

Roles of Zinc on Intestinal Barrier Function

Takuya Suzuki¹, Soichi Tanabe¹, Radhakrishna K Rao²

¹ Graduate School of Biosphere Science, Hiroshima University

² Health Science Center, University of Tennessee

Summary

Tight junctions (TJs) represent the major component of intestinal barrier function. In the impaired intestinal TJ barrier, the noxious substances permeate through the epithelium and induce chronic activation of intestinal immune system. Recent studies demonstrate that zinc, an essential trace element, has a crucial role in maintaining the intestinal homeostasis, however, its role for intestinal TJ barrier remains unclear. This study aimed to understand the physiological roles of zinc for intestinal TJ barrier and its interaction with pathogenesis of inflammatory bowel diseases.

The intracellular zinc was depleted using a zinc chelating agent, TPEN (N, N, N', N'-Tetrakis (2-pyridylmethyl) ethylenediamine) in human intestinal Caco-2 cells. The cellular zinc depletion induced the decreased transepithelial electrical resistance and increased dextran flux, indicating the impairment of TJ barrier. Immunoblot analysis showed that the TPEN treatment decreased the 2 TJ proteins, claudin-3 and occludin, at the protein levels in cells. Quantitative PCR analysis showed that TPEN decreased the mRNA level of claudin-3, but not occludin. The luciferase reporter assays revealed that 2 transcription factors, Sp1 and Egr-1, carrying zinc finger motifs in the molecules, have the important roles in the zinc-mediated transcriptional regulation of claudin-3. Whereas, a cell surface biotinylation technique showed that the zinc depletion increased the cellular degradation of occludin at the protein level. Further, the decrease in intestinal ZIP5, a zinc transporter, was observed in colitic mice with showing the impaired expressions of claudin-3 and occludin.

Taken together, the intestinal zinc has crucial roles on maintaining the TJ barrier integrity. Zinc regulates the transcriptional activity of claudin-3 and survival ability of occludin protein in cells. In addition, our results suggest that the decreased ZIP5 is possibly involved in the pathogenesis of inflammatory bowel diseases.