Development of therapeutic strategy for Crohn's disease by targeting microbiota-derived metabolites

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Abstract

The number of patients with inflammatory bowel diseases (IBD), such as Crohn's disease (CD), has been increasing worldwide. IBD patients are shown to harbor dysbiotic microbial communities associated with alterations of intestinal metabolite concentrations. The enzymes phospholipase A generates lysoglycerophospholipids and release free fatty acids by hydrolyzing cell membrane glycerophospholipid. Among lysoglycerophospholipids, concentrations of lysophosphatidylserine (LysoPS) and lysophosphatidylcholine are elevated in the stool and blood of patients with CD. However, the roles of lysoglycerophospholipids in the pathogenesis of CD remains poorly understood. We found that LysoPS promotes Th1 responses by the P2Y10 receptor-mediated promotion of glycolysis, thereby exaggerating intestinal pathology. These results reveal the mechanism exacerbating Th1-meditaed intestinal pathology through modulation of Th1 cell metabolism and may serve to identify therapeutic targets for CD.

Background & Results

Dysbiosis-mediated alterations of intestinal metbolites and IFN-γ-producing CD4$^+$ T cell overactivation are implicated in Crohn's disease (CD) pathogenesis. However, it remains unclear how dysbiotic microbiota-derived metabolites enhance Th1 responses, leading to intestinal inflammation. We previously reported that some lysophospholipid species, including LysoPS, were elevated in the plasma of patients with CD. However, much less is known about how lysophospholipids are generated in the intestine and whether they modulate intestinal immune reposes.

Patients with CD showed elevated concentrations of 18:0 LysoPS and 18:1 LysoPS in their feces compared with those in healthy controls, accompanied by a higher relative abundance of microbiota possessing a gene encoding the phospholipid-hydrolyzing enzyme phospholipase A. LysoPS induced metabolic reprogramming (promotion of glycolysis), thereby eliciting aberrant effector responses in both human and mouse IFN-γ-producing CD4$^+$ T (Th1) cells. We found that activation level of glycolysis in effector memory CD4$^+$ T cells from the blood positively correlated with fecal18:1 LysoPS concentration in patients with CD, suggesting that dysbiotic microbiota-derived LysoPS promotes glycolysis in effector memory T cells.

Administration of 18:1 LysoPS into mouse colitis models promoted large intestinal inflammation. LysoPS-induced aggravation of colitis was impaired in mice lacking *P2ry10* and *P2ry10b*, and their CD4$^+$ T cells were hyporesponsive to LysoPS. Thus, our findings elaborate on the mechanism by which metabolites elevated in patients with CD harboring dysbiotic microbiota promote Th1-mediated intestinal pathology.

Significance of the research and Future perspective

Our study provides evidence for the contribution of excessive accumulation of dysbiotic microbiota-derived LysoPS to intestinal inflammation progression via perturbations of host Th1 immunity through promoting glycolysis. Modulation of glycolysis in lymphocytes and myeloid cells by small molecule dimethyl fumarate abrogates chemically induced colitis in mice. Thus, LysoPS, P2Y10 receptor, and glycolysis could be a putative therapeutic target for CD.

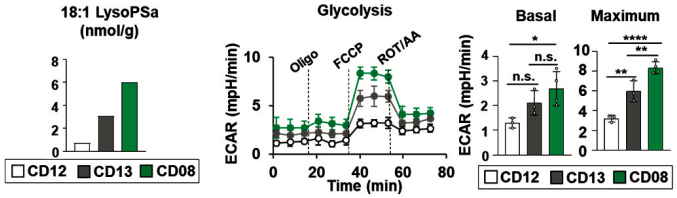

Figure 1: LysoPS-mediated promotion of glycolytic activity in T cells from patients with CD.
Basal and maximum levels of the extracellular acidification rate (ECAR: glycolytic activity index) in effector memory CD4$^+$ T cells positively correlated with fecal LysoPS concentration.

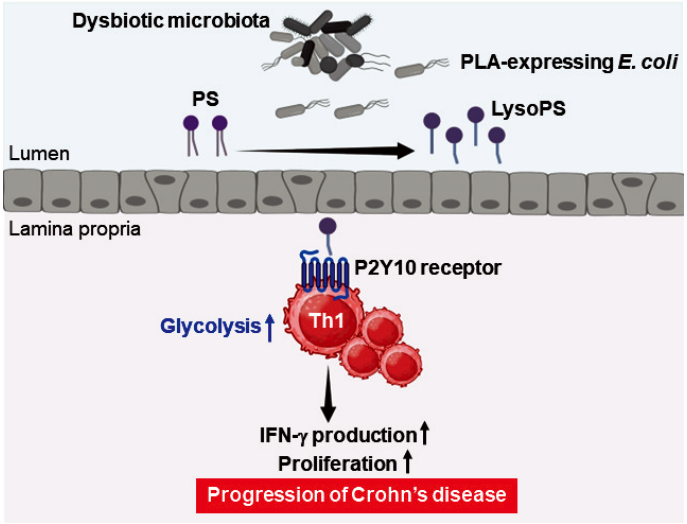

Figure 2: Dysbiotic microbiota-derived LysoPS progresses Crohn's disease.
Lysophosphatidylserines (LysoPS) generated by *E. coli* possessing ECSF_3660 gene encoding phospholipase A elicit immunopathological Th1 cell response through P2Y10 receptor-mediated modulation of glycolysis, thereby leading to progression of Crohn's disease.

Patent
Treatise Otake-Kasamoto, Yuriko; Kayama, Hisako; Takeda, Kiyoshi et al. Lysophosphatidylserines derived from microbiota in Crohn's disease elicit pathological Th1 response. J Exp Med. 2022, 219(7), e20211291. doi: 10.1084/jem.20211291
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