NEUROIMMUNOLOGY

MAFG activity in astrocytes drives CNS inflammation

“ astrocytes in the active white matter lesions of patients with multiple sclerosis showed increased MAFG and decreased NRF2 expression ”

Astrocytes contribute to the pathogenesis of multiple sclerosis, but the mechanistic basis of this is poorly understood. A new study from the Quintana laboratory describes a potentially pathological role for a subpopulation of astrocytes that are characterized by decreased expression of the antioxidant transcription factor NRF2 and increased expression of MAFG, a member of the small MAF (sMAF) transcription factor family.

Wheeler et al. used single-cell RNA sequencing (scRNA-seq) to compare astrocytes isolated from the central nervous system (CNS) of control mice with those from mice with experimental autoimmune encephalomyelitis (EAE). They identified multiple cell populations that differed between control mice and mice with EAE, including several subpopulations of astrocytes. The most expanded subpopulation of astrocytes in the inflamed CNS was a population of *Gfap*⁺ astrocytes, which were characterized by the expression of genes

related to pro-inflammatory and neurotoxic pathways, such as the NF- κ B, GM-CSF and iNOS signalling pathways and the unfolded protein response. Further analysis showed that this *Gfap*⁺ astrocyte subpopulation showed decreased expression of NRF2 target genes, and this was linked to the increased pro-inflammatory gene expression seen in these astrocytes. Accordingly, targeted deletion of NRF2 in *Gfap*⁺ cells was associated with heightened CNS inflammation and more severe EAE.

The authors used Ribotag^{Gfap} mice to identify additional regulators of these astrocytes in the inflamed CNS. They found that peak EAE disease coincided with decreased expression of NRF2-driven genes and increased levels of MAFG. MAFG interacts with other proteins to regulate gene expression, with MAFG–NRF2 heterodimers promoting NRF2-driven gene expression and MAFG homodimers suppressing NRF2-driven genes. Notably, inactivation of *Mafg* in astrocytes ameliorated EAE and this was associated with increased expression of NRF2 target genes and decreased pro-inflammatory gene expression. Therefore, decreased expression of NRF2 and increased expression of MAFG in astrocytes seems to promote CNS inflammation during EAE.

MAFG has been shown to cooperate with DNA methyltransferase 3B (DNMT3B) to limit gene expression and, in keeping with this, the authors showed that inactivation of *Mafg* decreased DNA methylation at NRF2 target genes. They also identified a role for the sMAF cofactor methionine adenosyltransferase IIa (MAT2a), which generates substrates for DNA methylation. They found that *Mafg* and *Mat2a* are coexpressed in astrocytes and that inactivation

of *Mat2a* ameliorates disease in mice with EAE. Mice with an astrocyte-specific deletion of the GM-CSF receptor also showed reduced EAE disease and this was associated with decreased expression of *Mafg*, *Mat2a* and pro-inflammatory pathways in astrocytes. Expression of GM-CSF by CNS-infiltrating T cells preceded the downregulation of NRF2 and upregulation of *Maf* and *Mat2a*, suggesting a key role for GM-CSF in promoting the pathogenicity of astrocytes in the inflamed CNS.

Finally, the authors conducted scRNA-seq analyses on CNS samples from patients with multiple sclerosis. Similarly to their findings in mice, they identified an astrocyte population that was markedly expanded in the CNS of patients with multiple sclerosis and characterized by decreased NRF2 activation, along with increased MAFG activation, DNA methylation, GM-CSF signalling and pro-inflammatory pathway activity. Moreover, astrocytes in the active white matter lesions of patients with multiple sclerosis showed increased MAFG and decreased NRF2 expression.

The authors propose that in the inflamed CNS, reduced NRF2 expression enables MAFG and MAT2a to drive epigenetic changes in astrocytes that promote pathological activity, with GM-CSF from infiltrating T cells amplifying this pro-inflammatory programme. Targeting this pathway could therefore enable the suppression of neurotoxic astrocyte activity in multiple sclerosis.

Yvonne Bordon

Credit: S. Braddock-Springer Nature Limited

ORIGINAL ARTICLE Wheeler, M. A. et al. MAFG-driven astrocytes promote CNS inflammation. *Nature* <https://doi.org/10.1038/s41586-020-1999-0> (2020)