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Astrid Kritzinger, Boris Ferger, Frank Gillardon, Birgit Stierstorfer, Gerald Birk, Stefan Kochanek, Thomas Ciossek



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1 Age-related pathology after adenoviral overexpression of the leucine-rich repeat kinase 2 2 in the mouse striatum

3 Astrid Kritzinger^{a,b,1}, Boris Ferger^b, Frank Gillardon^b, Birgit Stierstorfer^c, Gerald Birk^c, Stefan
4 Kochanek^a, Thomas Ciossek^{b,1,2}

5 ^aDepartment of Gene Therapy, Ulm University Medical Center, 89081 Ulm, Germany; ^bCNS Diseases
6 Research/^cTarget Discovery Research, Boehringer Ingelheim Pharma GmbH & Co. KG, 88400 Biberach an der
7 Riß, Germany

8 Abstract

9 Mutations in LRRK2 age-dependently cause Parkinson's disease and are associated with several
10 inflammatory diseases. So far, the potential role of LRRK2 expression in glial cells as mediators of
11 neuroinflammation and the influence of aging have not been investigated in viral vector-based
12 LRRK2 animal models. In this study we compared the effect of striatal injection of high-capacity
13 adenoviral vectors expressing either kinase-overactive LRRK2 with the familial G2019S mutation or
14 a kinase-inactive LRRK2 variant in young and old C57BL/6J mice. The intrinsic adenovirus tropism
15 guided preferential glial transduction and the vector design led to stable expression for at least 6
16 months. In histopathological analysis young mice expressing either LRRK2 variant presented with
17 transient vacuolization of striatal white fiber tracts accompanied by accumulation of microglial cells
18 and astrogliosis, but inflammation resolved without permanent damage. Old mice had a stronger and
19 prolonged inflammatory reaction and experienced permanent damage in form of partial neuron loss
20 after 3 months exclusively in case of LRRK2_G2019S expression. The autophagic receptor p62
21 accumulated in cells with high levels of either LRRK2 variant, even more so in old mice. We
22 conclude that the aging mouse brain is more susceptible to LRRK2-associated pathology and in this
23 model glial LRRK2 expression significantly contributes to neuroinflammation, ultimately causing
24 neurodegeneration.

25 **Keywords:** LRRK2; Age; Glia; Neuroinflammation; Autophagy; Parkinson's disease; Adenoviral vector

26 Abbreviations²

¹ Corresponding authors: astrid.kritzinger@uni-ulm.de, thomas.ciossek@boehringer-ingelheim.com

² Abbreviations: ALP, autophagy-lysosome pathway; CAG, CMV-IE enhanced chicken β -actin promoter with rabbit β -globin splice acceptor; CMV-IE, cytomegalovirus-immediate early; DAB, 3,3'-diaminobenzidine; dpi, days post-injection; HC-AdV, high-capacity adenoviral vector; IU, infectious units; (i)MOI, (infectious) multiplicity of infection; mpi, months post-injection; LFB, Luxol Fast Blue; LRRK2, leucine-rich repeat kinase 2; OD, optical density; PD, Parkinson's disease; SNpc, Substantia Nigra pars compacta; wpi, weeks post-injection

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