

## Spotlight

## TREM1 Blockade: Killing Two Birds with One Stone

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**Infectious and sterile injuries cause the release of PAMPs and DAMPs. A study by Liu *et al.* (*Nat. Immunol.* 2019) reports that DAMP-induced sterile brain inflammation from stroke is associated with sympathetic nervous system activation, enhancing intestinal permeability, the release of microbiota-derived PAMPs, and inflammation. TREM1 is implicated as a potential target to treat stroke and DAMP- and PAMP-induced inflammation.**

Inflammation is the primary response of the innate immune system to tissue injuries. It initiates with a prompt vascular reaction enhancing blood flow and vascular permeability in the injured area, subsequently enabling the influx of soluble inflammatory mediators, [e.g., tumor necrosis factor (TNF), interleukin (IL)-1, complement, and prostaglandins], as well as phagocytic cells (e.g., granulocytes and monocytes/macrophages). This protective response can localize to, and clear, the injury site, as well as eliminate damaged tissue, thus enabling repair. However, the inflammatory response is not very selective and may also cause destruction of normal tissue. Thus, inflammation must be adequately controlled.

Inflammation also triggers systemic reactions; the best known of which is fever, reflecting the influence of inflammatory mediators on areas of the central nervous system (CNS) controlling body temperature. Inflammation also impacts the peripheral/systemic nervous system (SNS): sensory neurons innervating the

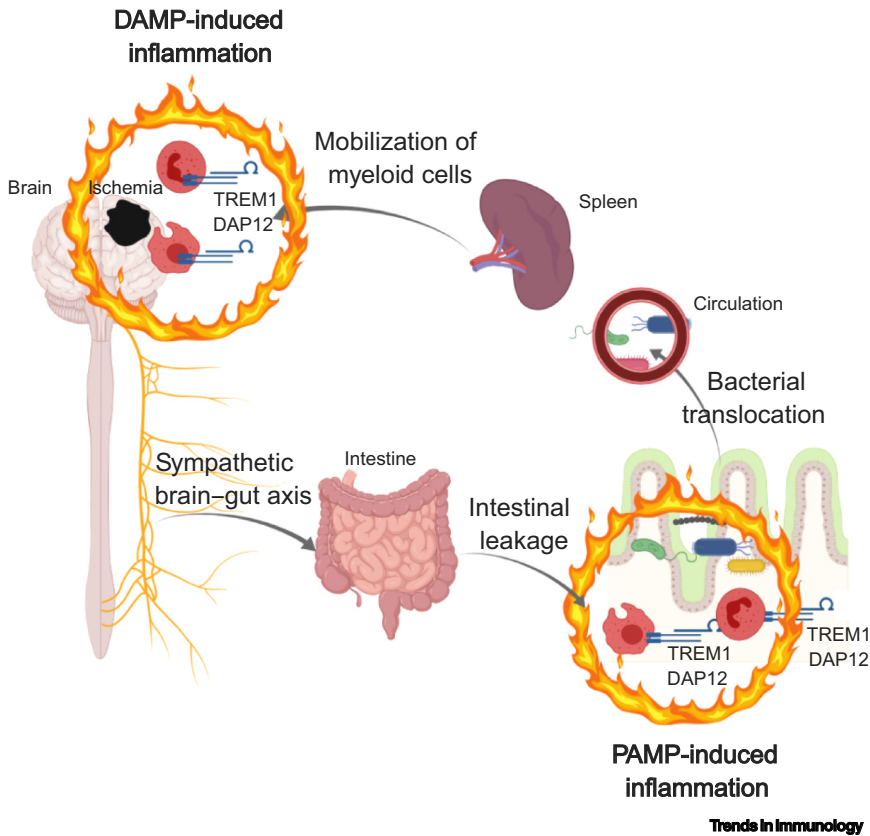
inflammatory site generate inputs that trigger complex somatic and autonomic reflex arcs, affecting both local and distal locations [1,2]. Indeed, the involvement of the CNS and the SNS in inflammation can constitute a double-edged sword that not only promotes defense mechanisms, but can also engender detrimental effects (e.g., excessive body temperature) and enable the unwarranted involvement of vital organs, such as the intestine.

