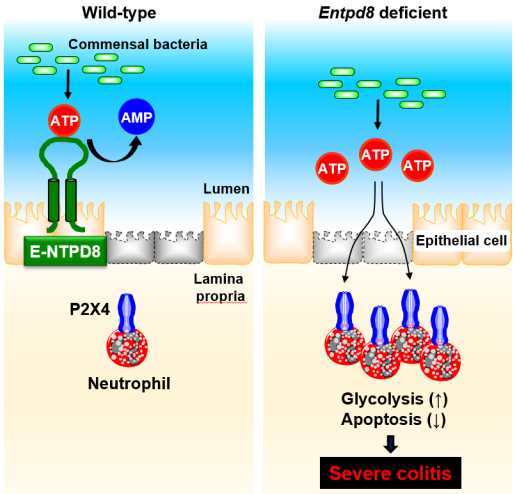
The ATP-hydrolyzing ectoenzyme E-NTPD8 attenuates colitis.

<Abstract>

Extracellular adenosine triphosphate (ATP) released by mucosal immune cells and by microbiota in the intestinal lumen elicits diverse immune responses that mediate the intestinal homeostasis via P2 purinergic receptors, while overactivation of the ATP signaling leads to mucosal immune system disruption, which leads to pathogenesis of intestinal inflammation. In the small intestine, hydrolysis of luminal ATP by E-NTPD7 in epithelial cells is essential for control of the number of Th17 cells. However, the molecular mechanism by which microbiota-derived ATP in the colon is regulated remains poorly understood.

Hisako Kayama (the Institute for Advanced Co-Creation Studies), Kiyoshi Takeda (IFReC/Graduate School of Medicine, Osaka University) and their research group showed that E-NTPD8 is highly expressed in large intestinal epithelial cells and hydrolyzes microbiota-derived luminal ATP. Compared to wild-type mice, *Entpd8*$^{-/-}$ mice develop more severe DSS-induced colitis, which can be ameliorated by either the depletion of neutrophils and monocytes by injecting with anti-Gr-1 antibody or the introduction of *P2rx4* deficiency into hematopoietic cells. An increased level of luminal ATP in the colon of *Entpd8*$^{-/-}$ mice promotes glycolysis in neutrophils through P2X4 receptor-dependent Ca^{2+} influx, which is linked to prolonged survival and elevated ROS production in these cells. Thus, E-NTPD8 limits intestinal inflammation by controlling metabolic alteration toward glycolysis via P2X4 receptor in myeloid cells.



E-NTPD8 prevents neutrophil-mediated colitis by hydrolyzing luminal ATP.
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).

<Message by Dr. Hisako Kayama>

This study elucidates a mechanism that reduces the number of neutrophils in colon tissues and prevents the severity of colitis. We hope that our research results will lead to the pathogenesis of ulcerative colitis and the development of new therapies. We would like to express our deepest gratitude to all colleagues and the patients who provided specimens.

<Information>

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