Taming microglia in neuroinflammation and neurodegeneration

Guy C. Brown

Department of Biochemistry, University of Cambridge, Cambridge, United Kingdom
gcb3@cam.ac.uk ***www.guybrown.net***

Microglia play multiple roles in neuroinflammation and neurodegeneration. Activated microglia can be neuroprotective either by phagocytosis of amyloid and debris or by release of proteins such as soluble triggering receptor expressed on myeloid cells 2 (sTREM2), calreticulin (CRT) and receptor-associated protein (RAP). However, activated microglia can contribute to neurodegeneration by release of opsonins and surface-sugar-modifying enzymes or by phagocytosis of synapses or neurons. Genome-wide association studies (GWAS) strongly link genes affecting microglial phagocytosis to Alzheimer's disease (AD). Increasing microglial phagocytosis of amyloid beta (Aβ) may be beneficial early in AD, but blocking microglial phagocytosis of synapses and neurons may be beneficial later in disease. The microglial P2Y6 receptor (P2Y6R) stimulates microglial phagocytosis of synapses and neurons in response to uridine diphosphate released by stressed neurons. We find that knockout or inhibition of P2Y6R prevents microglial phagocytosis of synapses and neurons induced by neuroinflammation, Aβ or Tau in culture, and prevents loss of synapses, neurons and memory in mouse models of AD, Parkinson's, neuroinflammation and aging. Thus, blocking microglial phagocytosis of synapses and neurons can prevent neurodegeneration.