Granulocytes and macrophages express a broad array of activating receptors, including Toll-like receptors and NOD-like receptors, detecting distinct types of tissue injury to elicit inflammatory responses. One of these receptors, triggering receptor expressed on myeloid cells 1 (TREM1), is a cell surface receptor expressed on neutrophils and inflammatory macrophages derived from blood monocytes, which has a crucial role in amplifying the inflammatory response [3]. TREM1 forms a complex with transmembrane adaptor DAP12 and, upon TREM1 engagement, a protein tyrosine kinase Syk-mediated cascade of tyrosine phosphorylation is initiated, activating multiple downstream mediators (e.g., PLC $\gamma$ , PI-3K, and MAPK). This cascade promotes the neutrophil- and macrophage-mediated release of proinflammatory cytokines and/or chemokines, as well as their migration [4].

Previous studies have shown that pathogenic infections induce TREM1 expression on neutrophils and inflammatory macrophages infiltrating the injured site from the blood, but not on tissue-resident macrophages [3]; in turn, TREM1 amplifies inflammation in the context of sepsis and multiple bacterial infections [3,5]. A recent study by Liu *et al.* has extended the role of TREM1 to sterile inflammation [6] (Figure 1). While infections trigger inflammation via the release of microbial products known as pathogen-associated molecular patterns (PAMPs), sterile inflammation is induced by physical, chemical, and metabolic injuries that

damage tissues, allowing the release of nuclear and/or cytosolic molecules [e.g., high mobility group box-1 (HMGB-1) and ATP], known as damage-associated molecular patterns (DAMPs). Sterile inflammation occurs during atherosclerosis, myocardial infarction, kidney ischemia, nonalcoholic and alcoholic steatohepatitis, and drug-induced liver injury. Liu and colleagues focused on a human disease known as transient focal cerebral ischemia, stemming from a blood clot blocking a cerebral vessel [6]. While ischemia causes cell death and tissue damage, re-establishment of blood flow paradoxically results in further tissue damage from the infiltration of myeloid cells, promoting inflammation. To recapitulate this disease in mice, Liu *et al.* performed transient middle cerebral artery occlusion-reperfusion (MCAo): this model triggers sterile inflammation with a strong influx of myeloid cells into the ischemic area, including neutrophils and inflammatory macrophages. These cells are mobilized primarily from the spleen in response to chemoattractants released from the ischemic tissue.

The authors noticed that neutrophils and inflammatory macrophages infiltrating the ischemic brain exhibited high expression of TREM1 relative to controls [6]. Given its role as an inflammation amplifier, Liu and coworkers examined whether TREM1 impacted disease in the MCAo model. Indeed, *Trem1*<sup>-/-</sup> mice presented significantly smaller infarct volumes and improved neurological scores following MCAo, and more animals survived the procedure, compared with wild-type (WT) mice. RNA-seq analysis of ischemic versus nonischemic hemispheres showed that TREM1 deficiency paralleled the expression of genes controlling antioxidant glutathione metabolism and lysosomal pathways, concurring with cerebral protection [6]. Moreover, lack of TREM1 was mirrored by increased expression of TREM2, another myeloid cell receptor associated with DAP12 and shown to mediate protective functions in the brain



**Figure 1. Double Impact of the Triggering Receptor Expressed on Myeloid Cells 1 (TREM1)-DAP12 Complex during Stroke.** During stroke, sterile inflammation occurs in the brain ischemic area, which is infiltrated by neutrophils and inflammatory macrophages expressing the TREM1-DAP12 complex. These myeloid cells are recruited primarily from the spleen reservoir. In tandem, stroke activates a sympathetic brain-gut axis, which heightens intestinal permeability and facilitates the translocation of bacteria through the intestinal barrier into the circulation. In turn, bacterial translocation elicits intestinal inflammation via recruitment of neutrophils and inflammatory macrophages expressing the TREM1-DAP12 complex. Abbreviations: DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern.

