Nature Reviews Neuroscience | Published online 2 Feb 2017; doi:10.1038/nrn.2017.13

GLIA

A toxic reaction

> These data suggest that IL-1α, TNF and C1q are released from activated microglia and induce A1 astrocytes

Brain injury and disease can induce astrocytes to enter a 'reactive' state in which gene expression is markedly changed. The function of these reactive astrocytes is debated, with different studies indicating that these cells promote damage to, or recovery of, the CNS. Now, Liddelow *et al.* show that activated microglia can induce a subtype of inflammation-associated reactive astrocytes that promotes neuron and oligodendrocyte death and that is found in various neurological disorders.

In a previous study, the authors discovered that lipopolysaccharide (LPS), an inflammatory stimulus, could induce reactive astrocytes — which they termed A1 astrocytes — that had a gene expression profile that differed from that exhibited by reactive astrocytes induced by ischaemic conditions. Here, the authors first examined how LPS induces A1 astrocytes.

LPS can activate Toll-like receptor 4 (TLR4). In the rodent CNS, TLR4 is expressed by microglia but not by astrocytes, suggesting that microglia may have a role in A1 astrocyte induction. Supporting this assertion, gene expression profiling of purified astrocytes from LPS-treated mice lacking microglia revealed that none of the astrocytes had an A1 profile. Moreover, LPS treatment failed to induce A1 astrocytes in cultures of purified non-reactive astrocytes, but conditioned medium from LPS-induced activated microglial cultures could induce this transformation.

IL-1α, tumour necrosis factor (TNF) and complement component C1q are highly expressed by microglia. Here, these molecules all induced A1 astrocyte-associated gene expression changes in cultured purified non-reactive astrocytes and were elevated in the conditioned medium from activated microglial cultures. Furthermore, in mice, knocking out the genes that encode these molecules together blocked the formation of A1 astrocytes following LPS treatment. These data suggest that IL-1α, TNF and C1q are released from activated microglia and induce A1 astrocytes.

The authors next explored the functional properties of A1 astrocytes and found that retinal ganglion cells (RGCs) co-cultured with A1 astrocytes developed 50% fewer synapses and exhibited fewer and lower-amplitude miniature excitatory postsynaptic currents than those grown in the presence of non-reactive astrocytes. Moreover, A1 astrocytes exhibited a decreased capacity to phagocytose synaptosomes and myelin debris *in vitro* and to phagocytose synapses in the lateral geniculate nucleus *in vivo*.

The authors also noticed that the viability of various neuronal types and mature oligodendrocytes rapidly decreased when they were cultured with medium that included increasing concentrations of A1 astrocyte-conditioned medium. Furthermore, optic nerve crush in rats and mice induced the generation of these astrocytes alongside RGC death. Together, these findings suggest that A1 astrocytes not only lose various functional properties but also release factors that may be toxic to some cell types.

Activated microglia are a feature of various neurological disorders. Thus, the authors explored whether A1 astrocytes are also found in these diseases, and indeed they detected abundant expression of complement component C3 — a marker of A1 astrocytes — in human tissue from cases of Alzheimer disease, Huntington disease, amyotrophic lateral sclerosis, Parkinson disease and multiple sclerosis.

These findings indicate that activated microglia may induce a subtype of reactive astrocytes that has neurotoxic properties and that may have a role in various neurological disorders.

Darran Yates

Jennie Vallis/Macmillan Publishers Limited

ORIGINAL ARTICLE Liddelow, S. A. *et al.* Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* http://dx.doi.org/10.1038/nature21029 (2017)

FURTHER READING Ben Haim, L. & Rowitch, D. H. Functional diversity of astrocytes in neural circuit regulation. *Nat. Rev. Neurosci.* **18**, 31–41 (2017)