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SUMOylation Enhances Nurr1/1a Mediated Transactivation in a Neuronal Cell Type

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Abstract : Nuclear receptor-related 1 protein (also known as Nurr1 or NR4A2) is an orphan nuclear receptor which plays a vital role in the development, survival and maintenance of dopaminergic (DA) neurons particularly in the substantia nigra (SN). Increasing research has investigated Nurr1's additional role within microglia and astrocytes where it has been suggested to act as a negative regulator of inflammation; potentially offering neuroprotection. Considering both DA neurodegeneration and neuroinflammation are commonly accepted constituents of Parkinson's Disease (PD), understanding the mechanisms by which Nurr1 regulates inflammatory processes could provide an attractive therapeutic target. Nurr1 regulates inflammation via a transrepressive mechanism possibly dependent upon SUMOylation. In addition, Nurr1 can transactivate numerous genes involved in DA synthesis, such as Tyrosine Hydroxylase (TH). A C-terminal splice variant of Nurr1, Nurr-1a, has been reported in both neuronal and glial cells. However, research into its transcriptional activity is minimal. We employed in vitro methods such as SUMO-Pulldown experiments alongside Luciferase reporter assays to investigate the SUMOylation status and transactivation capabilities of Nurr1 and Nurr-1a respectively. The SUMO-Pulldown assay demonstrated Nurr-1a undergoes significantly more SUMO modification than its full-length variant. Consequently, despite having less transcriptional activation than Nurr1, Nurr1a may play a more prominent role in repression of microglial inflammation. Contrary to published literature we also identified that SUMOylation enhances transcriptional activation by Nurr1 and Nurr1a. SUMOylation-dependent increases in Nurr1 and Nurr1a transcriptional activation were only evident in neuronal SHSY5Y cells but not in HEK293 cells. This research provides novel insight into the regulation of Nurr-1a and indicates differential effects of SUMOylation dependent regulation in neuronal and inflammatory cells.

Keywords : nuclear receptors, Parkinson's disease, inflammation, transcriptional regulation
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