during neurodegeneration [6,7]. To further explore the potential of TREM1 as a putative therapeutic target, the authors treated mice undergoing MCAo with the LP17 peptide spanning the complementary-determining region 3 region of TREM1 and acting as a TREM1 decoy to prevent cell membrane TREM1 binding to its putative ligands [8]. Early treatment of mice at the time of reperfusion resulted in remarkable improved neurological scores, smaller infarct volumes, less infiltration of inflammatory macrophages, and increased survival, relative to WT mice; these findings recapitulated the *Trem1*<sup>-/-</sup> mouse phenotype. Treatment at a later time point led to improved

neurological scores and smaller infarct volumes, but did not affect survival, suggesting that TREM1 blockade at the onset of inflammation is crucial to achieving overall survival [6].

The most surprising finding came from the analysis of whole-body TREM1 expression after MCAo, using positron electron tomography (PET) [6]. By monitoring MCAo mice injected with a <sup>64</sup>Cu-labeled anti-TREM1 antibody, an increased TREM1 signal after cerebral ischemia was reported not only in the brain and spleen, but also in the intestine, relative to sham-treated mice. How could stroke

induce TREM1 expression in the gut? Stroke is known to activate the SNS, affecting the balance between adrenergic and cholinergic signaling remotely, within the submucosal plexus in the gut. Activation of this brain-gut axis impairs host antibacterial and intestinal barriers and increases gut permeability, thereby promoting the translocation and dissemination of commensal bacteria [9]. Thus, one consequence of bacterial translocation (revealed by PET), was the induction of TREM1 expression on gut inflammatory macrophages amplifying intestinal inflammation and, in turn, exacerbating intestinal barrier leakage and systemic inflammation. Accordingly, tempering of sympathetic signaling by  $\beta$ -adrenergic blockade with propranolol curbed TREM1 expression in the gut, blood, and splenic macrophages relative to controls [6].

The study by Liu *et al.* shows that, although sterile and nonsterile inflammation are usually viewed as distinct, they in fact occur simultaneously and enhance each other during and after stroke [6]. Indeed, genetic deletion or pharmacological blockade of TREM1 subdued both types of inflammation ('killing two birds with one stone'). TREM1 amplified inflammatory responses to both DAMPs in the brain and PAMPs in the gut, thereby aggravating poststroke inflammation and tissue damage and jeopardizing survival [6]. Thus, blockade of TREM1 might effectively dampen both of these mechanisms and, if performed early enough, might substantially improve pathology and clinical outcomes following a stroke, although this warrants further investigation. TREM1 has also been implicated in kidney ischemia-reperfusion injuries and liver fibrosis [10,11]; thus, it will be interesting to test whether these pathways also lead to intestinal leakage and TREM1-mediated gut inflammation in these cases.

In addition to its therapeutic significance, the study by Andreasson's laboratory

may have important prognostic ramifications [6]. For instance, TREM1 is cleaved from the cell surface of granulocytes and inflammatory macrophages by proteases activated at inflammatory sites, leading to the release of a soluble form of TREM1 [8]. Thus, the amount of soluble TREM1 in circulation during stroke might provide a useful putative marker to estimate, to some extent, the amount of tissue damage, and ideally predict the outcome of disease. Finally, recent work has shown that TREM1 expression can be induced on myeloid cells not only by PAMP and DAMPs, but also by oxysterols released by tumor cells [12]. Therefore, it will be important to evaluate the role of TREM1-induced inflammation in tumor microenvironments where myeloid cells can suppress antitumor immunity: indeed, will

TREM1 blockade harbor any therapeutic efficacy?

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