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NEUROLOGICAL DISORDERS

DAMPening damage after stroke

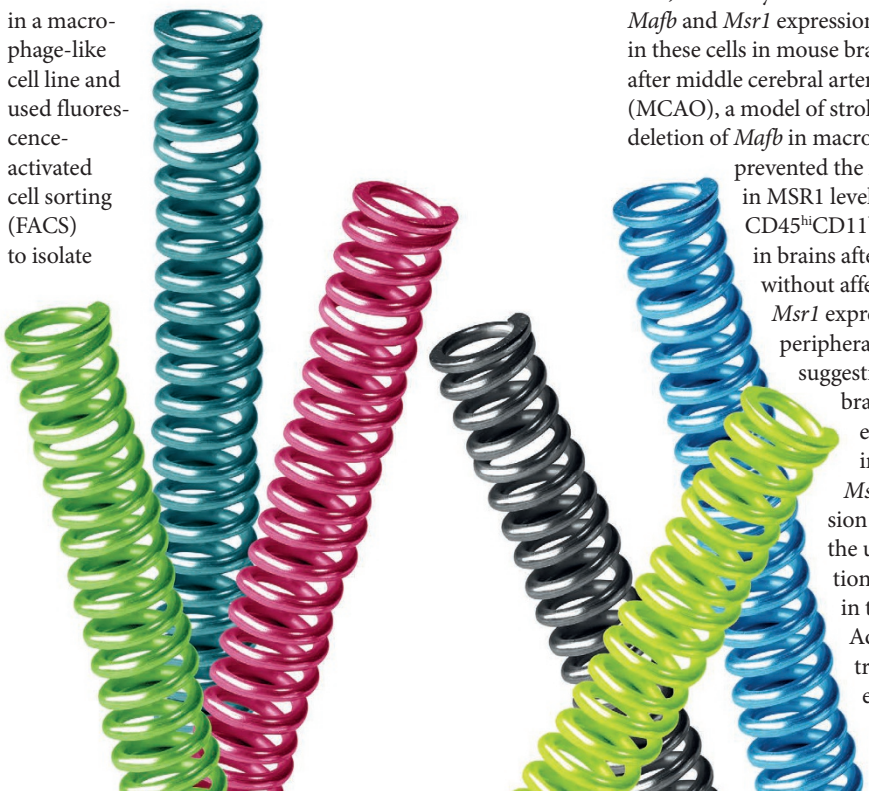
Much of the tissue injury that occurs following ischaemic stroke is caused by sterile inflammation, which lasts for about a week after the initial artery blockade. Shichita and colleagues have found that increasing transcription of macrophage scavenger receptor 1 (*Msr1*) reduced neurological deficits in a mouse model of stroke, likely by promoting the uptake of damage-associated molecular patterns (DAMPs) by infiltrating myeloid cells.

Cellular debris from dead cells is a major source of DAMPs in ischaemic conditions. DAMPs taken up by immune cells promote inflammation, which can exaggerate tissue injury. To identify factors involved in DAMP internalization, the authors induced random mutations in a macrophage-like cell line and used fluorescence-activated cell sorting (FACS) to isolate those cells that were incapable of internalizing a type of DAMP, the peroxiredoxins (PRXs), that were fluorescently labelled. Analysis of gene expression profiles of the cell lines revealed that *Msr1* and the transcription factor *Mafb* were necessary to induce DAMP internalization. Overexpression of MSR1 or MAFB in these cells increased DAMP uptake.

> “administration of Am80 up to 24 hours after MCAO reduced the resulting neurological deficits and infarct volume”

Interestingly, MAFB overexpression induced the expression of *Msr1*. The *Msr1* promoter contains MAF-recognition elements, and MAFB drove reporter gene expression from the *Msr1* promoter. The effects of MAFB are thus likely due to transcription of *Msr1*.

$CD45^{hi}CD11b^{hi}$ cells, which are thought to be infiltrating myeloid cells, efficiently internalize DAMPs. *Mafb* and *Msr1* expression is induced in these cells in mouse brains 3 days after middle cerebral artery occlusion (MCAO), a model of stroke. Genetic deletion of *Mafb* in macrophages prevented the increase in MSR1 levels in $CD45^{hi}CD11b^{hi}$ cells in brains after MCAO without affecting *Msr1* expression in peripheral organs, suggesting that the brain microenvironment induces *Msr1* expression through the upregulation of *Mafb* in these cells. Adoptive transfer experiments supported this conclusion.



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Combined deficiency of *Msr1* and *Marco*, another macrophage receptor involved in DAMP uptake, resulted in higher levels of PRX-containing debris in mouse brains 4 days after MCAO. Correspondingly, infarct volumes were larger, and neurological deficits were more severe in *Msr1;Marco*-deficient mice as soon as 3 days after MCAO. These deficits were also apparent in wild-type mice transplanted with *Msr1;Marco*-deficient bone marrow, suggesting that these receptors are required specifically on infiltrating myeloid cells. In addition, mice that lack *Mafb* in circulating myeloid cells also had increased amounts of PRX debris, larger infarct volumes and exaggerated neurological deficits after MCAO, lending further support to the importance of the MAFB–MSR1 axis in infiltrating immune cells.

Retinoid X receptor (RXR) agonists induce *Mafb* expression. One of these, Am80, is used to treat patients with acute promyelocytic leukaemia. Intravenous administration of Am80 up to 24 hours after MCAO reduced the resulting neurological deficits and infarct volume; Am80 had no effect in *Msr1;Marco*-deficient mice or mice lacking *Mafb* in circulating myeloid cells.

The dose of Am80 required in these experiments is probably too high to be clinically useful, but similar compounds that increase MSR1-mediated DAMP uptake by infiltrating myeloid cells in individuals with ischaemic stroke could improve outcomes.

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ORIGINAL ARTICLE Shichita, T. *et al.* MAFB prevents excess inflammation after ischemic stroke by accelerating clearance of damage signals through MSR1. *Nat. Med.* http://dx.doi.org/10.1038/nm.4312 (2017)

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