NRF2-DEFICIENT MICE EXHIBIT EXACERBATE NIGROSTRIATAL NEURODEGENERATION INDUCED BY AAV6-Α-SYNUCLEIN

I. Lastres-Becker¹, A. Ulusoy², N.G. Innamorato¹, A.I. Rojo¹, L. Stefanis³, D. Kirik², A. Cuadrado¹

¹Instituto de Investigaciones Biomédicas ‘Alberto Sols’, Universidad Autónoma de Madrid, CIBERNED, Madrid, Spain, ²Department of Experimental Medical Science, Brain Repair and Imaging in Neural Systems, Lund University, Lund, Sweden, ³Division of Basic Neuroscience, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

Overexpression of α-synuclein lead to inherited forms of PD. Animal models of PD have been developed using recombinant viral vectors to overexpress human α-synuclein protein in the substantia nigra pars compacta (SNpc), which provides a relevant model that recapitulates many cardinal features of the human disease. On the other hand, formation of reactive oxygen species (ROS) is a key step in selective neuronal vulnerability in PD. Oxidative stress causes α-synuclein aggregation in vitro, and α-synuclein in turn is able to cause mitochondrial alterations leading to an increase in ROS in neuronal cell lines. In this study we wanted to investigate the role of the transcription factor Nrf2 (erythroid 2 related factor 2), who regulates the expression of a battery of phase II detoxification enzymes, in the neurodegeneration caused by overexpression of human α-synuclein. For this purpose a recombinant adeno-associated virus vector that induce overexpression of α-synuclein was injected in the Nrf2-knockout mouse SNpc and compared to the wild-type. Immunohistochemistry at eight weeks following injection with AAV6-α-synuclein showed an extensive loss of the dopaminergic neurons in the substantia nigra of wild-type animals, which was significantly increased in the Nrf2-knockout mice. The loss of dopaminergic neurons at the SNpc came with an increase in neuroinflammation. In wild-type mice, increased density of reactive glia, including astrocytes and microglia, was observed at the SNpc surrounding the lesioned area. The absence of Nrf2 intensifies this reactive gliosis at the SNpc, indicating that this transcription factor is implicated in the vulnerability to α-synuclein neurodegeneration.