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INSIGHTS

Fueling the fire in the gut

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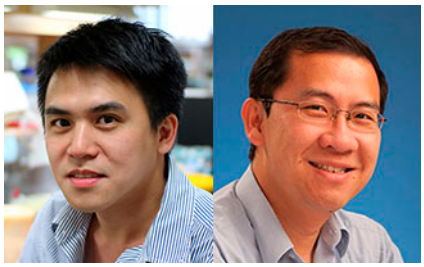
Gut dysbiosis has long been associated with the development of Crohn's disease and other gastrointestinal disorders. Otake-Kasamoto et al. (2022. *J. Exp. Med.* https://doi.org/10.1084/jem.20211291) report that dysbiotic microbiota-derived bioactive lipids, lysophosphatidylserines, can promote pathological Th1 cell responses through inducing metabolic reprogramming and epigenetic changes.

Crohn's disease (CD) is a chronic disease that causes inflammation in the gastrointestinal track. Together with ulcerative colitis (UC), another major type of inflammatory bowel disease (IBD), these intestinal disorders affect millions of people in the U.S. and worldwide. Excessive T helper 1 (Th1) and Th17 cell responses have been documented to act as important mediators of the pathogenesis of CD and that neutralizing Th1 cell–activating IL-12 and Th17 cell–activating IL-23 by an anti–IL-12/IL-23p40 antibody was shown to induce clinical responses and maintain remissions in patients with active CD (Roda et al., 2020). On the other hand, patients with CD (and UC) have also been found to harbor significantly reduced numbers of regulatory T (Treg) cells (Maul et al., 2005). Considering the well-recognized role of Treg cells in establishing immunological tolerance, it is thus not surprising that an imbalance between Treg cells and effector T cells in the intestinal tissue microenvironment is crucial to promote gut inflammation in CD. Consistent with this notion, administration of antigen-specific Treg cells to CD patients has been reported to demonstrate positive signs of dose-related efficacy (Desreumaux et al., 2012).

In the last decade, gut dysbiosis has been extensively investigated for its role in CD by impacting the host immune system. In CD patients, a reduced representation of *Firmicutes* and *Bacteroidetes* and an overrepresentation of *enterobacteria* have been reported, suggesting that a shift in the balance between colitogenic and protective bacteria could be accounted for the development of intestinal inflammation (Pascal et al., 2017). Similarly, *Faecalibacterium prausnitzii* and adherent-invasive *Escherichia coli* have also been associated with the protection against and the promotion of CD, respectively (Roda et al., 2020). Mechanistically, gut microbiome can confer benefits to CD patients through the production of anti-inflammatory short-chain fatty acids such as butyrate via anaerobic fermentation of dietary fibers in the intestine (Segain et al., 2000). On the other hand, while it was recently shown that *E. coli* enriched in the small intestine of patients with CD can promote CD pathogenesis through the induction of IFNγ-producing CD4 T cells in the intestine (Nagayama et al., 2020), how exactly do these pathobionts enhance Th1 responses that exacerbate intestinal inflammation remains unclear.

By performing lipidomic analysis and shotgun metagenomic sequencing, Otake-Kasamoto et al. (2022) observed that lysophosphatidylserine (LysoPS) was increased in feces of patients with CD, in addition to elevated relative abundance of microbes expressing phospholipid-hydrolyzing enzyme phospholipase A, the enzyme that generates lysoglycerophospholipids by hydrolyzing cell membrane phospholipid molecules. Moreover, when germ-free mice were inoculated with *E. coli*–enriched feces derived from patients with CD but not from the healthy donors, elevated concentration of LysoPS was also detected. These results suggested that colonization by the dysbiotic microbiota found in patients with CD links to the LysoPS generation in the intestine. Next, by employing multiple animal colitis models, the authors have shown that administration of LysoPS was detrimental in T cell–driven colitis, including 2,4,6-trinitrobenzenesulfonic acid solution– and T cell adoptive transfer–induced colitis models, while having no significant impact on the pathogenesis of T cell–independent dextran sodium sulfate–induced colitis. Mechanistically, LysoPS enhances IFNγ-producing Th1 cell responses by promoting glycolytic activity through binding to P2ry10 and



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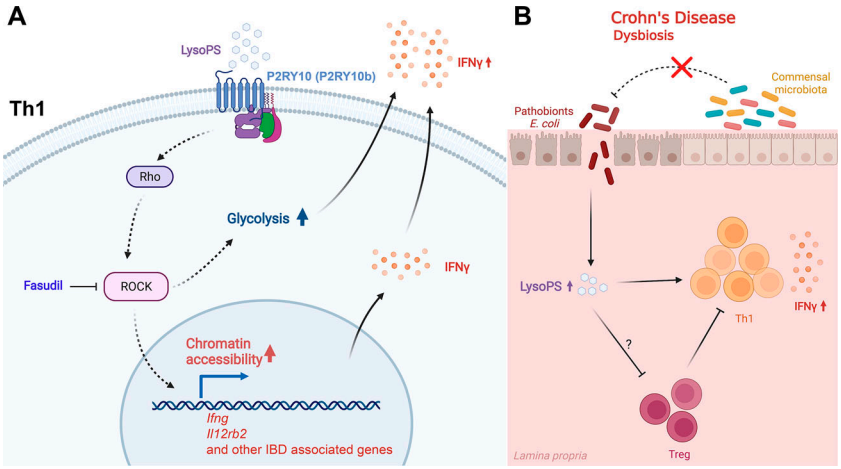

Dysbiotic microbiota–derived LysoPS promotes Th1-mediated pathogenesis in patients with CD. (A) Upon binding to P2Y10 receptors, LysoPS enhances IFNγ-producing Th1 cell responses by promoting glycolytic activity and introducing epigenetic changes that result in increased accessibility to Ifng and Il12rb2 loci as well as other IBD-associated genes. This effect was impaired upon treatment of Fasudil, an inhibitor for the Rho-ROCK signaling pathway. (B) LysoPS produced by dysbiotic microbiota found in the colon of patients with CD promotes pathogenic Th1 responses in a cell-intrinsic manner. Created with BioRender.com.

