Multiple sclerosis discovery could end disease's chronic inflammation

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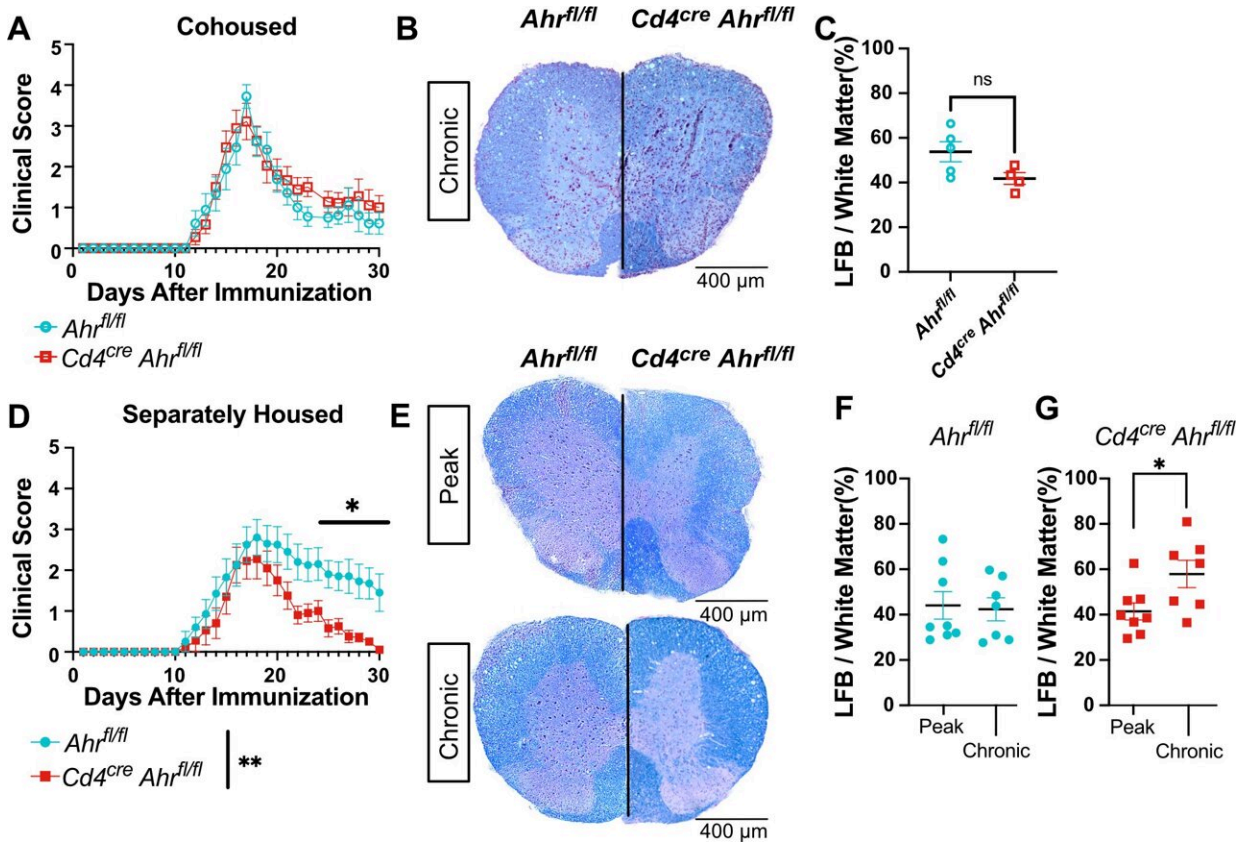

