



## A venomous relationship: Inflammation, the gut barrier and the STING pathway



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Sepsis kills over 6 million people annually worldwide and leads to long-term devastating health consequences for many survivors [1]. Despite an expanding understanding of its pathophysiology, early antibiotic administration and supportive care remain the only effective therapy for sepsis. Given the high morbidity and mortality and the absence of adjuvant therapy, novel insights and potential therapeutic targets are urgently needed.

The gut has long been hypothesized to be the “motor” of sepsis, playing a key role in both initiating and propagating critical illness [2]. Sepsis induces profound disturbances in the gut epithelium, immune system and microbiome in patients and in mechanistic animal studies [3]. Targeting intestinal integrity (permeability, apoptosis, pathobiome) leads to improved survival in rodent models of sepsis [4]. The mechanisms through which targeting intestinal integrity are diverse; however, one common theme is that host inflammation – both locally and systemically – can be directly modulated by changing the complex microenvironment of the gut, in which a single cell epithelium separates the host from 40 trillion microbes living inside at an interface with the largest number of lymphocytes in the body.

The stimulator of interferons genes (STING) is an adaptor protein, which modulates the innate immune response to both bacterial products and host DNA after nuclear DNA damage or mitochondrial disruption [5]. STING signalling has previously been shown to a) help maintain gut homeostasis, b) modulate gut barrier dysfunction following chemotherapy, and c) alter the host inflammatory response in sepsis [6,7]. As such, Hu et al. examined the role of the STING pathway in the intestine in patients with intra-abdominal sepsis and in mechanistic studies in septic mice (REFERENCE EBIO MEDICINE 2019). Intestinal biopsies taken from five patients with complicated enterocutaneous fistulas were compared to biopsies from a similar number of controls undergoing elective surgery. Septic patients had elevated STING expression, predominantly in the lamina propria, and this was associated with increased histological injury and evidence of elevated apoptosis.

Further, intestinal inflammation was correlated to STING expression and intestinal interferon regulatory factor3 (IRF3) and nuclear factor-kappaB (NF-κB) activation were also increased in septic patients, which is notable since STING signalling induces both of these, leading to enhanced type 1 interferon and inflammatory cytokine expression. These results suggested a possible role for STING signalling in the pathophysiology of sepsis and mediating intestinal dysfunction. While these pilot studies had the benefit of sampling intestinal tissue from live septic patients – which is technically challenging and extremely rare in the literature – they were associative in nature.

The authors therefore examined wild type and STING knockout mice subjected to cecal ligation and puncture. Knockout mice had improved survival following sepsis. This was associated with improved intestinal histology, decreased intestinal inflammation and decreased apoptosis. Further, septic knockout mice had improvements in intestinal barrier function, associated with improvements in the tight junction proteins ZO-1 and occludin. In contrast, the STING agonist DMXAA induced the opposite effects with worsened mortality, histologic damage, inflammation and barrier dysfunction.

Taken together, these results convincingly add to existing literature that STING plays a role in mediating mortality from sepsis in rodents and is, at least, associated with intestinal damage in septic patients. It is important not to overinterpret the results obtained. STING knockout mice have a germline deletion of the protein, and STING deletion positively impacted the lung, the liver and the kidney as well as systemic inflammation. Without tissue-specific STING knockouts, there is no way to know how much of the improvement in the gut is due to a direct effect of STING signalling as opposed to a secondary effect. Further, knockout mice have a lifelong genetic deletion of the protein. As such, this can be considered a pre-treatment model since animals did not have STING prior to the onset of sepsis. The optimal timing to block the STING pathway after sepsis is unclear, especially considering the theoretical possibility of dampening innate immunity by inhibiting STING. A pharmacologic approach targeting STING would be more clinically relevant, and while the authors demonstrated that augmenting STING leads to worse outcomes, this does not inherently mean that pharmacologic deletion would improve outcome. In addition, subunits of NF-κB were augmented in sepsis, which was further exacerbated by the STING agonist DMXAA. In theory, blocking this would be beneficial; however,

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mice lacking NF- $\kappa$ B in their intestinal epithelium actually have increased mortality following sepsis [8]. In addition, the sepsis model utilized in these studies had a mortality of 75% which is significantly higher than that seen in patients. Considering that a survival benefit is not present in STING knockouts following cecal ligation and puncture with a more clinically relevant 35% mortality [9], this leads to questions about the generalizability of the findings. While each of these concerns preclude the rapid translatability of targeting STING for therapeutic gain in patients, the study by Hu et al., adds to a growing knowledge of STING biology in sepsis and gut injury in sepsis that may one day lead to pharmacologic intervention to improve outcomes in a disease that still carries a remarkably high mortality.

#### Author disclosure

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