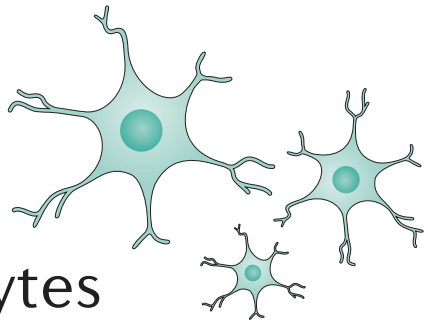


NEURODEGENERATIVE DISEASE

Factoring in astrocytes

> hippocampal neurons that were cultured with *Ikba*-knockout astrocytes … showed reductions in synaptic density, dendritic complexity and dendritic length

Activation of nuclear factor-κB (NF-κB) — a transcription factor that regulates neuroinflammation — has been linked to several neurodegenerative diseases, including Alzheimer disease (AD), but whether it has a neuroprotective or neurotoxic role in this context remains unclear. Now, Zheng and colleagues show that prolonged NF-κB activation in astrocytes leads to the production and release of complement factor 3 (C3), which impairs neuronal function. Moreover, they report that amyloid-β, which is widely implicated in AD pathophysiology, can activate astrocytic NF-κB.

Under non-inflammatory conditions, NF-κB is kept within the cytoplasm by an inhibitor protein termed IκBα. During inflammation, IκBα is degraded and NF-κB translocates to the nucleus, where it induces the expression of various genes, including *Ikba* (which encodes IκBα), thereby providing a means of 'turning off' NF-κB activation.

To further understand the gene targets of NF-κB, the authors conducted gene expression profiling on hippocampal samples from transgenic mice in which *Ikba* was specifically deleted in the CNS and from littermate controls. They found that the knockout samples showed changes in the expression levels of many genes, including an upregulation in the expression of the gene encoding C3, which suggests that it is a target gene of NF-κB.

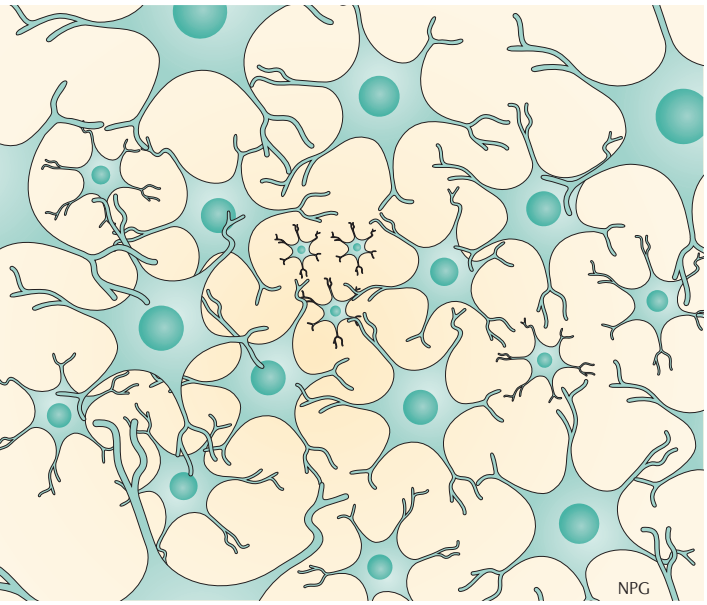
Interestingly, in culture, wild-type astrocytes expressed higher levels of IκBα than did neurons under basal conditions and this differential was even greater following treatment with tumour necrosis factor, a pro-inflammatory cytokine. Moreover, the selective knockout of *Ikba* in astrocytes, but not in neurons, led to an increase in C3 levels, as determined in hippocampal samples from transgenic mice and in primary cultures of cells from wild-type and germline *Ikba*-knockout mice. In the cultures, this effect could be blocked through application of an NF-κB inhibitor. Together, these findings suggest that astrocytes may be the main site of NF-κB action in the CNS and provide further evidence that NF-κB can induce C3 expression.

Next, the authors examined whether overexpression of C3 in astrocytes affected neurons. They found that hippocampal neurons that were cultured with *Ikba*-knockout astrocytes or treated with recombinant C3 showed reductions in synaptic density, dendritic complexity and dendritic length. Moreover, hippocampal neurons that were co-cultured with *Ikba*-knockout astrocytes showed an increase in the amplitude of miniature excitatory postsynaptic currents. These data suggest that increased NF-κB activation in astrocytes — by increased transcription and release of C3 — impairs dendritic tree morphology and affects neuronal function.

Last, the authors explored the link between abnormal NF-κB activation in astrocytes and AD. They found that cultured wild-type astrocytes showed nuclear translocation of NF-κB and increased *C3* mRNA levels following treatment with amyloid-β. Increased *C3* mRNA levels were also detected in a mouse model of AD, and post-mortem brain samples from patients with this disease showed increased levels of C3, NF-κB and IκBα. Finally, the authors showed that disrupting C3 signalling — by antagonizing the C3 receptor — in the mouse model of AD improved working memory performance, as assessed in the Morris water maze.

Together, these results reveal the astrocytic *C3* gene as a target for NF-κB activation. Moreover, they suggest that abnormal activation of such signalling may impair neuronal morphology and function, and that this mechanism may have relevance to AD and be of therapeutic interest.

Darren Yates



ORIGINAL RESEARCH PAPER Lian, H. *et al.* NFκB-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease. *Neuron* **85**, 101–115 (2015)