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MUCOSAL IMMUNOLOGY

Probiotic induction of tolerogenic T cells in the gut

Upon reaching the small intestinal epithelium, lamina propria $CD4^+$ T cells can reactivate the CD8 T cell lineage programme, in part by downregulating levels of the transcription factor THPOK, to differentiate into $CD4^+CD8\alpha\alpha^+$ αβ T cells (also known as double-positive intraepithelial lymphocytes (DP IELs)), which promote tolerance to dietary antigens. Cervantes-Barragan *et al.* now show that a species of probiotic bacteria, *Lactobacillus reuteri*, induces the differentiation of $CD4^+$ T cells into DP IELs by activating their aryl hydrocarbon receptor (AHR), leading to a decrease in THPOK levels.

> *Lactobacillus reuteri* … induces the differentiation of $CD4^+$ T cells into DP IELs

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The authors observed that DP IELs were present in mice from Charles River Laboratories (CR), but not in those from the Jackson laboratories (JAX), and that the DP IEL-positive phenotype could be transferred to JAX mice by colonizing them with ileal or faecal microbiota from CR mice. Treating CR mice with antibiotics that target Gram-positive bacteria abrogated DP IEL development, suggesting that DP IELs are induced by Gram-positive bacteria in the gut. Indeed, *L. reuteri* was present in the ilea of CR but not JAX mice, and two strains of *L. reuteri* induced DP IELs in JAX mice.

L. reuteri metabolizes dietary tryptophan to indole derivatives that activate AHR, and the authors found that cell-free supernatant from *L. reuteri* grown in tryptophan-containing medium stimulated the differentiation of $CD4^+$ T cells into DP IELs, as did an AHR agonist. By contrast, an AHR antagonist inhibited the differentiation of $CD4^+$ T cells into DP IELs. These data suggest that the *L. reuteri* supernatant acts through AHR. Indeed, a *L. reuteri* mutant that cannot metabolize tryptophan into AHR ligands could not induce DP IELs in JAX mice, and the frequency of DP IELs was reduced in mice harbouring $Ahr^{-/-}$ T cells compared with that in wild-type littermates. Further data suggested that the absence of AHR blocks the differentiation of IELs into DP IELs upstream of THPOK downregulation.

In summary, *L. reuteri* induces DP IELs by activating AHR, leading to downregulation of THPOK. Of note, although a high-tryptophan diet increased the frequency of DP IELs in CR mice, it could not induce DP IELs in germ-free mice monocolonized with *L. reuteri*, suggesting that *L. reuteri* acts as part of the microbiota to induce DP IELs in the presence of tryptophan.

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