Microbial metabolite harmaline protects against virus-induced systemic inflammation

This work shows that *Akkermansia muciniphila* and its metabolite, harmaline, upregulate the production of bile acid-coenzyme A: amino acid *N*-acyltransferase (BAAT) in hepatocytes. As a result of enhanced BAAT production, increased synthesis of conjugated primary bile acids suppresses the severe systemic inflammation caused by severe fever with thrombocytopenia syndrome virus infection.

This is a summary of:
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The problem

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease caused by SFTS bunyavirus (SFTSV, also known as Huaiyangshan banyangvirus), a Phlebovirus in the *Bunyaviridae* family[1]. Some infected patients develop severe symptoms including haemorrhagic fever, encephalitis and multiple organ dysfunction syndrome, which carries a high mortality rate of 12–50% because of the overwhelming virus-induced production of proinflammatory cytokines[2]. As no antiviral treatments or vaccines are currently available for SFTS, therapeutic inventions that can dampen and redirect SFTSV-induced severe inflammatory responses and, ultimately, exert antiviral effects are urgently needed. The intestinal microbiome can inhibit viral infections both locally and systemically through microbial metabolites or constituents[3]. Thus, a mechanistic understanding of the molecular links between microbiota-derived metabolites and SFTSV-induced inflammatory responses is crucial for the development of microbiome-associated therapy for SFTSV infection.

The discovery

We described the important role of a commensal bacterium, *Akkermansia muciniphila*, in protection from the life-threatening effects of SFTSV infection by screening the intestinal microbiomes of recovered and deceased patients with SFTS (Fig. 1a) and performing faecal microbiota transplantation assays in an antibiotic-treated mouse model. In *A. muciniphila*-colonized, antibiotic-treated or germ-free mice, SFTSV infection resulted in substantially alleviated systemic inflammation. Untargeted metabolomics of serum samples from patients with SFTSV infection revealed markedly increased bile acid levels in those who survived, but not in those who succumbed, and bile acid levels were positively correlated with *A. muciniphila* abundance in the gut. We further demonstrated that two bile acids, glycochenodeoxycholic acid (GCDCA) and taurochenodeoxycholic acid (TCDCA), protect against SFTS by suppressing systemic inflammatory responses in mice. These phenotypes correlated with greatly upregulated expression of bile acid-coenzyme A: amino acid *N*-acyltransferase (BAAT) in hepatocytes of *A. muciniphila*-colonized antibiotic-treated and germ-free mice.

Liquid chromatography with tandem mass spectrometry analysis of *A. muciniphila* culture supernatants revealed that harmaline, a β-carboline alkaloid, enhances TCDCA production by upregulating BAAT production in hepatocytes (Fig. 1b), and that increased BAAT levels protected against SFTSV-induced severe inflammatory response syndrome in mice. Finally, we determined that GCDCA suppresses SFTSV-induced inflammatory responses via downregulating the activity of nuclear factor (NF)-κB in a manner dependent on G-protein coupled bile acid receptor 1 (TGR5) and independent of bile acid receptor (also known as farnesoid X-activated receptor). Taken together, we demonstrated that harmaline, a metabolite secreted by the commensal bacterium *A. muciniphila*, possesses probiotic effects that mitigate systemic inflammatory responses to viral infection through a bile acid–TGR5–NF-κB signalling axis.

The implications

We identified a microbiota–bile acid–inflammation axis that integrates metabolic and immune system cues to modulate host inflammatory responses during SFTSV infection in mice. Our findings build on very limited understanding of the signalling pathways that link host anti-inflammatory responses with microbial metabolites under systemic viral infection. More importantly, our work might have implications for the rational design of microbiome-based diagnostic and therapeutic agents for individuals at risk of life-threatening systemic infection.

As an efficient, standardized approach to genetically manipulate *A. muciniphila* is lacking, the gene(s) responsible for harmaline synthesis have not been characterized. Therefore, we could not establish a harmaline gene-silenced *A. muciniphila* strain to build direct correlations between *A. muciniphila* and harmaline production. Future studies need to be performed to identify which genes are involved in harmaline synthesis within the genome of *A. muciniphila*, and to understand the specific mechanisms through which *A. muciniphila*-synthesized harmaline mitigates the systemic consequences of SFTSV infections. Research is still needed to determine the missing molecular link between bile acid signalling and suppression of NF-κB during SFTSV infection to facilitate a deeper understanding of how the therapeutics work.

