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NEURODEGENERATIVE DISEASE

NURR1 puts a dampener on inflammation

The nuclear receptor NURR1 (also known as NR4A2) has an essential role in the development and maintenance of dopaminergic neurons, and mutations in this protein cause a familial form of Parkinson's disease (PD). Now, a study from Saijo *et al.* suggests a previously unknown function of NURR1 in microglia and astrocytes in protecting dopaminergic neurons from inflammation-induced death.

Growing evidence suggests that inflammatory processes contribute to neuropathology in PD. For example, experimentally infusing inflammatory substances such as lipopolysaccharide (LPS) into the brain can replicate some of the pathology of PD. In macrophages, NURR1 expression can be induced by LPS, prompting the authors to investigate the influence of NURR1 on the effects of LPS in the CNS. They found that injecting lentiviruses encoding short hairpin RNAs against NURR1 (shNURR1) into the substantia nigra of mice significantly accelerated and augmented the loss of dopaminergic neurons in this region in response to LPS, suggesting that NURR1 can protect neurons from LPS-induced cell death.

Next the authors investigated the mechanisms and cell types involved in NURR1's protective effects. Expressing shNURR1 in cultured microglia or astrocytes increased their production of inflammatory mediators, such as tumour necrosis factor-α and inducible nitric oxide synthase, in response to LPS. The conditioned media taken from shNURR1 microglia cultures was highly toxic to cultured dopaminergic neurons. Moreover, when the media was sequentially used to culture shNURR1-treated microglia and then shNURR1-treated astrocytes, its toxicity for dopaminergic neurons was increased further, indicating that NURR1 inhibits the production of toxic inflammatory factors in both microglia and astrocytes.

In subsequent experiments, the authors dissected the mechanism by which NURR1 influences the expression of inflammatory genes in astrocytes and microglia. They revealed that NURR1 represses the transcription of these genes by interacting with the transcription factor complex nuclear factor-κB–p65 on the gene promoter, a process known as transrepression. This interaction was shown to rely on both the sumoylation of NURR1 and the phosphorylation of p65 by glycogen synthase kinase 3β. Furthermore, the authors showed that the co-repressor COREST, together with the chromatin-modifying enzymes that it recruits (histone methyltransferase G9a, lysine-specific demethylase and histone deacetylase 1), is required for NURR1-mediated transrepression. The interaction between NURR1 and COREST required the activity of Nemo-like kinase.

This study describes a previously unknown role for NURR1 in suppressing potentially neurotoxic inflammatory gene expression in microglia and astrocytes and suggests that the loss of this ability might contribute to some forms of PD. The transrepression pathway uncovered may provide further clues to the cause of PD pathology as well as potential therapeutic targets.

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ORIGINAL RESEARCH PAPER Saijo, K. *et al.* A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. *Cell* **137**, 47–59 (2009)