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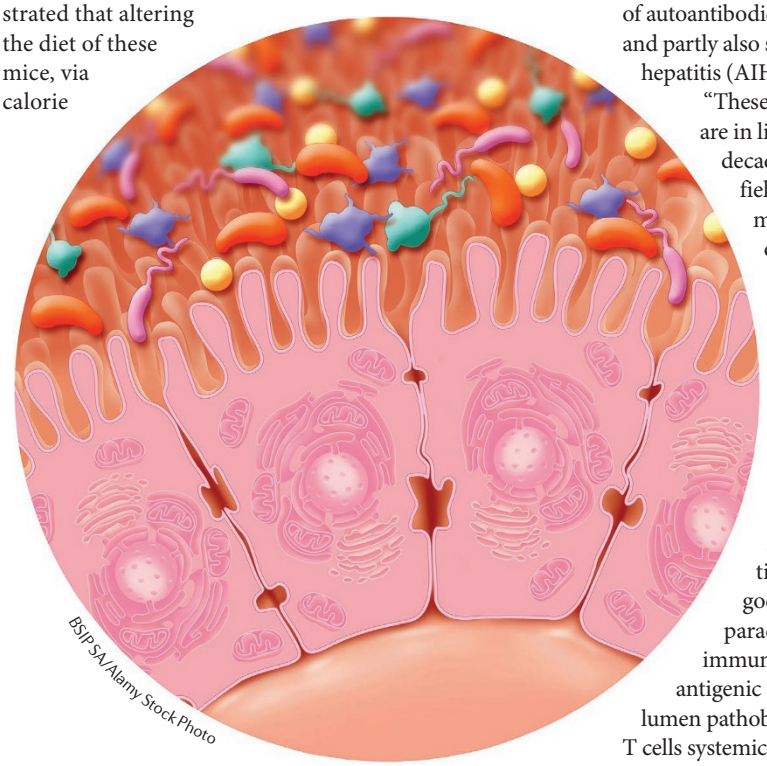
SYSTEMIC LUPUS ERYTHEMATOSUS

Escape of gut microbe to the liver drives autoimmunity

Translocation of a gut microbe, *Enterococcus gallinarum*, to the liver and other systemic organs drives autoimmunity in lupus-prone mice, according to the results of a new study. Vieira et al. demonstrate that antibiotic treatment or vaccination against this bacterial strain prevents disease in a mouse model of systemic lupus erythematosus (SLE).

"A unique feature of the model we studied is that the mice die from antiphospholipid syndrome (APS), an autoimmune clotting disorder frequently associated with SLE in humans," explains Martin Kriegel, corresponding author of the study. A previous study had demonstrated that altering the diet of these mice, via calorie restriction, prevented mortality. "As dietary changes are a major modulating factor of the gut microbiota we investigated the role of the gut microbiome in this model," Kriegel adds.

> "Antibiotic treatment or intramuscular vaccination against *E. gallinarum*... suppressed autoimmune manifestations"



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The gut barrier normally prevents the passage of bacteria to other organs. However, in the lupus-prone mice, gut barrier function was impaired and the mice had notable growth of *E. gallinarum* in their veins, mesenteric lymph nodes and liver. "An important finding was that *E. gallinarum* alone, when colonizing the gut of germ-free non-autoimmune-prone mice, was sufficient to break the gut barrier and lead to induction of autoantibodies typical [of] SLE and partly also seen in autoimmune hepatitis (AIH)," remarks Kriegel.

"These elegant findings are in line with over two decades of research in the field where intestinal microbes have been demonstrated to initiate or perpetuate local and systemic autoimmunity," explains Jose Scher, who was not involved in this study. "The novelty here is related to the finding of the microbe in distal tissues. This concept goes against the current paradigm of systemic autoimmunity being triggered by antigenic determinants of gut lumen pathobionts but executed by T cells systemically."

Antibiotic treatment or intramuscular vaccination against *E. gallinarum* reduced bacterial translocation to the liver, suppressed autoimmune manifestations, including the induction of pathogenic autoantibodies and T helper 17 (T_H17) cells, and prolonged the survival of the lupus-prone mice. Furthermore, disruption of the aryl hydrocarbon receptor (AhR) pathway (which is a known activator of T_H17 cells and can be induced via bacterial ligands) with an AhR antagonist reduced *E. gallinarum*-mediated induction of T_H17 cells and autoantibodies, suggesting the involvement of this pathway in *E. gallinarum*-induced autoimmunity.

"The most notable findings, however, might be that we identified DNA of the … same species (*E. gallinarum*) in the liver of patients with SLE or AIH," remarks Kriegel. Most of these patients also had elevated serum levels of antibodies towards *E. gallinarum* RNA, compared with healthy individuals. Coculture of primary human or murine hepatocytes with *E. gallinarum* or *E. gallinarum* RNA induced the expression of autoantigens (including endogenous retroviral proteins and AhR) and type I interferon.

"We are working on developing a standardized test for this gut commensal as well as other commensal microbes in human diseases," explains Kriegel. "We also would like to translate the interventional work performed in animals to humans with the hypothesis that depleting this pathobiont in the right patient population would lead to remission of autoimmune disease without the need for conventional immunosuppression."

Jessica McHugh

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