

Regulation of intestinal homeostasis by epithelial barriers

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Intestine is a unique tissue, where many commensal bacteria, called microbiota, inhabit. Therefore, intestinal mucosa is protected from microbiota as well as pathogenic bacteria by several types of barriers. One of these barriers is constructed by mucus layers, composed of the inner firm mucus layer and outer loose mucus layer in the large intestine. Microbiota is present in the outer mucus layer, whereas there is no microbiota in the inner mucus layer. Separation of microbiota from the intestinal epithelial cells contributes to prevention of intestinal inflammation. Indeed, invasion of bacteria into the epithelial surface of the large intestine was shown in several mouse models of intestinal inflammation. However, the precise mechanisms by which the inner mucus layer is free of microbiota in the large intestine remain unknown.

Ly6/PLAUR domain-containing protein 8 (Lypd8) was found to be selectively expressed on the uppermost layer of colonic glands. In mice lacking Lypd8, bacterial free space in the inner mucus layer disappeared and they were highly susceptible to intestinal inflammation. On the intestinal epithelial cell layer of the large intestine of the mutant mice, flagellated bacteria such as *Escherichia*, *Helicobacter* and *Proteus* were present. Depletion of these bacteria by antibiotics restored the bacterial free space in the inner mucus layer and ameliorated the intestinal inflammation of the mutant mice. Lypd8 bound to bacterial flagella and suppressed motile activity of flagellated bacteria. These findings demonstrated that Lypd8 mediates segregation of microbiota from the intestinal epithelial layer in the large intestine, and thereby contributes to the maintenance of gut homeostasis.