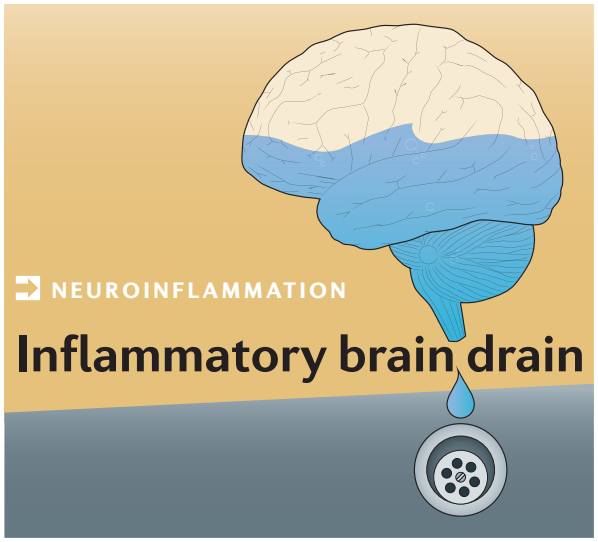
Nature Reviews Immunology | AOP, published online 21 January 2013; doi:10.1038/nri3392



NPG

Failure to regulate central nervous system (CNS) inflammation may contribute to the development of neurodegenerative disorders. Two recent reports in *Nature* support this idea. They show that loss of the astrocytic dopamine D2 receptor (DRD2) or activation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome enhances CNS inflammation that can contribute to pathology in models of Parkinson's disease and Alzheimer's disease, respectively.

As loss of DRD2 expression has previously been linked to declining cognitive and motor functions in the elderly, Shao *et al.* examined whether DRD2 signalling affects inflammatory responses in the CNS. Compared with controls, DRD2-deficient mice showed increased spontaneous activation of astrocytes in the substantia nigra and striatum (areas of the brain that are affected in Parkinson's disease), and they experienced a more severe loss of nigral dopaminergic neurons following treatment with the neurotoxin MPTP. The expression of pro-inflammatory mediators was increased in the striatum of DRD2-deficient mice, with the levels of these mediators increasing further in aged DRD2-deficient mice. Closer examination of the cell types involved suggested that DRD2 deficiency leads to increased astrocyte activation but does not affect the activation status of microglial cells or neurons.

To identify the mechanisms involved, the authors compared gene transcript profiles in the striatum of wild-type and DRD2-deficient mice. Levels of αB-crystallin (CRYAB) — a small heat-shock protein with anti-inflammatory and neuroprotective activities — were decreased in DRD2-deficient mice, suggesting that DRD2 suppresses CNS inflammation by inducing CRYAB production. In support of this, knockdown of *Cryab* expression in astrocytes led to their upregulation of pro-inflammatory mediators, whereas overexpression of *Cryab* in DRD2-deficient astrocytes suppressed their production of pro-inflammatory mediators.

The authors used a mouse model of MPTP-induced Parkinson's disease to examine the physiological relevance of these findings. Treatment with a DRD2 agonist prevented the loss of nigral dopaminergic neurons and reduced the levels of pro-inflammatory mediators in the substantia nigra of wild-type mice, but did not attenuate disease in DRD2-deficient or CRYAB-deficient mice. Thus, DRD2-mediated signalling in astrocytes appears to suppress the pro-inflammatory functions of these cells by inducing the upregulation of CRYAB.

In the second study, Heneka *et al.* assessed the role of the NLRP3 inflammasome in Alzheimer's disease. Previous studies showed that amyloid-β deposits (which are found in the brains of patients with Alzheimer's disease) promote the activation of the NLRP3 inflammasome, but it is not clear whether this contributes to disease pathology. Heneka *et al.* detected elevated levels of cleaved caspase 1 in brain lysates from patients with Alzheimer's disease and also in the brains of APP/PS1 mice, which develop an Alzheimer's-like disease. As expected, APP/PS1 mice showed severe defects in spatial memory formation and in object-recognition memory tests. By contrast, APP/PS1 mice that were also deficient in NLRP3 or caspase 1 were protected from these memory defects. In addition, deficiency of NLRP3 or caspase 1 prevented the loss of hippocampal synaptic plasticity and reduced neurobehavioural disturbances in APP/PS1 mice.

Deficiency in NLRP3 or caspase 1 did not affect the overall amounts of the amyloid precursor protein or its processing in APP/PS1 mice. However, *Nlrp3*$^{-/-}$ APP/PS1 and *Casp1*$^{-/-}$ APP/PS1 mice had reduced levels of amyloid-β aggregates compared with control APP/PS1 mice, apparently owing to altered microglial cell activity. Microglial cells from *Nlrp3*$^{-/-}$ APP/PS1 mice or *Casp1*$^{-/-}$ APP/PS1 mice were more efficient than those from APP/PS1 mice in phagocytosing amyloid-β aggregates. Furthermore, higher levels of insulin-degrading enzyme (which is produced by microglial cells and contributes to amyloid-β clearance) were found in *Nlrp3*$^{-/-}$ APP/PS1 and *Casp1*$^{-/-}$ APP/PS1 mice. Finally, deficiency of NLRP3 or caspase 1 in APP/PS1 mice appeared to skew microglial cells from a pro-inflammatory 'M1-like' phenotype to a more reparatory 'M2-like' phenotype. The authors conclude that preventative therapies that target the NLRP3 inflammasome may have a beneficial effect in Alzheimer's disease.

Yvonne Bordon

> "therapies that target the NLRP3 inflammasome may have a beneficial effect in Alzheimer's disease"

ORIGINAL RESEARCH PAPERS Shao, W. *et al.* Suppression of neuroinflammation by astrocytic dopamine D2 receptors via αB-crystallin. *Nature* 16 Dec 2012 (doi:10.1038/nature11748) | Heneka, M. T. *et al.* NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* 19 Dec 2012 (doi:10.1038/nature11729)