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Commensal bacteria play a fundamental role in maintaining gut immune homeostasis

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The intestinal microbiome, which is a key factor in the maintenance of host gut homeostasis, enhances intestinal mucosal barrier function and immune tolerance (Rooks and Garrett, 2016; Skelly et al., 2019). However, the specific immunomodulatory functions of microbiota-derived metabolites in mucosal inflammatory responses remain largely unknown. The effects of microbial metabolites may vary across different immune cell types and host homeostasis (Hu et al., 2023; Zhao et al., 2023). Hence, it is fundamental to understand how specific intestinal microbes and their metabolic small molecules cause or mitigate gut-related diseases like inflammatory bowel disease (IBD). It has been uncovered that during the pathogenesis of IBD, excessive T helper 1 cell (Th1)/Th17 activation and impaired function of colonic regulatory T cells (Tregs) occur (Subramanian, 2020). Given that colonic Tregs play an important role in inhibiting IBD via secreting immunosuppressive cytokines, the molecular mechanisms linking certain intestinal microbes and their metabolites to Treg-mediated immune tolerance are yet to be fully understood.

By utilizing various broad-spectrum antibiotics (ampicillin, neomycin, vancomycin, and metronidazole) in a mouse model of dextran sulphate sodium (DSS)-induced colitis, Zhang et al. (2024) observed a substantial amelioration in colitis phenotypes with neomycin administration. Furthermore, subsequent fecal microbiota transplantation (FMT) from neomycin-treated mice reconstituted the gut microbiota in the recipient mice, abating colitis severity. Because the profound augmentation of bacterial abundance of an understudied genus, *Dubosiella*, was noted in the neomycin-treated animals, they used the prototype strain, *Dubosiella newyorkensis* (Dub), to colonize both conventional and antibiotic-treated mice and demonstrated a protective role against inflammation-induced colitis by reducing inflammation and improving mucosal barrier protection. Interestingly, the protective effects of Dub appeared to be associated with Dub-derived metabolites rather than bacterial components. Furthermore, they showed that Dub colonization in conventional and antibiotic-treated mice led to significantly elevated cluster of differentiation 25-positive ($CD25^+$) forkhead box P3-positive ($Foxp3^+$) Tregs and decreased interleukin-17-positive ($IL\text{-}17^+$) $CD4^+$ T cells in the colonic lamina propria, mesenteric lymph nodes, and spleen, demonstrating the capability of Dub to rebalance Treg/Th17 responses and promote inflammatory remission in the settings of IBD.

Based on the close genetic relationship of Dub with a well-known robust short-chain fatty acid (SCFA) producer *Faecalibaculum rodentium* (Cox et al., 2017), Zhang et al. (2024) performed gas chromatography-mass spectrometry (GC-MS) on colon samples collected from Dub-colonized mice and showed that markedly elevated SCFA levels coincided with increased $CD25^+Foxp3^+$ Treg induction, mirrored by propionate administration, emphasizing the importance of G-coupled protein receptor 43 (GPR43)-mediated Treg/Th17 balance in Dub-associated protection against

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DSS-induced IBD. However, slight differences in Treg induction were found between Dub colonization and propionate administration, which pointed to other relevant metabolites or GPR43-independent pathways.

To further identify potential metabolites that promote $CD25^{+}Foxp3^{+}$ Treg induction, Zhang et al. (2024) performed untargeted metabolomics analysis on colon samples of Dub mice and revealed enhanced tryptophan (Trp) metabolism toward the kynurenine (Kyn) pathway. They found that augmented Kyn production driven by Dub contributes to the rebalanced Treg/Th17 responses during intestinal inflammation, attributed partly to the heightened indoleamine-2,3-dioxygenase 1 (IDO1) expression in dendritic cells (DCs) in the colonic lamina propria mononuclear cells (cLPMCs).

