GPR4 Deficiency Ameliorates Intestinal Inflammation in a Mouse Model of Inflammatory Bowel Disease

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Background: An acidotic tissue microenvironment commonly exists in many types of inflammatory disorders including inflammatory bowel disease (IBD). However, the role for acidosis and related molecular pathways in inflammation is poorly understood. GPR4 is a pH-sensing G protein-coupled receptor that can be activated by extracellular acidosis through protonation of several histidine residues. Upon activation of GPR4, multiple downstream signaling pathways are stimulated such as the Gs/cAMP, Gq/Ca2+/protein kinase C, and G13/Rho GTPase pathways. It has recently been demonstrated that activation of GPR4 by acidosis increases the expression of numerous inflammatory and stress response genes in vascular endothelial cells (ECs) and also augments the adhesion between ECs and leukocytes. Importantly, inhibition of GPR4 by siRNA or small molecule inhibitors reduces endothelial cell inflammation in vitro and alleviates arthritis in a mouse model in vivo.

Methods: In this study, we examined the role of GPR4 in IBD using a dextran sulfate sodium (DSS)-induced colitis mouse model. Wild-type and GPR4-deficient mice were treated with 3% DSS for 7 days to induce acute colitis.

Results: Our results showed that the severity of colitis was decreased in the GPR4-deficient mice in comparison to the wild-type mice. Clinical parameters such as body weight loss, fecal score, colon shrinkage, and mesenteric lymph node enlargement of the DSS treated GPR4-deficient mice were less severe than that of the DSS treated wild-type mice.

Conclusions: These results suggest that GPR4 deficiency ameliorates colitis in the DSS-induced IBD mouse model, and GPR4 small molecule and siRNA inhibitors may be explored as novel agents for the prevention and treatment of inflammatory bowel disease.