News Release

Title

Discovery of a New Mechanism of Infection Defense by Intestinal Epithelial Cells
-Hopes for elucidating the pathogenesis of intestinal infections and inflammatory bowel diseases and for therapeutic applications

Key Points

- **We found that intestinal epithelial cells sense the binding of pathogens to glycosphingolipids in the cell membrane and protect against infection.**
- **Intestinal epithelial cells inhibit pathogen infection by blocking endosomal function.**
- **The defense mechanism of intestinal epithelial cells is involved in the pathogenesis of intestinal infections and inflammatory bowel diseases. This research result is expected to lead to the elucidation of the pathogenesis and the development of treatment.**

Summary

The intestinal mucosa is in contact with pathogens such as bacteria and viruses, and intestinal epithelial cells, which are at the forefront of this contact, have a variety of defense mechanisms against pathogens. These defense mechanisms are essential to protect tissues from infection and to maintain intestinal homeostasis, and their disruption is deeply involved in the development of intestinal infection and inflammatory bowel disease. However, it remains unclear how intestinal epithelial cells recognize pathogens and protect against infection.
In this study, we identified a new infection defense mechanism in which intestinal epithelial cells sense the binding of viruses to the cell membrane and protect themselves from infection by inhibiting the function of endosomes. The analysis of this mechanism is expected to lead to the elucidation of the pathogenesis of intestinal infections and inflammatory bowel diseases and the development of therapeutic methods.
The results of this research were published in the electronic version of the American scientific journal Cell Host & Microbe on February 9, 2022.

Research Background

The intestinal mucosa is in contact with pathogens such as viruses and bacteria, and the intestinal epithelial cells, which are at the forefront of this contact, have their own defense mechanisms to prevent pathogens from entering the cells. The defense mechanism of intestinal epithelial cells is necessary to protect tissues from infection and to maintain intestinal homeostasis, and its disruption is deeply involved in the development of intestinal infection and inflammatory bowel disease. However, it remains unclear how intestinal epithelial cells detect and prevent pathogen invasion.

Research Results

The research group focused on the change in the localization of plasma membrane proteins from the luminal side of the intestine to the basement membrane side in small intestinal samples from rotavirus enteritis patients and conducted a comprehensive analysis using human intestinal organoids. As a result, we identified PARD6B as a molecule whose expression is down-regulated after rotavirus infection; as a function of PARD6B, it has been identified to promote endosome function (Nelms et al., 2017), and in rotavirus infection, the expression of PARD6B is down-regulated, leading to We hypothesized that there is a mechanism by which endosome function is inhibited.

Next, we measured the expression of PARD6B over time after rotavirus infection. When human intestinal epithelial cell lines and intestinal organoids were infected with rotavirus, the PARD6B/aPKC complex was degraded in a protease-dependent manner in the early stage of infection. Furthermore, infection of human intestinal organoids with an inactive form of rotavirus (virus-like particle), which does not enter cells and does not proliferate, induced degradation of PARD6B to the same extent as the active form of rotavirus. This indicates that the degradation of PARD6B is not induced by viral replication, but by binding to the cell membrane.

It has been reported that rotaviruses require sphingolipids for binding to cell membranes. When colonic epithelial cell lines were infected with cholera toxin or Shiga toxin, which bind to sphingolipids on cell membranes, degradation of PARD6B was similarly induced. In experiments using mutant strains of cholera toxin that do not bind to the receptor, degradation of PARD6B was not induced. This suggests that binding to glycosphingolipids is necessary to induce the degradation of the PARD6B/aPKC complex.

Finally, we hypothesized that epithelial cells prevent the entry of pathogens by inducing the degradation of the PARD6B/aPKC complex and inhibiting the function of endosomes. When the cells were infected with rotavirus and then Sendai virus, degradation of PARD6B was induced, and the amount of Sendai virus in the cells was significantly reduced compared to the group infected with rotavirus alone. Furthermore, cholera toxin infection followed by rotavirus infection resulted in a more pronounced decrease in the amount of rotavirus compared to the group infected with rotavirus alone.

These results indicate that intestinal epithelial cells sense when a virus or toxin binds to glycosphingolipids in the cell membrane and induces degradation of the PARD6B/aPKC complex, which inhibits endosomal function and protects against subsequent infection.

Research Summary and Future Perspective

In the future, we plan to elucidate the mechanism of the defense mechanism against infection identified in this study and analyze its function in vivo using knockout mice. In addition, we plan to study the relationship between the pathogenesis of intestinal infections and inflammatory bowel disease, which are caused by the breakdown of defense mechanisms, and the pathogenesis of villous atrophy, which is an abnormality of endocytosis.

Publication

Depletion of the apical endosome in response to viruses and bacterial toxins provides cell-autonomous host defense at mucosal surfaces

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