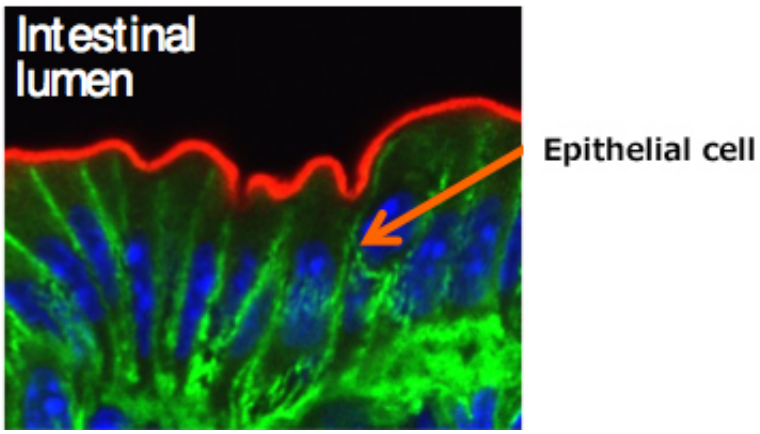
Identification of a novel protein that protects against bowel inflammation

September 25 2015



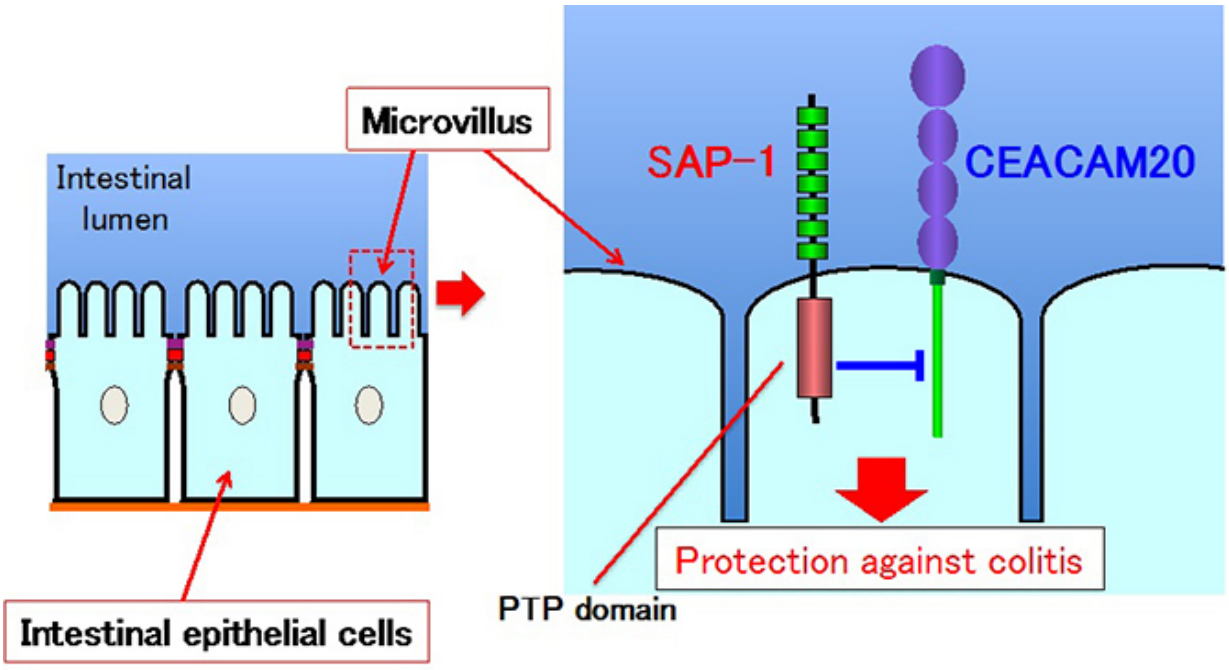
Immunofluorescence image of mouse colon. SAP-1 localizes to the microvillus of the brush border in colonic epithelial cells. SAP-1 (red), β-catenin (green), and nuclei (blue).

A group of researchers, led by Prof. MATOZAKI Takashi and Associate Prof. MURATA Yoji at the Kobe University Graduate School of Medicine Division of Molecular and Cellular Signaling, were the first to demonstrate the role of stomach cancer–associated protein tyrosine phosphatase (SAP)-1 in the pathogenesis and prevention of Crohn's disease, ulcerative colitis, and other inflammatory bowel disorders. Their findings, published online ahead of print on July 20, 2015, by the *Proceedings of the National Academy of Sciences* of the United States of America, are expected to accelerate the development of targeted therapies for inflammatory gastrointestinal diseases.

Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are disorders of unknown etiology that are often characterized by abdominal pain, diarrhea, bloody stool, fever, and weight loss. These symptoms frequently interfere with activities of daily living and place patients at an elevated risk of mortality. Patients are also associated with a high risk of developing colorectal cancer. In Japan, there are an estimated 200,000 patients with Crohn's disease and ulcerative colitis, who qualify for the special Government-led medical assistance system for intractable diseases. Currently, the administration of anti-inflammatory agents only provides palliative results, and the medical community is awaiting new definitive therapies.

Although recent studies have demonstrated that intestinal epithelial cells play a critical role in regulating bowel inflammation, the underlying mechanism remains largely unknown. Previously, Prof. Matozaki, Assistant Prof. Murata, and their colleagues found that SAP-1 localizes to the microvilli of the brush border in gastrointestinal epithelial cells. The transmembrane-type tyrosine phosphatase SAP-1 has an extracellular domain that protrudes into the intestinal lumen and a cytoplasmic domain that mediates tyrosine dephosphorylation of proteins. Here, they showed that SAP-1 ablation in a mouse model of inflammatory bowel disease resulted in a marked increase in the incidence and severity of bowel inflammation, suggesting that SAP-1 plays a protective role against colitis. In addition, carcinoembryonic antigen-related cell adhesion molecule (CEACAM) 20, an intestinal microvillus-specific membrane protein, was identified as the target of SAP-1 tyrosine dephosphorylation. Suppression of CEACAM20 functions via dephosphorylation was suggested to contribute to preventing colitis. By shedding light on the anti-inflammatory mechanism of the intestinal epithelial cells, Prof. Matozaki and colleagues believe that their findings will drive the development of drugs that target SAP-1 and CEACAM20 to overcome intractable inflammatory bowel diseases.

Prof. Matozaki stated, "Since the discovery of SAP-1 at Kobe University in 1994, we have clarified its major function thanks to the efforts of many joint researchers. Our future research interests are centered on the development of new therapeutics for inflammatory bowel disease that take advantage of our understanding of SAP-1 and CEACAM20 functions."



A schematic drawing illustrating the localization of SAP-1 on the brush-border microvilli of intestinal epithelial cells. The extracellular domain of SAP-1 extends into the intestinal lumen and its active tyrosine phosphatase domain resides in the cytoplasm. SAP-1 is thought to inhibit the development of colitis by suppressing CEACAM20 functions. Similar to SAP-1, CEACAM20 is localized to the epithelial microvilli. PTP, protein tyrosine phosphatase.

More information: "Protein tyrosine phosphatase SAP-1 protects against colitis through regulation of CEACAM20 in the intestinal epithelium." *PNAS* August 4, 2015 vol. 112 no. 31 E4264-E4271 DOI: 10.1073/pnas.1510167112

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