Exploring the gut-brain connection for insights into multiple sclerosis

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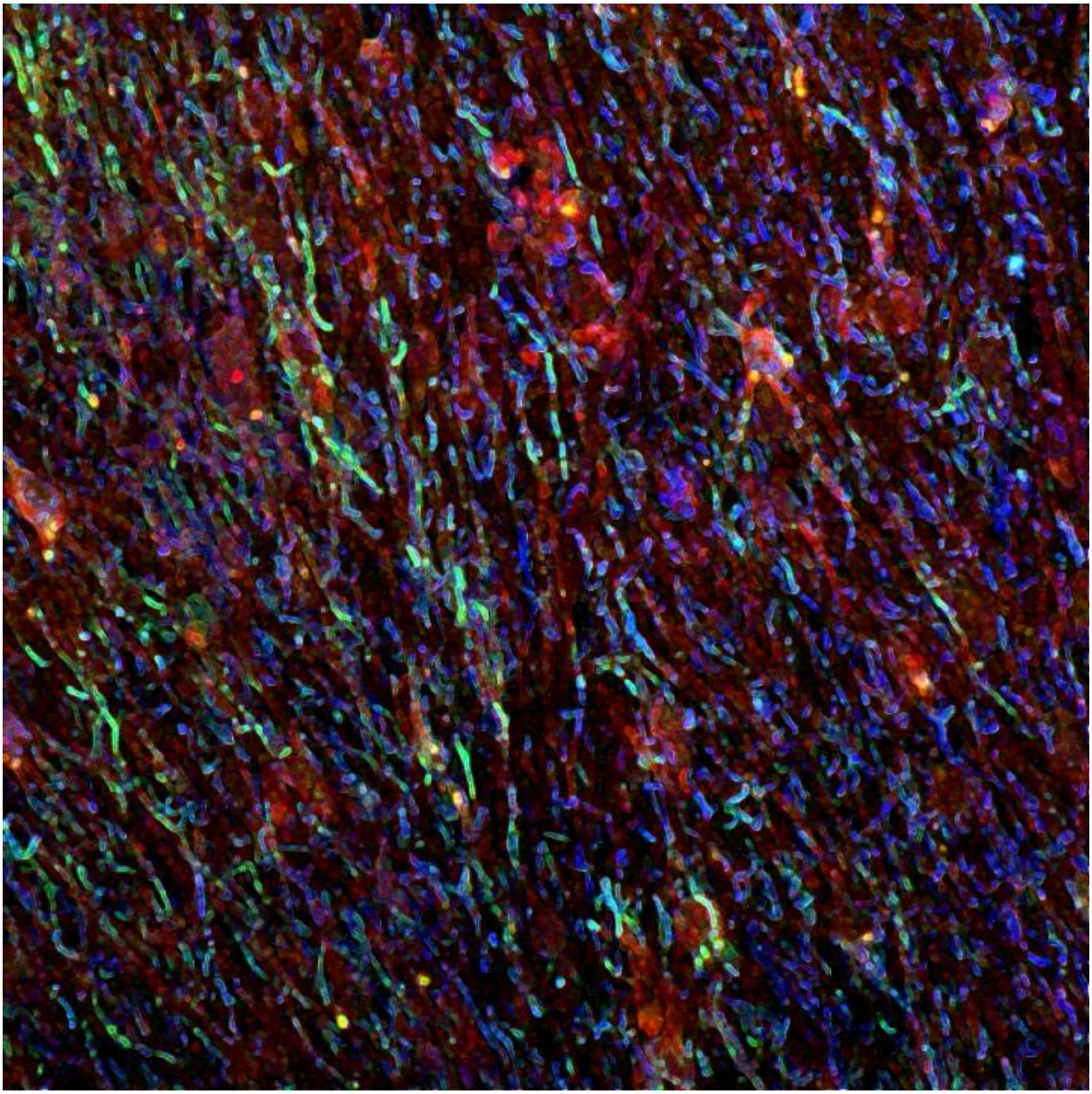

Immunofluorescence imaging of human brain tissue generated from an active lesion from an individual with multiple sclerosis shows astrocytes (blue), the Aryl hydrocarbon receptor (red) and the phosphorylated Signal transducer and activator of transcription 1 (green). Credit: Image courtesy of Jorge Ivan Alvarez, Assistant Professor at the Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

New research by investigators at Brigham and Women's Hospital (BWH) suggests that bacteria living in the gut may remotely influence the activity of cells in the brain that are involved in controlling inflammation and neurodegeneration. Using pre-clinical models for multiple sclerosis (MS) and samples from MS patients, the team found evidence that changes in diet and gut flora may influence astrocytes in the brain, and, consequently, neurodegeneration, pointing to potential therapeutic targets. The team's results are published this week in *Nature Medicine*.

"For the first time, we've been able to identify that food has some sort of remote control over central nervous system inflammation," said corresponding author Francisco Quintana, PhD, an investigator in the Ann Romney Center for Neurologic Diseases at BWH. "What we eat influences the ability of bacteria in our gut to produce small molecules, some of which are capable of traveling all the way to the brain. This opens up an area that's largely been unknown until now: how the gut controls brain inflammation."

Previous investigations have suggested a connection between the gut microbiome and brain inflammation, but how the two are linked and how diet and microbial products influence this connection has remained largely unknown. To explore this connection further, Quintana and colleagues performed genome-wide transcriptional analyses on astrocytes—star-shaped cells that reside in the brain and spinal cord - in

a mouse model of MS, identifying a molecular pathway involved in inflammation. They found that molecules derived from dietary tryptophan (an amino acid famously found in turkey and other foods) act on this pathway, and that when more of these molecules are present, astrocytes were able to limit brain inflammation. In blood samples from MS patients, the team found decreased levels of these tryptophan-derived molecules.

"Deficits in the gut flora, deficits in the diet or deficits in the ability to uptake these products from the gut flora or transport them from the gut—any of these may lead to deficits that contribute to disease progression," said Quintana.

The research team plans to investigate this pathway and the role of diet in future studies to determine if the new findings can be translated into targets for therapeutic intervention and biomarkers for diagnosing and detecting the advancement of disease.

More information: Veit Rothhammer et al, Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor, *Nature Medicine* (2016). DOI: 10.1038/nm.4106

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