Separately housed $Cd4^{cre}Ahr^{fl/fl}$ recover from EAE with increased myelin staining at chronic phase. (A) Clinical score of $Cd4^{cre}Ahr^{fl/fl}$ and $Ahr^{fl/fl}$ mice cohoused (females; representative plot includes n = 9 mice/group; total replicates of N = 2 experiments). Spinal cords sections of $Cd4^{cre}Ahr^{fl/fl}$ and $Ahr^{fl/fl}$ were stained with Luxol fast blue and hematoxylin/eosin stain at day 31 post EAE induction (B) Representative images and (C) quantification of myelin stain. Images from 4 equally spaced spinal cord levels were averaged for each mouse. (n = 5 mice/group; unpaired t test p = 0.0706) (D) Clinical score of $Cd4^{cre}Ahr^{fl/fl}$

and $Ahr^{fl/fl}$ littermate controls separated at weaning (3 weeks of age). (Females; representative plot includes n = 8–9 mice/group; total replicates of N = 2 experiments; Mann–Whitney U test on total scores reported in legend [p = 0.0096] and on single days reported on plot) (E) Luxol fast blue with hematoxylin/eosin stain at the peak stage of EAE (day 16) and at chronic phase (day 31). (F) Quantification of myelin stain by Luxol fast blue alone in $Ahr^{fl/fl}$ mice and (G) $Cd4^{cre}Ahr^{fl/fl}$ mice. (n = 7–8 mice/group; N = 2 experiments; unpaired t tests [p = 0.8343, 0.0322]) Scale bars represent 400 μm. Error bars represent standard error from the mean. Credit: *PLOS Biology* (2023). DOI: 10.1371/journal.pbio.3002000

University of Virginia Health neuroscientists have discovered a potential way to disrupt the chronic inflammation responsible for multiple sclerosis.

UVA's new study identifies a vital contributor to the hyperactive autoimmune response and neuroinflammation that are the hallmarks of MS. Blocking this lynchpin in a research model of MS alleviated the inflammation, giving researchers a prime target in developing new treatments for multiple sclerosis and other autoimmune diseases.

The research was conducted by Andrea Merchak, a doctoral candidate in neuroscience, and her colleagues in the lab of Alban Gaultier of the University of Virginia School of Medicine's Department of Neuroscience and its Center for Brain Immunology and Glia, or BIG.

"We are approaching the search for multiple sclerosis therapeutics from a new direction," Merchak said. "By modulating the microbiome [the collection of microorganisms that naturally live inside us], we are making inroads in understanding how the immune response can end up out of control in autoimmunity. We can use this information to find early interventions."

Multiple sclerosis affects nearly a million Americans. Symptoms can include muscle spasms, stiffness, weakness, difficulty moving, depression, pain and more. There is no cure. Instead, treatments focus on helping patients manage symptoms, control flareups and slow the disease's progression.

Scientists have struggled to understand the causes of MS, but recent research suggests an important role for the gut microbiome. UVA's new findings bolster that, determining that an immune system controller found in "barrier tissues" such as the intestine plays a vital role in the disease. This regulator can reprogram the gut microbiome to promote harmful, chronic inflammation, the researchers found.

Gaultier and his collaborators blocked the activity of the regulator, called "aryl hydrocarbon receptor" in immune cells called T cells, which led to a dramatic effect on the production of bile acids and other metabolites in the microbiomes of lab mice. With this receptor out of commission, inflammation decreased and the mice recovered.

The findings suggest that doctors may one day be able to take a similar approach to interrupt the harmful inflammation in people with MS. That will take much more research, however. Scientists will need a better understanding of the interactions between the immune system and the microbiome, the UVA researchers say.

Still, UVA's new research lays an important foundation for future efforts at targeting the microbiome to reduce inflammation responsible for multiple sclerosis and other autoimmune diseases.

"Due to the complexity of the gut flora, probiotics are difficult to use clinically. This receptor can easily be targeted with medications, so we may have found a more reliable route to promote a healthy gut microbiome," Merchak said. "Ultimately, fine-tuning the immune

response using the microbiome could save patients from dealing with the harsh side effects of immunosuppressant drugs."

Gaultier and his collaborators have published their findings in the scientific journal *PLOS Biology*.

More information: Andrea R. Merchak et al, The activity of the aryl hydrocarbon receptor in T cells tunes the gut microenvironment to sustain autoimmunity and neuroinflammation, *PLOS Biology* (2023). DOI: 10.1371/journal.pbio.3002000

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