Shu J. Zhu[1] & Wei Liu[2]
[1]Center for Veterinary Sciences, Zhejiang University, Hangzhou, China.
[2]Beijing Institute of Microbiology and Epidemiology, Beijing, China.

EXPERT OPINION

"The role of the microbiota in the outcome of viral infections is increasingly appreciated, but it has been difficult to pinpoint the specific contributions of individual bacterial species. Xie et al. propose that harmaline secreted by *Akkermansia muciniphila* mitigates inflammatory disease during systemic viral infection through the bile acid–TGR5–NF-κB signalling axis. It is particularly impressive that the authors were able to start with patient samples and arrive at a mechanistic model." **Ken Cadwell, New York University Grossman School of Medicine, New York, NY, USA.**

FIGURE

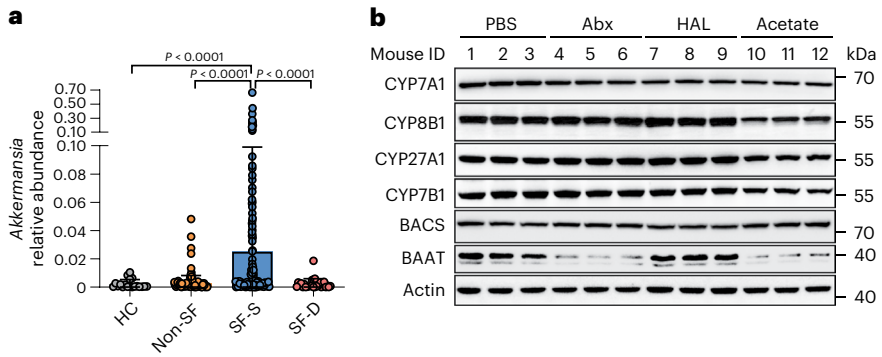

Fig. 1 | The relative abundance of harmaline-producing *A. muciniphila* correlates with the outcome of SFTSV infection. a, The relative abundance of *Akkermansia* spp. among healthy control (HC) individuals, patients with non-SFTSV febrile infection (Non-SF), surviving patients with SFTSV (SF-S) and deceased patients with SFTSV (SF-D). Screening of faecal samples from 260 hospitalized patients with SFTSV infection showed that the relative abundance of *A. muciniphila* was significantly higher in the SF-S than the SF-D group. **b**, Western blot of bile acid biosynthesis enzymes in mouse liver cells, 5 days after treatment with phosphate buffered saline (PBS), antibiotics (Abx), harmaline (HAL) or acetate. Harmaline markedly increased the production of BAAT but not that of cytochrome P450 family members CYP7A1, CYP8B1, CYP27A1 and CYP7B1 or bile acyl-coenzyme A synthetase (BACS) in the livers of antibiotic-treated animals.

BEHIND THE PAPER

This project was born when S.J.Z. approached W.L. in May 2019 with the idea of collaborating to study the infectious microecology of SFTSV. The W.L. laboratory has been studying the epidemiology, virology and pathogenesis of SFTSV for years and seeking to interpret SFTSV-induced systemic inflammation from a novel angle. The S.J.Z. laboratory mainly focuses on the mechanisms of how microbiota-associated metabolites (including short-chain fatty acids, bile acids and polyamines) act on host mucosal innate immune systems in the context of infection or inflammation. Brainstorming between these two young principal investigators catalysed a successful collaboration achieved by frequent discussion and unremitting efforts by the members of both laboratories under the very difficult circumstances of the COVID-19 pandemic. We believe this work offers an excellent example of how combining clinical and mechanistic studies using data from patients and animal models could ultimately translate into microbiome-based diagnostics and therapeutics for individuals at risk of critical systemic infection. **S.J.Z.**

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FROM THE EDITOR

"Here the authors focus on a relatively understudied tick-borne viral infection and find that *Akkermansia muciniphila*, a commensal gut microorganism with increasing relevance to host health, produces the metabolite harmaline that can indirectly modulate bile acid signalling to generate an anti-inflammatory response during infection. Given the increasing threat of emerging infectious viral diseases, understanding the role of the microbiome and its potential for therapeutic intervention is critical." **Emily White, Senior Editor, *Nature Microbiology*.**