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Rationing AHR ligands

> constitutive CYP1A1 activity decreases the availability of AHR ligands, with effects on T_H17 cells and ILC3

Signalling through the aryl hydrocarbon receptor (AHR) — which recognizes endogenous metabolites, dietary components and microbiota products — promotes the survival and function of immune cells at mucosal surfaces. Tight regulation of this signalling pathway by cytochrome P4501 (CYP1) enzymes that metabolise AHR ligands has been shown *in vitro*, but it was unclear whether CYP1 enzymes also regulate the mucosal immune response *in vivo*. Stockinger and colleagues report that experimentally inducing constitutive *Cyp1a1* expression throughout the body or restricted to intestinal epithelial cells decreases AHR-dependent intestinal immune responses in mice and increases their susceptibility to enteric infection.

$CD4^+$ T cells from $R26^{Cyp1a1}$ mice (which constitutively express *Cyp1a1* under control of the *Rosa26* promoter) were cultured under T helper 17 (T_H17) cell-inducing conditions in the presence of the endogenous AHR ligand 6-formylindolo[3,2-*b*]carbazole (FICZ). $R26^{Cyp1a1}$ T_H17 cells had accelerated clearance of FICZ compared with wild-type T_H17 cells and they produced less interleukin-22 (IL-22) in response to low levels of FICZ. Furthermore, $R26^{Cyp1a1}$ mice had decreased numbers of group 3 innate lymphoid cells (ILC3) in colon and small intestine. Thus, constitutive CYP1A1 activity decreases the availability of AHR ligands, with effects on T_H17 cells and ILC3. As a result, $R26^{Cyp1a1}$ mice infected with *Citrobacter rodentium* had increased intestinal pathology, increased bacterial dissemination and increased fatality compared with wild-type mice. In the converse experiment, mice lacking CYP1A1, CYP1A2 and CYP1B1 (*Cyp1*-knockout mice) failed to metabolise FICZ, had increased IL-22 production and had decreased pathology after *C. rodentium* infection.

Using a mouse strain that reports AHR activity through the induction of a fluorescent protein, the authors showed that *Cyp1*-knockout mice had increased AHR activity mainly in intestinal epithelial cells (IECs). In keeping with an important role for IECs in AHR signalling, mice in which constitutive *Cyp1a1* expression was restricted to IECs (IEC^{Cyp1a1} mice) had reduced numbers of intestinal ILC3, whereas mice in which *Cyp1a1* expression was restricted to adaptive immune cells had normal ILC3 numbers. IEC^{Cyp1a1} mice rapidly succumbed to infection with *C. rodentium* as a result of decreased levels of ILC3, T_H17 cells and IL-22. In bone-marrow chimaeras generated by transferring wild-type bone marrow into *Cyp1*-knockout recipients, the mice had increased levels of ILC3, T_H17 cells and IL-22 compared with wild-type recipients and less pathology in response to infection. This supports a crucial role for AHR ligand metabolism by non-haematopoietic cells (specifically IECs) in regulating the supply of AHR ligands to the intestinal immune system.

Further studies showed that dietary supplementation with AHR ligands could enhance immunity to *C. rodentium* infection in $R26^{Cyp1a1}$ mice in an IL-22-dependent manner. Therefore, the important function of CYP1 activity in maintaining intestinal immune homeostasis through regulating the availability of AHR ligands could be open to therapeutic dietary manipulation.

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