Through an untargeted metabolome analysis of the Dub-cultured supernatant, Zhang et al. (2024) further spotlighted the potential of lysine (Lys) in modulating IDO1-driven Trp metabolism in DCs. Mechanistically, Lys treatment drives the translocation of the aryl hydrocarbon receptor (AhR) into the nucleus and upregulates IDO1 expression, which skews Trp metabolism to the Kyn pathway in DCs, and the resulting Kyn ultimately induces immune tolerance mediated by colonic Treg responses. Moreover, they identified the human homologue of Dub, *Clostridium innocuum*, and unveiled its possible protective effect against human colitis, leveraging a similar IDO1-upregulating property.

As detailed in the present study, Zhang et al. (2024) uncovered a novel role for the commensal bacterium, Dub, in sustaining gut homeostasis via the production of microbiota-derived metabolites, propionate and Lys. This builds on our understanding of the mechanisms underpinning the interplay between gut microbiome and host immune responses from a different angle of cellular metabolism. Importantly, these findings are conducive to the research and development of probiotics and microbiome-based therapeutics in the treatment of colitis and other gut-related disorders. Yet, studies on the role of Dub and its associated metabolites in the maintenance of intestinal health are very limited. Although a molecular link between Dub-derived Lys and the regulation of Treg/Th17 responses has been established, it remains uncertain whether other microbial metabolites or pathways are also involved in the process. Further investigations are needed to identify other metabolites or bioproducts synthesized by Dub that contribute to gut homeostasis, and also to elucidate the specific mechanisms through which these products exert their immunomodulatory effects. Attention should also be given to the role of Lys in the AhR-IDO1-Kyn circuitry and the exact molecular mechanisms underlying AhR activation.

This study raises several interesting questions. First, does the immunomodulatory effect of microbiota-derived metabolites vary under the different circumstances of the host immune responses? This is vital question given that gut microbiota is important for not only the maintenance and restoration of local and systemic homeostasis but also the host defense against pathogenic microorganisms. Second, does the same microbial metabolite function differently at the occurrence of IBD or enteric viral infection? For example, Zhang et al. (2024) and Du et al. (2022) have determined that propionate can regulate the size and function of the colonic Treg pool and protect against colitis in a GPR43-dependent manner, while a recent study conducted by Wang et al. (2023) pointed out that propionate, produced by *Blautia* spp., primes type I interferon (IFN-I)-mediated innate antiviral immunity to enteric viral challenge via GPR43-cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) signaling. Wang et al. (2023) found that the two specific signals are required for optimal activation of IFN-I response to confer full protection from enteric virus infection (Fig. 1). For signal 1, acetate or propionate from *Blautia* spp. induces intracellular Ca^{2+} release and mitochondrial antiviral signaling protein (MAVS)-dependent mitochondrial DNA (mtDNA) release through GPR43 activation, and for signal 2, viral infection triggers mitochondrial stress and mtDNA release through MAVS-dependent events. These signaling pathways converge in a cGAS-STING-dependent expression of IFN-I, which activates signal transducer and activator of transcription 1 (STAT1) signaling through the engagement of the IFN-I receptor (IFNAR). This finding indicates a fine-tuned sensory system that maintains a poised basal state of immune cells to fight viral infection and, at the same time, avoids autoimmunity resulting from excessive IFN-I expression.

In conclusion, the above two recent studies coming from the Zhu's lab are in line with the acknowledgment

