NATURE MEDICINE | ARTICLE

Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor

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Nature Medicine (2016) doi:10.1038/nm.4106

Received 07 December 2015 Accepted 09 April 2016 Published online 09 May 2016

Abstract

Astrocytes have important roles in the central nervous system (CNS) during health and disease. Through genome-wide analyses we detected a transcriptional response to type I interferons (IFN-Is) in astrocytes during experimental CNS autoimmunity and also in CNS lesions from patients with multiple sclerosis (MS). IFN-I signaling in astrocytes reduces inflammation and experimental autoimmune encephalomyelitis (EAE) disease scores via the ligand-activated transcription factor aryl hydrocarbon receptor (AHR) and the suppressor of cytokine signaling 2 (SOCS2). The anti-inflammatory effects of nasally administered interferon (IFN)-β are partly mediated by AHR. Dietary tryptophan is metabolized by the gut microbiota into AHR agonists that have an effect on astrocytes to limit CNS inflammation. EAE scores were increased following ampicillin treatment during the recovery phase, and CNS inflammation was reduced in antibiotic-treated mice by supplementation with the tryptophan metabolites indole, indoxyl-3-sulfate, indole-3-propionic acid and indole-3-aldehyde, or the bacterial enzyme tryptophanase. In individuals with MS, the circulating levels of AHR agonists were decreased. These findings suggest that IFN-Is produced in the CNS function in combination with metabolites derived from dietary tryptophan by the gut flora to activate AHR signaling in astrocytes and suppress CNS inflammation.

Subject terms: Autoimmunity Neuroimmunology

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V.R., I.D.M., L.B., M.C.T., J.E.K., L.M., C.-C.C., H.K., J.I.A., M.B. and C.B.C. performed *in vitro* and *in vivo* experiments; B.P., R.Y., N.O. and N.P. performed bioinformatics analysis; N.A., G.I., C.B.C., A.P., S.J., M.P. and J.A. provided unique reagents, and discussed and/or interpreted findings; V.R. and F.J.Q. wrote the manuscript; and F.J.Q. designed and supervised the study and edited the manuscript.

Competing financial interests

The authors declare no competing financial interests.

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Supplementary information

PDF files

1. Supplementary Text and Figures (6,419 KB)
   Supplementary Figures 1–7 and Supplementary Table 1–4

Nature Medicine ISSN 1078-8956 EISSN 1546-170X