

Dopaminergic neuronal death via necroptosis in Parkinson's disease: a review of the literature

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Abstract

Parkinson's disease is a neurodegenerative disorder characterized by the progressive dysfunction and loss of dopamine (DA) neurons of the substantia nigra pars compacta (SNc). Several pathways of programmed cell death are likely to play a role in DA neuron death, such as apoptosis, necrosis, pyroptosis, ferroptosis as well as cell death associated with proteasomal and mitochondrial dysfunction. A better understanding of the molecular mechanisms underlying DA neuron death could inform the design of drugs that promote neuron survival. Necroptosis is a recently characterized regulated cell death mechanism that exhibits morphological features common to both apoptosis and necrosis. It requires activation of an intracellular pathway involving receptor-interacting protein 1 (RIP1) and its kinase (RIP1 kinase, RIPK1), receptor-interacting protein 3 (RIP3) and its kinase (RIP3 kinase, RIPK3), and mixed lineage kinase domain like pseudokinase (MLKL). The potential involvement of this programmed cell death pathway in the pathogenesis of PD has been studied by analyzing the biomarkers for necroptosis, such as the levels and oligomerization of pRIPK3 and pMLKL, in several PD preclinical models and in PD human tissue. While there is evidence that other types of cell death also have a role in DA neuron death, most studies support the hypothesis that this cell death mechanism is activated in PD tissues. Thus drugs that prevent or reduce necroptosis may provide neuroprotection for PD. In this review, we summarize the findings from these studies. We also discuss how manipulating necroptosis might open a novel therapeutic approach to reduce neuronal degeneration in PD.

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