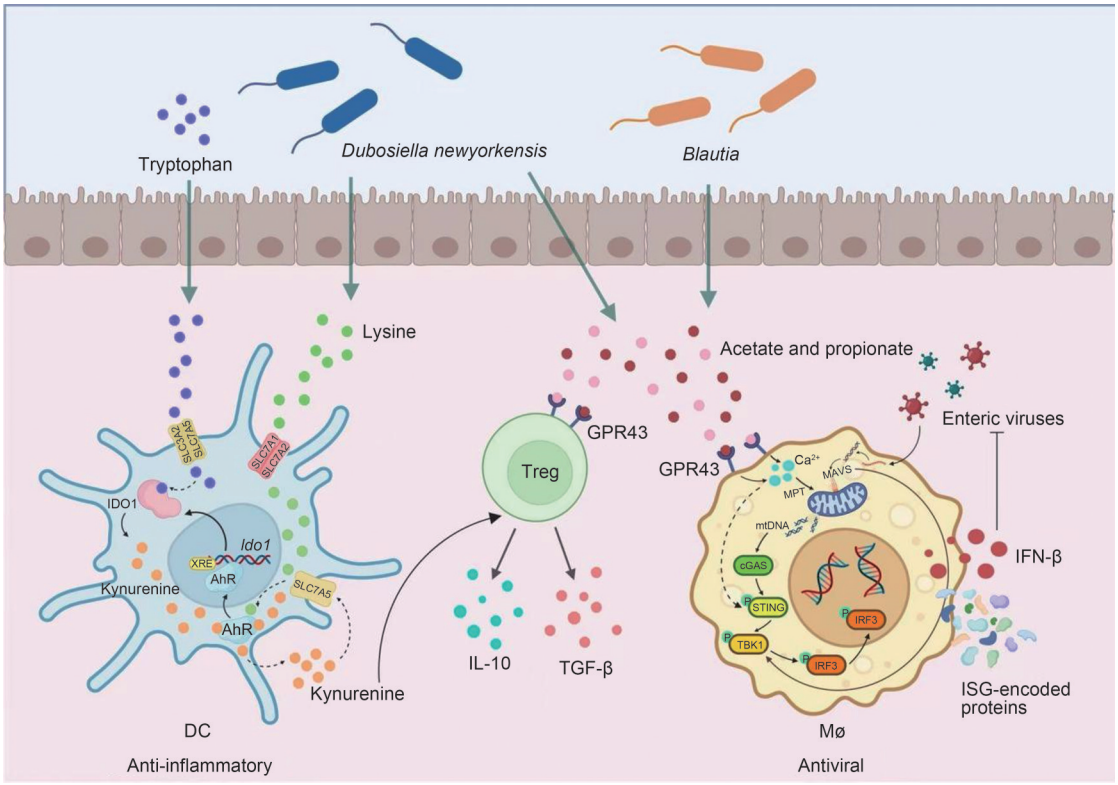

Fig. 1 Schematic illustration of how specific intestinal microbes and their metabolic small molecules maintain gut immune homeostasis. Created by BioRender.com. AhR: aryl hydrocarbon receptor; IDO1: indoleamine-2,3-dioxygenase 1; XRE: xenobiotic responsive element; DC: dendritic cell; Treg: regulatory T cell; IL-10: interleukin-10; GPR43: G-coupled protein receptor 43; TGF-β: transforming growth factor-β; Mø: macrophage; cGAS: cyclic guanosine monophosphate-adenosine monophosphate synthase; STING: stimulator of interferon genes; MAVS: mitochondrial antiviral signaling protein; mtDNA: mitochondrial DNA; MPT: mitochondrial permeability transition; TBK1: TANK-binding kinase 1; IRF3: interferon regulatory factor 3; ISG: interferon-stimulated gene; IFN-β: interferon-β; SLC3A2: solute carrier family 3 member 2.

that the extensive crosstalk between the different cellular and microbial metabolites regulates both the mucosal and systemic immune system to ensure efficient host defense, maintaining and restoring homeostasis. In this case, the same microbial metabolites could act very differently in regulating immune responses under a different situation of the host, emphasizing the urgent need for future work to fully understand how intestinal microbiota and their bioactive metabolic byproducts influence host anti-infectious and anti-inflammatory immunity. By expanding on this comparison and exploring the underlying mechanisms in the future, we can gain deeper insights into the therapeutic potential of microbial metabolites in different diseases.

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Author contributions

Shu Jeffrey ZHU, Yanan ZHANG, and Shuyu TU wrote the paper. Li ZHANG commented on and revised drafts of the manuscript. Shu Jeffrey ZHU and Li ZHANG supervised research, coordination, and strategy. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Shuyu TU, Yanan ZHANG, Li ZHANG, and Shu Jeffrey ZHU declare that they have no conflicts of interest.

This paper does not contain any research with human or animal subjects performed by any of the authors.

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