NEUROIMMUNOLOGY

Calming inflammation to prevent stroke damage

> *Trem1*-null mice had improved neurological scores and a decreased infarct volume

A stroke is characterized by an initial phase of cerebral ischaemia, followed by an inflammatory response. Currently, the only treatments for stroke-induced injury are thrombolytic therapy and embolectomy, which have to be initiated right after the event. Now, using a rodent model of transient focal cerebral ischaemia, Katrin Andreasson and colleagues demonstrate that TREM1, an inflammatory receptor expressed by myeloid cells, amplifies cerebral damage and that targeting inflammation may be a novel treatment for stroke.

Brain ischaemia leads to the release of cellular proteins, lipids and other immunogenic material into the systemic circulation. To investigate the ensuing immune response, the authors used middle cerebral artery occlusion–reperfusion (MCAo) to induce a stroke in *Cx3cr1*$^{GFP/+}$*Ccr2*$^{RFP/+}$ mice, which allowed them to track microglia in the brain and peripheral monocytes/macrophages and polymorphonuclear neutrophils (PMNs) that traffic to the site of ischaemia. An early increase of monocytes/macrophages and PMNs in the brain after MCAo correlated with a corresponding decline of microglia. There was a marked upregulation of TREM1 on peripheral and infiltrating monocytes/macrophages, whereas PMNs showed consistently high expression of TREM1. Closer investigation showed that TREM1 expression on peripheral and splenic monocytes/macrophages was induced within 4.5 h after MCAo, followed by an infiltration of TREM1$^+$ myeloid cells into the ischaemic brain hemisphere within 48 h.

Interestingly, *Trem1*-null mice had improved neurological scores and a decreased infarct volume at 24 h and 48 h post-MCAo. This translated to improved survival, indicating that TREM1 indeed plays a detrimental role in the post-stroke innate immune response.

Whole transcriptome analysis of *Trem1*$^{-/-}$ and *Trem1*$^{+/+}$ monocyte/macrophages, PMNs and microglia after MCAo revealed notable differences between knockout and wild-type cells, particularly in the pathways for antioxidant defence, immune clearance and protein synthesis. Of note, TREM2, an immune receptor that functionally opposes TREM1, was highly expressed by *Trem1*$^{-/-}$ myeloid cells. Together with results from further in vitro experiments, this suggests that loss of *Trem1* allows for cerebroprotection via the antioxidant glutathione metabolism, anti-inflammatory TREM2 expression and enhanced lysosomal clearance of ischaemic debris.

The authors then tested whether targeting TREM1 systemically might protect from stroke injury. For this, they used the decoy peptide LP17, corresponding to a highly conserved extracellular region of TREM1, that had previously been shown to suppress the pro-inflammatory cascade in sepsis. Indeed, mice treated with LP17 (but not a corresponding scrambled peptide) right after MCAo showed the same level of protection from stroke injury as *Trem1*$^{-/-}$ mice.

Next the extent of stroke-induced TREM1-mediated immune activation was investigated using non-invasive PET imaging and a radiolabelled TREM1-targeted antibody. This revealed a surprising finding: MCAo did not only induce an influx of TREM1-expressing myeloid cells into the infarcted area of the brain but also increased the numbers of TREM1$^+$ cells in the intestine.

It had previously been shown that sympathetic inputs to the intestine can increase gut permeability in response to stroke, which can lead to post-stroke bacterial infections. The authors speculated that TREM1 is induced in intestinal and peripheral monocytes/macrophages in response to microbial antigens that breach the gut barrier. Indeed, β-adrenergic blockade, which reduces gut permeability, decreased TREM1 induction in response to MCAo in monocytes/macrophages in both the intestine and periphery. Further, it was found that intestinal TREM1 activation aggravates the already compromised intestinal barrier. To what extent TREM1 expression on peripheral myeloid cells is driven by pathogen-associated molecular patterns that cross the gut barrier or damage-associated molecular patterns released from the ischaemic brain remains to be determined.

Overall, these results demonstrate that TREM1 drives a substantial component of stroke-induced brain injury and that the inhibition of TREM1 may have the potential to limit post-stroke injury. The authors speculate that targeting the post-stroke immune response may also offer an extended window for therapeutic intervention.

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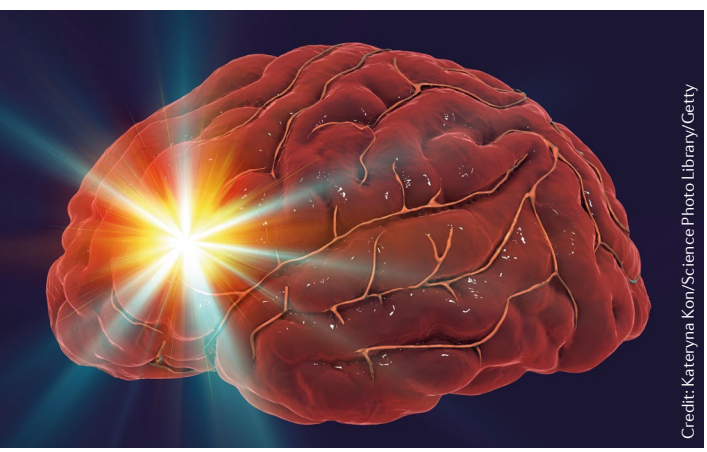

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