FUNCTION AND DYSFUNCTION OF LRRK2

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Introduction: Dominantly inherited mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common genetic cause of Parkinson's disease (PD), but how these mutations cause the disease is unclear.

Aims: To investigate the pathogenic mechanism underlying LRRK2 mutations and the normal physiological role of LRRK2.

Methods: Generation and multidisciplinary analyses of LRRK2 knockin (R1441C) and knockout mouse models.

Results: R1441C knockin mice exhibit defects in dopamine neurotransmission, including decreases in amphetamine-induced locomotor activity and evoked catecholamine release as well as impairment in dopamine D2 receptor-mediated function. More interestingly, LRRK2 knockout mice show striking age-related disruption of protein homeostasis in the kidney, where the loss of LRRK proteins is most severe, compared to other organs. Strikingly, α-synuclein accumulate (60-fold) and aggregate in an age-dependent manner. The autophagy-lysosomal pathway is also impaired in the absence of LRRK2, as indicated by accumulation of lipofuscin granules as well as altered levels of LC3-II and p62. Furthermore, loss of LRRK2 dramatically increases apoptotic cell death, inflammatory responses, and oxidative damage. These age-related cellular changes bear striking resemblance to processes thought to be involved in PD pathogenesis.

Conclusions: Our data show that LRRK2 plays an essential and unexpected role in the regulation of protein homeostasis during aging, and suggest that LRRK2 mutations may cause PD and cell death via impairment of protein degradation pathways. We are in the process of determining how LRRK2 regulates autophagy function and whether inactivation of both LRRK1 and LRRK2 would result in protein aggregation and dopaminergic cell death.