs. In contrast, erythrocytes, granulocytes and platelets did not express detectable LRRK2. LRRK2 reactivity was seen in leukocytes (but not neurons) of human midbrain and the submucosal vasculature of terminal ileum. The expression of LRRK2 was confirmed in EBV-transformed lymphoblasts. Its presence was also demonstrated in sections of human (and mouse) spleen, Peyer's patches and lymph nodes. Note, human LRRK2 cDNA-transgenic flies were used as controls in all immunodetection efforts. Initial experiments with stimulated bone-marrow-derived-macrophages (BMDM) from murine R1441C Lrrk2 knock-in mice revealed a reduction in inflammatory cytokine release from mutant (versus wild-type) mice. LRRK2's function in inflammation is currently also being studied from the angle of autophagy, implicated in PD and Crohn's disease.

Conclusions: The robust LRRK2 expression in mammalian monocytes, lymphocytes and immune organs together with known concepts of PD pathophysiology and Crohn's disease suggest a role for LRRK2 in the innate immune response.