Nature Reviews Neuroscience | AOP, published online 17 January 2014; doi:10.1038/nrn3678

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SYNAPTIC PLASTICITY

A synaptic role for microglia

> The authors created mice expressing tamoxifen-inducible Cre recombinase under the control of the CX3C chemokine receptor 1 promoter, which enables specific genes to be manipulated in microglia.

Interest in the role of microglia in inflammatory processes in the CNS has surged in the past few years, but much less is known about the functions of these cells in the normal brain. Parkhurst *et al.* now show that microglia promote learning-induced formation of glutamatergic synapses and that this effect is mediated by microglial brain-derived neurotrophic factor (BDNF).

The authors created mice expressing tamoxifen-inducible Cre recombinase under the control of the CX3C chemokine receptor 1 promoter, which enables specific genes to be manipulated in microglia. They used this approach to express the diphtheria toxin receptor in microglia; subsequent administration of the toxin resulted in microglia depletion in these mice.

Transcranial two-photon microscopy showed that microglia depletion on postnatal day 19 (P19) or P30 reduced basal levels of dendritic spine formation and elimination over the subsequent 4 days in layer 5 pyramidal cells in the motor cortex. Microglia depletion on P30 or P60 also reduced spine remodelling in response to 3 days of motor training on a rotarod. Moreover, such training failed to improve rotarod performance in these mice. This behavioural effect was not limited to motor learning, as microglia-depleted mice also showed impaired memory in auditory fear-conditioning and novel object-recognition tasks, which involve the amygdala and the hippocampus, respectively.

The authors next assessed whether any synaptic alterations were associated with the effect of microglia depletion on spine remodelling. A quantitative proteomic screen of whole-brain protein extracts of microglia-depleted and control mice revealed 61 proteins whose concentrations changed in response to microglia depletion. These included 21 proteins with known synaptic functions, such as the NMDA receptor subunit GluN2B and vesicular glutamate transporter 1 (VGluT1). An additional analysis showed that levels of GluN2B, VGluT1 and the AMPA receptor subunit GluA2 were decreased in synaptosome fractions of microglia-depleted mice compared with those of control mice. This indicates that microglia depletion affected synaptic protein levels at glutamatergic synapses.

At a functional level, patch-clamp recordings from layer 5 pyramidal cells in the motor cortex showed that the frequency of NMDA receptor- and AMPA receptor-mediated miniature excitatory postsynaptic currents was reduced in mice 1 day after microglia depletion relative to control mice, suggesting that microglia depletion decreased spontaneous glutamate release.

What might be the molecular mechanism linking microglia depletion to synaptic alterations in neurons? The authors focused on BDNF, a well-known regulator of synaptic plasticity that is produced in microglia (among other cells). They created mice in which *Bdnf* expression could be suppressed specifically in microglia. BDNF depletion did not alter synapse density in the cortex or hippocampus, but synaptosome analysis showed that levels of GluN2B and VGluT1 (but not GluA2) were reduced in synaptosomes from microglial-BDNF-depleted mice compared with control mice. In addition, microglial-BDNF-depleted mice showed less improvement in rotarod performance after training than control mice, and these mice had impaired memory in the auditory fear-conditioning task (but not in the novel object-recognition task) compared with control mice. The authors further showed that levels of the phosphorylated form of the BDNF receptor TRKB (also known as NTRK2) were reduced in synaptosomes of microglial-BDNF-depleted mice.

Together, these findings show that microglia contribute to learning-induced formation of glutamatergic synapses and that this role depends at least partly on microglial BDNF. The mice generated in this study will enable further investigation of the role of microglia in the normal brain.

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ORIGINAL RESEARCH PAPER Parkhurst, C. N. *et al.* Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell* **155**, 1596–1609 (2013)