Mechanism of LRRK2 dysfunction in Parkinson’s disease

The molecular mechanisms underlying dopaminergic cell death in Parkinson’s disease (PD) are largely unknown. Autosomal-dominant mutations in leucine-rich repeat kinase 2 (LRRK2) cause late-onset familial PD which is clinically and neurochemically indistinguishable from sporadic PD. In addition, LRRK2 mutations contribute to sporadic PD and variations increase risk for PD, suggesting that LRRK2 may be a rate-limiting factor for idiopathic disease progression as well. LRRK2 is a large protein kinase whose physiological function is largely unknown. We and others have previously shown that the most prominent pathogenic mutation (G2019S), located within the kinase domain, enhances kinase activity in vitro, suggesting that it may display a dominant, gain-of-function phenotype. Overexpression of this disease-segregating mutation leads to neurotoxicity in vivo, and such neurotoxicity is linked to the kinase activity. However, the mechanism(s) leading to LRRK2-mediated cell death are not understood. Here I will discuss our recent findings which indicate that LRRK2 impairs basal macroautophagy in cultured cells, with reference to the underlying molecular mechanism. The LRRK2-mediated impairment of autophagy leads to decreased cell survival in the presence of protein aggregation-induced stress, and can be blocked by a specific antagonist. Collectively, our data indicate that LRRK2 deregulates autophagic degradation and reveals previously unidentified therapeutic targets.

Selected references


