PARKINSON DISEASE

LAG3 facilitates cell-to-cell spread of α -synuclein pathology

“absence of LAG3 reduced the induction and spread of α -synuclein pathology”

The idea that the pathogenesis of Parkinson disease (PD) involves ‘prion-like’ cell-to-cell transmission of misfolded α -synuclein in the brain is well established, but the underlying molecular mechanisms remain unclear. In a paper recently published in *Science*, researchers from Johns Hopkins University in Baltimore, USA provide new insights into these mechanisms by showing that the lymphocyte-activation gene 3 (LAG3) protein can mediate the spread of α -synuclein fibrils between neurons.

The work was prompted by a 2011 paper by Volpicelli-Daley *et al.*, which demonstrated that α -synuclein

fibrils could induce the formation and propagation of α -synuclein pathology in neuronal cell cultures. “We felt that the transmission hypothesis had legs, and that there had to be a molecular mechanism by which pathological α -synuclein gained entry into cells,” explains Ted Dawson, who led the new study.

By screening a library of trans-membrane proteins, the authors identified LAG3 as a receptor that could bind robustly to preformed fibrils (PFFs) — but not monomers — of α -synuclein. In cultured cortical neurons, depletion or knockout of LAG3 blocked the endocytosis of α -synuclein PFFs. Moreover, both

in vitro and *in vivo*, absence of LAG3 reduced the induction and spread of α -synuclein pathology by PFFs.

In wild-type mice, injection of α -synuclein PFFs into the dorsal striatum led to dopaminergic neurodegeneration and PD-like motor deficits. By contrast, *Lag3*^{-/-} mice that were subjected to the same intervention showed relative preservation of dopaminergic neurons, and had no detectable motor impairments.

“We are currently working on understanding the downstream signalling pathways of LAG3 and its interacting partners,” says Dawson. “In addition, we are developing strategies to interfere with its ability to internalize α -synuclein fibrils and initiate α -synuclein pathology.” The researchers hope that their work will lead to the development of new preventive and therapeutic strategies for PD.

Heather Wood

Binding of exogenous α -synuclein preformed fibrils to neurons is markedly reduced in the absence of LAG3 expression. Image courtesy of T. M. Dawson.

ORIGINAL ARTICLE Mao, X. *et al.* Pathological α -synuclein transmission initiated by binding lymphocyte-activation gene 3. *Science* <http://dx.doi.org/10.1126/science.aah3374> (2016)

FURTHER READING Volpicelli-Daley, L. A. *et al.* Exogenous α -synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* **72**, 57–71 (2016)