Targeting the NLRP3 Inflammasome in an enhanced Parkinson's disease mouse model

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Parkinson's disease (PD) is the second most common neurodegenerative disease and a leading motor disorder, affecting around 10 million people worldwide. Mutations in LRRK2 gene are the most common genetic variants associated with familiar and sporadic PD. However, the molecular pathogenesis is not fully understood. To date, there is no proven disease-modifying treatment yet. Recent studies suggest that activation of NLRP3 inflammasome has implications in neuroinflammation underlying PD pathogenesis. To explore new treatment strategies, we employed a new genetic approach to in-vivo knockdown of NLRP3 using an enhanced mouse model of PD, in which overexpressing G2019S-LRRK2 (Leucine Rich Repeat Kinase 2) mice with a sub-toxic dose of MPTP (G2019S-LRRK2/MPTP) displays robust dopaminergic neuron degeneration and neuroinflammation with significant motor impairment mimicking key features of human PD and providing an accelerated disease progression timeline. The novel genetic circuit containing siRNA-NLRP3 were intravenously injected into mice, then entered the liver, underwent self-assembly in exosomes that could be auto-delivered through the circulating system to ultimately enter the brain to knockdown NLRP3. We found that knockdown of NLRP3 reduced inflammasome activation and rescued motor impairment in G2019S-LRRK2/MPTP comparing with control-RNA-circuit injection group. Our studies suggest that NLRP3 inflammasome may be a therapeutic target for LRRK2-linked PD and other related disorders. This work is supported by NIH grants to WWS: •R01NS119208 • R01 NS120879, and NIH PREP training grant to JM.