NEURODEGENERATIVE DISORDERS

A biomarker and a target for progressive MS

The course of multiple sclerosis (MS) typically has two phases: relapsing–remitting MS (RRMS), which is characterized by acute autoimmune attacks on the central nervous system (CNS) followed by complete recovery, and secondary progressive MS (SPMS), in which there is progressive and irreversible damage to the CNS. Although various treatments that target the adaptive inflammatory response have beneficial effects on RRMS, such treatments are not usually effective in SPMS, and the mechanisms underlying this phase of the disease are unclear. Reporting in *Nature Immunology*, Farez and colleagues have identified a pathway involving Toll-like receptor 2 (TLR2) and poly(ADP-ribose) polymerase 1 (PARP1) as a potential therapeutic target for SPMS.

The authors began by investigating the role of 15-oxysterols (oxidized cholesterol derivatives) in SPMS, as higher concentrations of antibodies against these derivatives have been detected in patients with MS. Among the various 15-oxysterols measured, 15α-hydroxicholestene (15-HC) was detected at higher serum concentrations in patients with SPMS than in those with RRMS. Increases in the concentration of 15-HC were also seen only in the progressive phase of experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, suggesting that this oxysterol could be linked to the progressive impairment that characterizes both human SPMS and secondary progressive EAE in mice.

The team went on to show that 15-HC promotes neuroinflammation in EAE mice by a PARP1-dependent mechanism, as the worsening of symptoms following 15-HC administration was absent in PARP1-knockout mice. Reverse transcriptase PCR analysis indicated that the underlying mechanism involves CC-chemokine ligand 2, inducible nitric oxide synthase and tumour necrosis factor, as higher expression of these hallmarks of CNS inflammation was detected in 15-HC-treated wild-type mice, but not PARP1-knockout mice.

Furthermore, administration of the PARP1 inhibitor 5-aminoisoquinoline inhibited the clinical signs of secondary progressive EAE and reduced demyelination and axonal loss. This effect was found to be due to decreased activation of microglia, CNS-infiltrating macrophages and astrocytes, rather than an effect on the adaptive encephalitogenic response.

Using antibody probes on protein microarrays, the authors also identified a role for TLR signalling in this process. Subsequently, specific receptor inhibition with antibodies was used to show that TLR2 signalling is required for PARP1 activation by 15-HC. Studies in cells that expressed PARP1 but not TLR2, and in TLR2-knockout mice, confirmed these findings.

Overall, the study identifies a viable, stage-specific biomarker of SPMS, as 15-HC can be detected in the serum and could therefore be used in a clinical setting, and highlights the PARP1–TLR2 axis as a promising target for this therapeutically challenging stage of MS.

Katie Kingwell

ORIGINAL RESEARCH PAPER Farez, M. F. *et al.* Toll-like receptor 2 and poly(ADP-ribose) polymerase 1 promote central nervous system neuroinflammation in progressive EAE. *Nature Immunol.* **10**, 958–964 (2009)
FURTHER READING Lopez-Diego, R. S. & Weiner, H. L. Novel therapeutic strategies for multiple sclerosis — a multifaceted adversary. *Nature Rev. Drug Discov.* **7**, 909–925 (2008)