SYSTEMIC LUPUS ERYTHEMATOSUS

The choroid plexus: a cellular site of entry into the brain in NPSLE?

The pathogenesis of neuropsychiatric systemic lupus erythematosus (NPSLE) is incompletely understood. In a new study, detailed phenotypic analysis has revealed the presence of tertiary lymphoid structures (TLSs) in the choroid plexus of lupus-prone mice and provides evidence that the choroid plexus can serve as a site for lymphocyte migration into the brain.

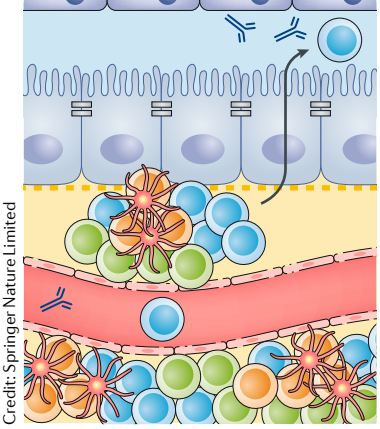
"The prevailing understanding of the pathogenesis of NPSLE implicates dysfunction of brain barriers, consequently exposing the brain to systemic neurotoxic agents," explains Ayal Ben-Zvi, co-author on the new study. "Most of the focus to date had been on the blood brain barrier; however, the blood-cerebrospinal fluid barrier, at the choroid plexus, has long been implicated in human NPSLE."

Previous studies had identified extensive cellular infiltrates in the choroid plexus of lupus-prone MRL/lpr mice. "Reports of the presence of TLSs in tissues affected by chronic inflammation in autoimmune diseases led us to hypothesize that the marked cellular infiltration may in fact be consistent with a TLS," says lead author Ariel Stock.

Immunofluorescence and transcriptomic analysis of these infiltrates revealed important features of TLSs, including follicular helper T cells, germinal centre B cells and IgG-producing plasma cells, as well as cytokine and chemokine signatures associated with lymphoid organization and aggregation.

Using transmission electron microscopy, the investigators also found evidence of lymphocyte transepithelial migration in the choroid plexus, suggesting a possible alternative route into the brain than through the parenchymal blood brain barrier. Histological evaluation of brain autopsy samples from patients with SLE also revealed the choroid plexus as a site of leukocyte migration in some patients.

> "the investigators… found evidence of lymphocyte transepithelial migration in the choroid plexus"



Credit: Springer Nature Limited

"Although we were able to demonstrate a temporal association between the development of TLSs and the appearance of neuropsychiatric deficits in the mouse model, it will be important in future studies to conclusively establish the pathogenic contribution of these lymphoid structures to NPSLE," states corresponding author Chaim Putterman.

Jessica McHugh

ORIGINAL ARTICLE Stock, A. D. et al. Tertiary lymphoid structures in the choroid plexus in neuropsychiatric lupus. *JCI. Insight.* https://doi.org/10.1172/jci.insight.124203 (2019)
FURTHER READING Schwartz, N., Stock, A. D. & Putterman, C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. *Nat. Rev. Rheum.* **15**, 137–152 (2019)

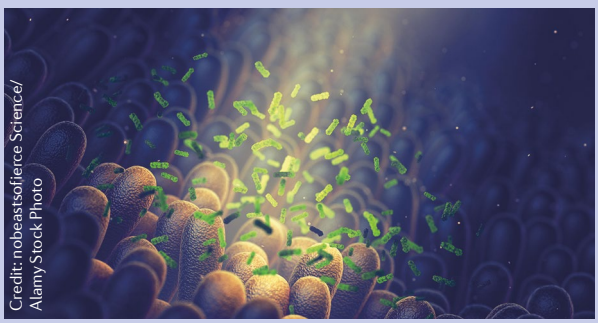
ANTIPHOSPHOLIPID SYNDROME

Gut commensal implicated in APS

β_2-glycoprotein I (β_2GPI) is a major autoantigen in antiphospholipid syndrome (APS). New findings implicate the human gut commensal *Roseburia intestinalis* in the development and maintenance of chronic autoimmune responses to this antigen in APS via cross-reactivity.

"To our knowledge, the human gut microbiome has not previously been linked with APS," says corresponding author Martin Kriegel. "Our study highlights the gut as a potential chronic trigger in patients with APS."

> "administration of *R. intestinalis* … triggered the development of anti-human-β_2GPI antibodies"



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Kriegel and colleagues found that *R. intestinalis* contains amino acid sequences that are highly homologous to sequences found in B cell and T cell epitopes within β_2GPI. Although the prevalence of this commensal was similar in individuals with anti-β_2GPI antibodies (including individuals with APS) and healthy individuals, anti-β_2GPI antibody-positive individuals had signs of chronic subclinical intestinal inflammation and systemic adaptive immune responses to *R. intestinalis*.

Furthermore, compared with healthy individuals, patients with APS had higher levels of antibodies that were cross-reactive with a bacterial DNA methyltransferase expressed by *R. intestinalis*, and levels of these antibodies correlated with levels of anti-β_2GPI antibodies in patients with APS.

Mice immunized with *R. intestinalis* lysates had higher levels of serum antibodies that could cross-react with human β_2GPI compared with sham-immunized mice. Importantly, oral administration of *R. intestinalis* in a mouse model of spontaneous APS triggered the development of anti-human-β_2GPI antibodies, as well as APS-related morbidity and mortality.

"An important finding was that an otherwise harmless bug, that is often considered beneficial, can be dangerous in patients who are genetically or otherwise prone to over-react to particular pieces of this gut microbe," explains Kriegel. "Selecting those patients who show reactivity to the bacterium and who have predisposing genes will be essential to identify who could possibly benefit in the future from attempts to remove this and similar cross-reactive triggers from the gut."

Jessica McHugh

ORIGINAL ARTICLE Ruff, W. E. et al. Pathogenic autoreactive T and B cells cross-react with mimotopes expressed by a common human gut commensal to trigger autoimmunity. *Cell Host Microbe.* https://doi.org/10.1016/j.chom.2019.05.003 (2019)