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Title

Microbiome modulation of host's adaptive immunity through bile acid modification

Authors

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Abstract

The microbiome is well-known to influence the immune response of the host. Song *et al.* now show that the microbiome modulates adaptive immunity in mice through formation of bile acid species acting on ROR γ^+ regulatory T cells *via* the Vitamin D Receptor, thereby lowering the vulnerability for chemically-induced colitis

Text

The intestinal tract is populated by a diverse, dynamic and metabolically-active microbial flora, the microbiome. It is well-established that an imbalanced microbiome (“dysbiosis”) contributes to onset and progression of diseases of the host, including cardiovascular disorders and inflammatory bowel disease (IBD), i.e., disorders associated with inflammation. Indeed, the microbiome modulates the immune system of the host through complex interactions in which metabolites produced by bacteria signal to intestinal epithelial cells and immune cells. A broad spectrum of metabolites is formed from diet components, such as short-chain fatty acids (SCFA), synthesized directly by bacteria, or produced by the host and modified by bacteria¹. Secondary bile acids (BA) belong to the last group. BA are increasingly recognized as important signaling molecules impacting on glucose, lipid and energy metabolism. BA exert these actions through activation of membrane-bound (G protein-coupled BA receptor 1 (GPBAR1/TGR5)) and nuclear receptors (Farnesoid-X-Receptor (FXR) and Vitamin D Receptor (VDR))². BA activation of TGR5, FXR and VDR has been implicated in shaping innate immune responses³. Song *et al.*⁴ now report a role of BA and VDR in the adaptive immune system, particularly in the modulation of a specific population of FOXP3⁺ regulatory T (T_{reg}) cells expressing the transcription factor ROR γ (ROR γ^+ T_{reg}) that are present in the colonic lamina propria.

The circulating BA pool consists of a mixture of primary and secondary BA with varying physico-chemical characteristics and signaling functions². Primary BA are synthesized from cholesterol in the liver and conjugated to either taurine or glycine prior to secretion into bile. After a meal, BA are expelled into the small intestine to facilitate fat absorption. BA are efficiently maintained within the enterohepatic circulation by ileal and hepatic transporter systems. A small fraction of BA escapes ileal absorption and enters the colon to interact with the microbiome. Bacteria alter BA in a sequential process that is initiated by deconjugation and followed by epimerization, dehydroxylation and/or oxidation of –OH groups, generating secondary BA. A part of these modified BA is reabsorbed from the colon, enabling them to exert signaling functions in the host. In general, more hydrophobic

secondary species show greatest potency for FXR and VDR activation⁵. Important differences in BA metabolism exist between mice and humans, e.g., mouse-specific C6 hydroxylation reactions that generate hydrophilic muricholic acids², which caution against direct translation of results obtained in mice to the human situation.

Song and colleagues⁴ searched for the mediators of diet-dependent induction of a distinct population of FOXP3⁺ T_{reg} cells which express ROR γ , ROR γ ⁺ T_{reg} cells, that are critical in maintaining immune homeostasis in the colon. Specified pathogen-free (SPF) mice fed a “rich”, fiber and cholesterol-containing diet from weaning onwards showed higher levels of these cells than mice fed a “minimal” diet without cholesterol or germ-free mice fed the rich diet, implying a role of the microbiome. After exclusion of SCFA as potential mediators, the authors showed that concentrations of both primary and secondary BA in the colon were higher in mice fed rich as compared to minimal diets, possibly related to induction of hepatic BA synthesis by dietary cholesterol⁶. Germ-free mice showed even higher colonic BA concentrations, but solely conjugated primary BA, indicating that bacterial BA transformations are essential for induction of ROR γ ⁺ T_{reg} cells. Transfer of BA-metabolizing microbiota from minimal diet-fed mice to rich diet-fed germ-free mice restored the ROR γ ⁺ T_{reg} cell population. To directly assess the role of BA, individual and mixtures of unconjugated primary and secondary BA were added to drinking water of minimal diet-fed mice for 28 days. Only certain mixtures of primary and secondary BA were found to regulate ROR γ ⁺ T_{reg} cell abundance. However, interpretation of these results is difficult since very high concentrations of BA were added to drinking water, above the reported maximal solubility of several species used⁷, corresponding to an estimated daily BA intake exceeding the size of the endogenous BA pool by a factor 3⁸. Unfortunately, colonic concentrations of administered BA and their metabolites were not reported and comparison to levels found in rich diet-fed mice is not possible. Yet, bacterial species capable of inducing ROR γ ⁺ T_{reg} cells lost this ability after genetic deletion of BA hydrolase, the enzyme responsible for BA deconjugation, the first and essential step in secondary BA formation. Studies employing several BA receptor knock-out mouse models revealed that BA-activated VDR mediates ROR γ ⁺ T_{reg} cell induction. Indeed, VDR is expressed at relatively high levels in the ROR γ ⁺ T_{reg} population. Studies in T_{reg}-specific VDR knock-out mice supported the role of VDR in programming of colonic ROR γ ⁺ T_{reg} cells. The pathophysiological relevance of the BA-VDR signaling axis in these cells was demonstrated by showing that mice fed the minimal diet were more vulnerable to dextran sodium sulfate (DSS)-induced colitis than mice fed the rich diet and that BA supplementation tended to normalize ROR γ ⁺ T_{reg} cell numbers and alleviated colitis. Lack of VDR in T_{regs} worsened DSS-induced colitis. Importantly, BA supplementation did not cure established colitis but prevented its development.

This interesting work leaves us with a number of questions. The identity of the components that functionally differentiate the rich from the minimal diet as well as the BA metabolites responsible for activation of VDR in this system remain unknown. Makishima *et al.*⁵ demonstrated that LCA and 3-oxo-LCA are the most potent BA activators of VDR, while primary BA appear inactive. This delineates the likelihood that primary BA upon their supplementation require conversion into LCA. Indeed, conversion to LCA has been reported to be critical for the protective effects of ursodeoxycholic acid (UDCA) in DSS-induced colitis⁹. It also remains to be established by which mechanism(s) the colonic shift of the BA pool occurs and how activated VDR modulates the ROR γ ⁺ T_{reg} cell population.

This study, complemented by recent work¹⁰ that identified two LCA metabolites as modulators of T_H17 and T_{reg} differentiation, underscores the (patho)physiological importance of BA as signaling molecules, now also in regulation of adaptive immunity. It will be important to assess whether the existing large inter-individual variations in human BA pool size and composition translate into inter-individual differences in adaptive immunity.

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