A novel C3-dependent mechanism of microglial priming relevant to multiple sclerosis
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Research question and background
Microglial priming predisposes the brain to neurodegeneration and affects disease progression. The signal to switch from the quiescent to the primed state is unknown. Identification of pathways that lead to microglial priming could support the design of therapies that interfere with priming to prevent neurological decline in people at risk. We hypothesize that the complement system—one of the most important humoral signaling systems, contributing substantially to immune surveillance and homeostasis, and highly expressed in the CNS—is involved in microglial priming.

Methods and tissues used
Mice deleted of the C3 convertase regulator complement receptor 1–related protein-y (Crry), which results in chronic activation of complement, were analyzed for signs of microglial priming morphologically by immunohistochemistry and functionally by challenge with lipopolysaccharide to mimic a systemic infection. Relevance for neurodegenerative diseases is exemplified by human multiple sclerosis (MS) and the experimental autoimmune encephalomyelitis (EAE) model of MS. Brain tissue from 9 MS cases and 4 matched non-neurological controls of the Netherlands Brain Bank were analyzed for evidence of microglial priming by immunohistochemistry whereas the effect of microglial priming on disease onset and progression was tested in EAE.

Results and conclusion
We show that Crry deletion induces microglial priming. Mice, double knockout for Crry and either C3 or factor B, did not show priming, demonstrating dependence on alternative pathway activation. Co-localisation of C3b/iC3b and CR3 implicated the CR3/iC3b interaction in priming. Systemic lipopolysaccharide challenge overactivated primed microglia with florid expression of proinflammatory molecules which could be blocked by complement inhibition.

In human MS, microglial priming was evident in perilesional white matter, in close proximity to C3b/iC3b deposits whereas EAE accelerated in Crry deficient mice. In summary, C3-dependent microglial priming confers susceptibility to other challenges. Our observations are relevant to progression in MS and other neurological diseases exacerbated by acute insults.