SEPSIS

New route to sepsis therapy

> “the anti-depressant fluvoxamine, an S1R agonist, protected mice from lethal septic shock”

There are currently very few therapeutic options for sepsis, in which uncontrolled systemic inflammation can lead to multiple organ failure. Now, writing in *Science Translational Medicine*, Gaultier and colleagues report that the endoplasmic reticulum (ER) sigma 1 receptor (S1R) is a critical regulator of ER-stress-driven inflammation. Furthermore, the antidepressant fluvoxamine, an S1R agonist, protected mice from lethal septic shock.

The role of the ER in the control of inflammatory signalling is increasingly being recognized. Inositol-requiring enzyme 1 (IRE1) is a major ER stress sensor that regulates inflammatory cytokine production via both its endonuclease activity and transcriptional regulation, and the control of cellular signalling pathways. Although IRE1 represents an interesting therapeutic target, its function is critical during homeostasis; therefore, the identification of alternative methods for targeting IRE1 signalling is necessary.

S1R is an ubiquitously expressed, ER-resident chaperone protein that associates with IRE1 during ER stress. Gaultier and colleagues therefore set out to determine whether S1R participates in ER-mediated inflammation and whether it might therefore represent a potential therapeutic target.

First, the authors investigated whether S1R modulates IRE1 activity during inflammation. In mouse bone marrow-derived macrophages (BMDMs), S1R knockout (KO) increased lipopolysaccharide (LPS)-induced IRE1 endonuclease activity and elevated expression of pro-inflammatory cytokines interleukin-6 (IL-6) and IL-1β. Conversely, overexpression of S1R in HEK293 cells decreased IL-8 production following LPS stimulation. Notably, the IRE1 inhibitor 4μ8C blunted the augmented inflammatory response in S1R-KO cells.

Next, the authors studied the effect of S1R KO in vivo. Following injection with a sublethal dose of LPS, 62% of S1R-KO mice died, in conjunction with significantly increased serum tumour necrosis factor-α and IL-6 levels, whereas wild-type mice experienced very low mortality (9%). The IRE1 inhibitor STF-083010 (which has a longer in vivo half-life than 4μ8C) spared S1R-KO mice from LPS-induced mortality, demonstrating that increased IRE1 activity is responsible for the reduced survival of S1R-KO mice.

Similarly, in the faecal-induced peritonitis (FIP) model of sepsis, mice deficient in S1R experienced significant mortality compared with wild-type mice, which correlated with increased serum IL-6 and lowered core body temperature. In addition, markers of liver, kidney and heart dysfunction were elevated in S1R-deficient mice.

The authors then assessed the potential of S1R as a pharmacological target. Co-injection of wild-type mice with LPS and fluvoxamine — a selective serotonin reuptake inhibitor with low nanomolar affinity to S1R and reported anti-inflammatory properties — protected wild-type mice (but not S1R-deficient mice) from mortality and reduced levels of serum IL-6.

Fluvoxamine was also therapeutically effective in ongoing mouse models of sepsis. Intraperitoneal treatment of mice with fluvoxamine 90 min after LPS treatment or FIP induction, when animals presented with clinical signs of sepsis, significantly enhanced survival. Fluvoxamine was as efficacious as ceftriaxone, an antibiotic currently used as a standard of care for patients with sepsis.

Importantly, fluvoxamine exerted anti-inflammatory effects in heparinized peripheral blood from healthy human donors stimulated ex vivo with LPS.

In summary, this study has identified S1R as a regulator of IRE1 function during inflammation and as a possible therapeutic target to treat bacterial-derived inflammatory pathology. The authors are currently looking for collaborators to assess the clinical potential of fluvoxamine in the treatment of inflammation and sepsis. They note that this approach would likely be most effective if begun as early as possible after sepsis diagnosis to overlap with the initial cytokine storm.

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ORIGINAL ARTICLE Rosen, A. et al. Modulation of the sigma-1 receptor–IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. *Sci. Transl Med.* **11**, eaau5266 (2019)