INFLAMMATION

Hope for sepsis treatment

The incidence of sepsis (and death from septic shock) is increasing, and treatments are still inadequate. Now a study in *Science* offers promise for a new treatment option involving blockade of sphingosine kinase 1 (SPHK1), which protected mice from lethal and uncontrolled systemic inflammation induced by bacterial products or polymicrobial sepsis.

Consistent with previous studies describing a link between SPHK1 and the inflammatory response, SPHK1 expression was found to be highly upregulated in neutrophils and macrophages stimulated with various bacteria or bacterial components, including lipopolysaccharide (LPS). Moreover, silencing of SPHK1 expression, using small interfering RNA (siRNA) or the specific inhibitor 5c, led to failed activation of nuclear factor- κ B (NF- κ B) and reduced production of the pro-inflammatory cytokines tumour necrosis factor, interleukin-1 β (IL-1 β) and IL-6 by LPS-stimulated macrophages, but it had no effect on interferon responses. Innate immune cells isolated from the peritoneal cavity of patients with septic shock showed a similar abrogation of inflammatory responses following treatment with 5c.

Next, the authors tested the effects of SPHK1 blockade on two mouse models of sepsis — the first involving intraperitoneal injection

of a lethal dose of LPS and the second involving caecal ligation and puncture (CLP) to trigger polymicrobial sepsis. 100% of mice survived the lethal LPS injection if they were pretreated with SPHK1-targeted siRNA. These mice showed lower levels of inflammatory cytokines in the blood and reduced immune cell infiltration of the liver and lungs. SPHK1-specific siRNA and 5c also protected mice against CLP-induced systemic inflammation and mortality. Blockade of SPHK1 with 5c was most effective (100%) if given 2 hours after CLP, and it had much reduced efficacy (10%) if given 12 hours after CLP. However, combined treatment with 5c and the broad-spectrum antibiotic co-amoxiclav (which is currently used to treat patients with sepsis) had synergistic effects, extending the time window for treatment and resulting in better outcomes than either drug alone.

It is therefore hoped that administration of SPHK1 inhibitors — alone or in combination with antibiotics — might prove to be a useful treatment for septic shock in humans.

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ORIGINAL RESEARCH PAPER Puneet, P. et al.
SphK1 regulates proinflammatory responses associated with endotoxin and polymicrobial sepsis. *Science* **328**, 1290–1294 (2010)