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An astrocytic axis

> dietary Trp supplementation ameliorated EAE symptoms in wild-type mice but not in mice lacking astrocytic AHR

The actions of astrocytes in CNS inflammation are influenced by various modulators and signals; however, little is known about the possible effects of peripheral modulators, such as diet and microbial products, on these cells. Using the experimental autoimmune encephalitis (EAE) mouse model of multiple sclerosis (MS), Quintana and colleagues show that gut-microbial metabolites of the dietary amino acid tryptophan (Trp) can, in combination with type I interferon (IFN) signalling, limit astrocyte-driven inflammation.

In the EAE model, immunization of mice with myelin antigens results in CNS inflammation and motor deficits, followed by gradual recovery. Here, RNA sequencing showed increases in the expression of genes involved in type I IFN signalling in astrocytes from EAE mice at peak disease compared with control astrocytes. Short hairpin RNA (shRNA)-mediated knockdown of type I interferon receptor 1 (*Ifnar1*) specifically in astrocytes after EAE induction worsened symptoms and increased mRNA levels of pro-inflammatory markers in astrocytes, suggesting that astrocytic type I IFN signalling dampens astrocyte-mediated inflammation in EAE.

Astrocyte-specific *Ifnar1* knockdown also reduced expression of the gene encoding the ligand-activated transcription factor aryl hydrocarbon receptor (AHR) in these cells, whereas *Ahr* expression was increased after application of IFNβ — a type I IFN that is used to treat MS — to mouse and human fetal astrocytes *in vitro*. Chromatin immunoprecipitation (ChIP) analysis confirmed that IFNAR1 activation promotes *Ahr* transcription, suggesting that AHR might mediate the anti-inflammatory effects of type I IFNs. Indeed, genetic deletion or shRNA-mediated knockdown of *Ahr* in astrocytes exacerbated EAE, and increased astrocyte expression of pro-inflammatory molecules. Moreover, intranasal administration of IFNβ reduced EAE severity in wild-type mice, but not mice in which *Ahr* was knocked out of astrocytes.

ChIP analysis revealed that IFNβ stimulates the recruitment of AHR to the promoter of suppressor of cytokine signalling 2 (*Socs2*) to initiate its transcription. In turn, SOCS2 suppresses the activation of nuclear factor-κB and consequently its ability to stimulate the transcription of pro-inflammatory mediators.

AHR activity is regulated by several molecules, including some that are derived from the diet and gut-microbial products. Dietary Trp, for example, can be metabolized into several AHR ligands. Here, it was shown that dietary Trp supplementation ameliorated EAE symptoms in wild-type mice but not in mice lacking astrocytic AHR.

Previous studies have shown that Trp is metabolized into AHR agonists by ampicillin-sensitive bacteria such as *Lactobacillus reuteri*. Here, ampicillin treatment of wild-type mice inhibited recovery from EAE and lowered levels of *L. reuteri* in the gut of these animals. In addition, bacterial tryptophanase (TnAse) helps to convert Trp to indole, which is used by the liver to produce the AHR agonist indoxyl-3-sulfate (I3S). In line with this, treatment with I3S, indole or recombinant TnAse reduced EAE severity in ampicillin-treated mice through a mechanism dependent on astrocytic AHR, and I3S reduced the expression of pro-inflammatory mediators in human astrocytes in response to an inflammatory stimulus. Together, these findings suggest that commensal bacteria aid in the production of AHR agonists.

Overall, this study identifies a signalling pathway whereby type I IFNs stimulate the production of AHR, which is activated by diet- and microbe-derived molecules and limits CNS inflammation in EAE. Interestingly, although the authors found that *AHR* expression is upregulated in human MS lesions, AHR target gene expression and AHR agonist levels (in brains and sera, respectively) were lower in people with MS than in healthy controls. Thus, a deficit in the production, uptake or stability of AHR agonists could have a role in the pathogenesis of MS.

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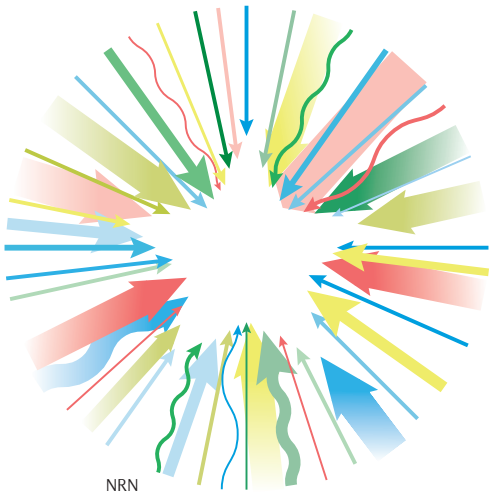

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