Development of therapeutic strategy for ulcerative colitis by targeting microbiota-derived metabolite

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Abstract

The number of patients with inflammatory bowel diseases (IBD), such as ulcerative colitis (UC), has been increasing worldwide. IBD patients are shown to harbor dysbiotic microbial communities, associated with alterations of intestinal metabolite concentrations. Extracellular adenosine triphosphate (ATP) released by microbes contributes to activation of host immune responses in the intestine through the P2X and P2Y receptors. To avoid inappropriate immune reactions linking to development of IBD, luminal ATP needs to be strictly controlled. However, the molecular mechanism underlying regulation of the luminal ATP concentration in the colon remains poorly understood. We found that the clearance of microbiota-derived ATP by E-NTPD8 in colonic epithelial cells is essential for inhibiting the prolonged survival of neutrophils by discouraging the P2X4R-mediated promotion of glycolysis, thereby abrogating innate intestinal pathology. These results reveal the mechanism preventing innate intestinal pathology through modulation of myeloid cell metabolism and may serve to identify therapeutic targets for IBD.

Background & Results

We previously demonstrated that extracellular ATP released by microbes contributes to induction of Th17 cells by activating dendritic cells in the intestine. To avoid inadequate immune responses, extracellular ATP is tightly regulated by epithelial ATP-hydrolyzing ectoenzymes, such as E-NPPs and E-NTPDs. We have found that E-NPP3 and E-NTPD7 control luminal ATP concentration in the small intestine, which are essential for regulation of innate and adaptive immune responses. However, the molecular mechanism underlying regulation of the luminal ATP concentration in the large intestine remains poorly understood.

Among E-NTPD and E-NPP family members, E-NTPD8 was highly expressed in colonic epithelial cells. Intriguingly, patients with UC exhibited low expression of *ENTPD8* mRNA in colonic epithelial cells. Therefore, we generated *Entpd8*$^{-/-}$ mice to assess the its physiological roles. A higher level of luminal ATP was observed in the colon of *Entpd8*$^{-/-}$ mice than wild-type mice. *Entpd8*$^{-/-}$ mice developed more severe dextran sodium sulfate-induced colitis accompanied by increased number of neutrophils in the colon compared with those in wild-type mice. In this context, the ablation of neutrophils by treatment with anti-Gr-1 antibody mitigated the severity of colitis in *Entpd8*$^{-/-}$ mice. In addition, the introduction of *P2rx4* deficiency into *Entpd8*$^{-/-}$ mice ameliorated DSS-induced colitis with lower levels of neutrophils accumulation. Extracellular ATP promoted glycolysis in neutrophils through a P2X4 receptor-dependent Ca^{2+} influx, which is linked to prolonged survival in these cells. Thus, E-NTPD8 limits intestinal inflammation by controlling metabolic alteration toward glycolysis via the P2X4 receptor in neutrophils.

Significance of the research and Future perspective

Our study provides evidence for the contribution of excessive accumulation of microbiota-derived luminal ATP to intestinal inflammation progression via perturbations of host innate immunity through promoting glycolysis. Modulation of glycolysis in lymphocytes and myeloid cells by small molecule dimethyl fumarate abrogates chemically induced colitis in mice. Thus, the extracellular ATP, P2X4 receptor, and glycolysis could be a putative therapeutic target for UC.

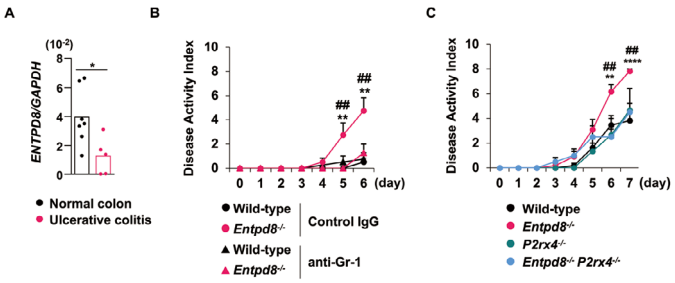

Figure 1: E-NTPD8 prevents neutrophil-mediated colitis
(A) Expression of ENTPD8 mRNA in colonic epithelial cells. (B and C) Severity of dextran sodium sulfate-induced colitis. The disease activity index score incorporates bleeding score (0-4) and pasty stool score (0-4).

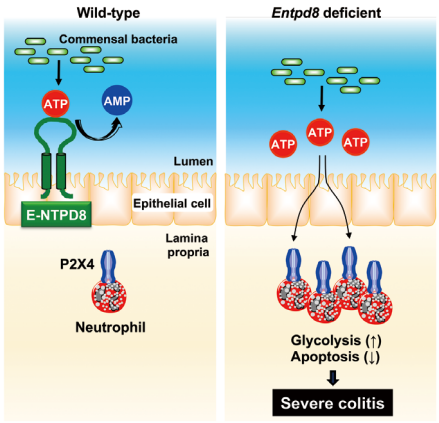

Figure 2: The role of E-NTPD8-mediated hydrolysis of extracellular ATP in maintenance of the gut homeostasis
E-NTPD8 in colonic epithelial cells maintains the gut homeostasis through hydrolysis of luminal ATP produced by commensal bacteria (left). An increased level of luminal ATP caused by lack of E-NTPD8 modulates neutrophil physiology, such as prolonged survival, through P2X4-mediated promotion of glycolysis, which links to aggravation of colitis (right).

Patent
Treatise Tani, Haruka; Kayama, Hisako; Takeda, Kiyoshi et al. The ATP-hydrolyzing ectoenzyme E-NTPD8 attenuates colitis through modulation of P2X4 receptor-dependent metabolism in myeloid cells. Proc Natl Acad Sci USA. 2021, 118(39): e2100594118. doi: 10.1073/pnas.2100594118
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