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NEWS AND COMMENTARY

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Bile acids mediate signaling between microbiome and the immune system

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The microbiome is increasingly recognized for its ability to modulate human health. Colonization with gut symbionts induces Foxp3-expressing regulatory T cells (Tregs) and expands their local numbers, a critical step in the suppression of intestinal inflammation and maintaining gut homeostasis. The molecular mechanism by which the microbiome interacts with peripherally induced Treg (pTreg) is likely complex and multifactorial; however, part of the effect is mediated via the release of microbial fermentation products, such as butyrate and other short-chain fatty acids.[1–3] In a string of recent studies, a role for host bile acids has also been shown to induce pTreg generation, with this function dependent on commensal colonization.[4–6] In the recent issue of *Nature*, Rudensky and colleagues dissect the molecular fermentation pathway where the gut microbiome converts an endogenous bile acid into an immunologically active bile acid with the capacity to induce pTreg in the gut.[4]

Primary bile acids are cholesterol-derived molecules that are produced in the liver and secreted into the duodenum following a meal. Because of their amphipathic nature, these molecules help to dissolve dietary lipids, as well as having key roles in glucose homeostasis and antimicrobial defense. Although most bile acids are reabsorbed in the small intestine, approximately 5% of primary bile acids transit to the colon. This bile acid waste can be metabolized by commensal gut flora, with the modified structures of the secondary bile acids altering signaling potential. Key modifications include deconjugation by bacterial bile salt hydrolases. Despite research into bile acids and their metabolic effects being a relatively mature field, it is not well understood how these molecules interact with the adaptive immune system.

To address this issue, Campbell *et al.*[4] set out to discover secondary bile acids capable of modulating pTreg generation in mice. Through an *in vitro* screen of major types of bile acids found in mice and humans on Treg differentiation, 3β-hydroxydeoxycholic acid (isoDCA) and ω-muricholic acid were identified as capable of enhancing Treg generation without impacting the conventional Th17 population. The Treg-promoting ability of isoDCA, one of the most abundant bile acids found in humans, was dependent on the presence of dendritic cells in the culture. Treatment of dendritic cells *in vitro* with isoDCA reduced the production of inflammatory cytokines tumor necrosis factor and interleukin-6, as well as reducing T-cell priming, demonstrating an immunosuppressive role for this bile acid. Transcriptome analysis of dendritic cells treated with isoDCA demonstrated that isoDCA reduced the expression of antigen-processing and antigen-presentation genes, potentially disturbing cognate interactions with T cells.

Many biological effects of bile acids are exerted through binding to the Farnesoid X receptor (FXR). Comparison of the transcriptome of FXR-deficient dendritic cells identified a mirrored transcriptional profile to isoDCA treatment, suggesting the isoDCA acts as a natural antagonist of FXR signaling. The Treg expansion effect observed for isoDCA was likewise replicated by FXR deficiency, with knockout dendritic cells demonstrating the same *in vitro* escalation of Treg induction even in the absence of isoDCA. *In vivo*, mice lacking FXR expression in the myeloid compartment ($Csf1r^{cre}Nr1h4^{fl/fl}$ mice) displayed increased numbers of $Foxp3^{+}$ $Ror\gamma t^{+}$ cells in the large intestine lamina propria, with this population predominantly representing pTreg induced in response to microbial antigens. Together, these data indicate that signaling through FXR in myeloid cells can inhibit pTreg generation. While FXR antagonism may account for much of the biological effect of isoDCA, however, isoDCA-induced transcriptional changes are still produced in FXR-deficient dendritic cells, indicating a still-hidden additional layer of mechanism.

Campbell *et al.*[4] formally linked microbial fermentation of isoDCA to colonic Treg expansion through the engineering of a minimal bacterial consortia. IsoDCA is generated from the primary bile acid cholic acid, with two structural changes required: cleavage of the 7α-hydroxyl group and

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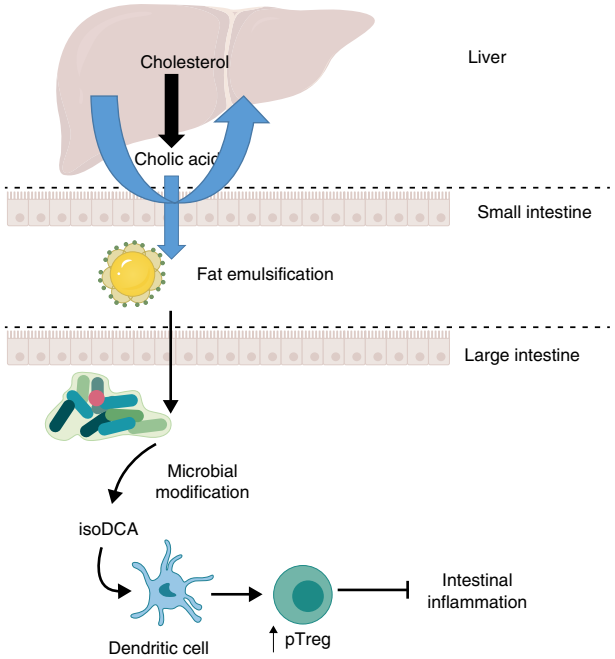

Figure 1. The secondary bile acid isoDCA can induce peripheral Treg (pTreg) generation in the large intestine. Primary bile acids, such as cholic acid, are synthesized from cholesterol in the liver, where they are then secreted into the duodenum after eating. In the small intestine, the detergent-like nature of bile acids acts to break up dietary fat and improve lipid absorption. Although most bile acids are reabsorbed in the ileum of the small intestine, a fraction that escapes reabsorption can undergo microbial fermentation in the large intestine. The generation of isoDCA from cholic acid can induce an anti-inflammatory profile in dendritic cells of the lamina propria and promote Rorγt^+ pTreg generation, critical for the maintenance of intestinal homeostasis. isoDCA, 3β-hydroxydeoxycholic acid; Treg, regulatory T cell.

epimerization of the 3α-hydroxyl group. To generate isoDCA *in vivo*, hydroxysteroid dehydrogenase was inserted into three independent *Bacteroides* species, to enable the epimerization of the 3α-hydroxyl group of cholic acid. These bacteria were inoculated into mice along with a commensal capable of 7α-dehydroxylation, providing the required microbial enzymes for *de novo* isoDCA generation. Colonization of germ-free mice with this consortium increased colonic Treg cells to a greater extent than the control strains, engineered with a catalytically dead hydroxysteroid dehydrogenase (Figure 1). The effect was also observed, to a lower degree, in the control strains, again demonstrating that there is more complexity in the situation than a single fermentation pathway.

The effect of isoDCA on dendritic cells in this study is in contrast to recent work of T-cell-modulating bile acids, which potentiate Treg generation in a cell-intrinsic manner.[5,6] This suggests that bile acids have diverse effects on the adaptive immune system and affect multiple cell types, opening the door for further research on how microbial metabolites can influence immune responses. Further complexity is added to the system through the effect of diet, which can influence the composition of both bile acids and the microbiota. A recent study in *Nature*[6] demonstrated that mice fed a nutrient-poor diet showed reduced presence of bile acids and subsequent reduction in pTreg generation. Mice fed a minimal diet were susceptible to intestinal inflammation, an effect which could be blocked through supplementation with select bile acids. Gastrointestinal health is therefore shaped through a complex interplay between bile acids, diet, the microbiome and our adaptive immune systems. The huge variation in these factors between individuals may contribute to the diversity we see in intestinal health, and provide attractive therapeutic strategies for intestinal disease.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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