doi 10.18699/bgrs2024-7.2-07

Ceramide affects intestinal epithelial barrier integrity via destabilization of actin cytoskeleton in chronic colitis

Medvedeva S.[1], Boldyreva L.[2]*, Achasova K.[1]*, Ogienko A.[1], Kozhevnikova E.[1, 3]**

[1] *Institute of Molecular and Cellular Biology, SB RAS, Novosibirsk, Russia*

[2] *Scientific Research Institute of Neurosciences and Medicine, Novosibirsk, Russia*

[3] *Novosibirsk State Agrarian University, Novosibirsk, Russia*

* *Equal contribution*

** *kozhevnikova@mcb.nsc.ru*

Key words: chronic colitis; intestinal barrier; filamentous actin; lipid metabolism

Motivation and Aim: Intestinal barrier dysfunction, also known as “leaky gut”, is characteristic of gastrointestinal diseases, especially inflammatory bowel diseases (IBD), celiac disease, enteric infections, irritable bowel syndrome (IBS), and others. Despite the extensive research in this field, there are only a few drugs available for the treatment of IBD in clinical practice. Although numerous works have investigated the mechanisms underlying the regulation of gut barrier function using models of acute inflammation, there is still a lack of understanding about how the barrier function of the intestine is compromised during the development of low-grade inflammation.

Methods: Metabolomic and transcriptomic analyses were combined with three alternative in vivo models of chronic colitis in mice to unravel common metabolic features of inflammation. Confocal microscopy was used to localize filamentous actin and tight- and adherence junctions’ proteins in the intestinal tissues. In vivo intestinal permeability was used in the functional test of barrier function.

Results: Here we show that phospholipid metabolism is impaired in transgenic Muc2 mouse model of chronic colitis, which is supported by the transcriptomic and metabolomic analysis of the descending large intestine. This data was supported in two alternative models of chronic colitis in mice in vivo: chemically-induced and associated with T-cells adoptive transfer colitis. We proposed that the upregulated ceramide metabolism might be responsible for the impairment of filamentous actin dynamics impairment, which in turn controls barrier function. The addition of ceramide and ceramide-synthase inhibitors affect actin polymerization, tight- and adherence junction proteins localization to the membrane, and intestinal barrier function in two independent mouse colitis models *in vivo*. This data agrees with current studies suggesting upregulation of ceramide in IBD patients.

Conclusion: Thus, our data provides a novel mechanism that underlies intestinal barrier disfunction upon chronic colitis.

Funding: The study is supported by funded by the Russian Science Foundation, grant number 20-74-10022-П.