Roles of GPR39, a Zinc-Sensing Receptor, in the Regulation of Barrier Function of Intestinal Epithelial Cells

Thanyatorn Chantivas¹, Pawin Pongkorpsakol¹, Chatchai Muanprasat²

¹Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, ²Department of Physiology, Faculty of Science, Mahidol University, Bangkok, Thailand

Abstract

Zinc deficiency is associated with several gastrointestinal diseases such as diarrhea and IBD, whose pathogenesis is partly due to impaired intestinal barrier function. This observation suggests the beneficial role of zinc in regulating intestinal barrier function. The aim of this study was to investigate the effect of GPR39, a zinc-sensing receptor, on intestinal barrier function and its underlying mechanisms. The results showed that treatment of T84 cell monolayers with TC-G 1008, a GPR39 agonist significantly increased their transepithelial electrical resistance (TEER), indicating increased intestinal barrier function. The TC-G 1008-induced increase in TEER was in a time- and dose-dependent manner. Moreover, co-treatment with compound C, an AMPK inhibitor, completely abolished the effect of GPR39 agonist on TEER. This result suggests that AMPK may mediate the action of GPR39 agonist. In support of this notion, western blot analysis demonstrated that TC-G 1008 time-dependently induced AMPK phosphorylation, which reached its maximum at 2 hours paralleling the change in TER. Taken together, our results indicate that GPR39 activation can improve intestinal barrier function through an AMPK-dependent pathway. This study provides an insight into the roles of GPR39 in the control of intestinal epithelial barrier integrity, which may be important for understanding pathogenesis or developing treatment of intestinal diseases.

Introduction

The intestinal epithelia serve as a physical barrier against antigens and virulence factors from microorganisms. The paracellular space is also sealed with many types of intercellular junctions: tight junction, adherens junction, and desmosome. If these structures are damaged, it could lead to impaired intestinal barrier function which has been associated with many diseases, both intestinal and systemic.

GPR39 is a G protein-coupled receptor which has been identified as a zinc-sensing receptor. It is very likely that GPR39 is a mediator of zinc effects in regulating immune response and tight junctions in gastrointestinal tract. GPR39’s main intracellular signaling pathway in intestinal epithelial cells is mainly mediated by the Gαq pathway-elicited intracellular calcium concentration. Of particular importance, Gαq-Ca2+ signaling is well-accepted to activate intestinal AMP-activated protein kinase (AMPK), an intracellular energy sensor known to promote tight junction assembly.

There is, however, very limited data on how GPR39 promotes tight junction assembly. Thus, we hypothesized that zinc treatment and GPR39 stimulation could lead to AMPK activation which contributes to tight junction assembly.

Objectives

1. To investigate the effects of zinc-sensing receptor activation on barrier function of intestinal epithelial cells
2. To determine the role of AMPK in mediating the effect of zinc-sensing receptor on enhancing barrier function of intestinal epithelial cells

Methods


Results


Conclusion

Although zinc supplement has long been known to have a beneficial impact on intestinal health, mechanisms of its action have never been fully elucidated. Herein, using in vitro intestinal epithelial cells we have demonstrated the roles of GPR39 on intestinal barrier function, which is related to several aspects of intestinal physiology and pathology. Activation of GPR39 by a pharmacological agonist improved intestinal barrier function indicated by TEER in an AMPK-dependent fashion. This study provides evidence accountable for a mechanism of zinc action that might be mediated, at least in part, by stimulating GPR39-AMPK pathway. Further studies are required to provide a proof-of-principle that activation of GPR39 can be a therapeutic approach for preventing or treating diseases associated with tight junction disruption, in particular, inflammatory bowel disease and enteric infection.

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