P2ry10b, two known LysoPS G-protein coupled receptors (GPCRs) in a Rho/Rho-associated kinase (ROCK) signaling pathway–dependent manner. In addition, LysoPS also promotes Th1 cell effector function by introducing epigenetic changes that result in increased accessibility to Th1-associated genes (such as *Ifng* and *Il12rb2*) and many other genes predicted to associate with IBD. Together, LysoPS exaggerates intestinal inflammation by fueling IFNγ-producing Th1 cells via P2Y10 receptor-mediated metabolic reprogramming and chromatin modification (see panel A of figure).

While this work has provided novel functional insights into the dysbiotic microbiota-derived LysoPS in CD pathogenesis (see panel B of figure), it also raises several questions. To this end, as opposed to its role in promoting pathological Th1 cell response as described in the current study, LysoPS has long been documented to exhibit immune-modulatory functions (Bellini and Bruni, 1993). Specifically, LysoPS was shown to suppress IL-2 production, T cell activation and proliferation, likely through the induction of cyclic AMP levels and protein kinase A activity (Barnes and Cyster, 2018). It is thus puzzling as to how LysoPS treatment could lead to aggravation of intestinal pathology in T cell–driven colitis when T cell responses are inhibited even if Th1 cell function is selectively enhanced. While LysoPS could potentially exacerbate colitis by suppressing Treg cell activities as suggested by a previous report (Barnes et al., 2015), the current study has also ruled out this possibility as the authors observed comparable Treg cell suppressor function with or without LysoPS signaling despite detecting a partial effect of LysoPS on reducing the glycolytic activity in Treg cells. It should be noted, however, that rather than signaling through the P2Y10 receptors, LysoPS was previously shown to exert its inhibitory function on both T cells and Treg cells through binding to GPR174, another LysoPS receptor. As the expression of GPR174 in Treg cells (and perhaps other T cell populations) in the gut is lower compared to that from other tissues, these results suggested that LysoPS could mediate distinct biological functions through binding to different receptors. To date, four mouse GPCRs that could respond to LysoPS have been identified: GPR34, GPR174, P2RY10, and P2RY10b (the latter is a pseudogene in humans; Inoue et al., 2012). Compared to GPR174 and P2Y10 receptors, whose expressions are mostly restricted to immune-related tissues and cell types, GPR34 was initially found in a human brain cDNA library (Omi et al., 2021). Nevertheless, a recent study has also shown that LysoPS plays a crucial role in a colitis-induced tissue injury model in a GPR34-dependent manner. Through acting on GPR34 expressed in type 3 innate lymphoid cells, LysoPS promotes tissue repair during colon injury (Wang et al., 2021). Finally, in addition to the aforementioned GPCRs, TLR2, a non-GPCR, has also been suggested to serve as a cellular receptor for LysoPS. To this end, dendritic cells were previously shown to acquire the ability to induce the differentiation of IL-10–producing Treg cells upon activation by schistosome-specific LysoPS via TLR2 (Van Der Kleij et al., 2002). Thus, depending on the receptors LysoPS interacts with, these bioactive lipids are capable of exerting their diverse activities in a context- and cell type–specific manner (Omi et al., 2021).

For many years, CD was managed inefficiently using steroids, 5-aminosalicylic acids, immune modulators, and antibiotics. The introduction of anti-TNF agents in the late 1990s has shown promises in managing this chronic incurable disease (Kumar et al., 2022). However, despite that anti-TNF therapies have transformed the care of patients with CD, it also became obvious that they are not universally effective, with high rates of primary non-responders, and with further attrition from subsequent loss of response. Considering the recent advance in understanding gut microbiota as the key drive in IBD, fecal microbiota transplantation (FMT) has been established as a potential therapeutic option to treat patients with either CD or UC. However, despite having some successes by taking such approaches, clinical results from FMT in treating IBD and other gastrointestinal disorders remain conflicting, reflecting the gap in our knowledge of the microbiome composition and their respective function (Sbahi and Di Palma, 2016). On the other hand, in addition to supplementation of bacteria, in recent years there has also been a growing interest in targeting the bacterial products (such as using postbiotics) to alter the immune system to treat IBD. The findings of Otake-Kasamoto et al. (2022) provide experimental evidence supporting LysoPS as a putative diagnostic biomarker and a future therapeutic target for CD. Nevertheless, considering the complex nature of LysoPS in regulating the responses of different immune cell types in a given tissue environment under a particular physiological or

pathological condition, more research is needed to elucidate the precise role of LysoPS in CD before targeting these multifunctional bioactive lipids to treat human gastrointestinal disorders becomes a reality.

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