Wenjing Yang, MD, PhD
Postdoctoral Researcher

GPR120 Suppresses Intestinal Inflammation Through Regulation of CD4+ T cell IL-10 Production

Dr. Yang has several years' research training in the field of IBD and mucosal immunology. As a medical student, she not only mastered the clinical knowledge of clinical medicine, especially gastroenterology, but also attended several biological courses, including medical cell biology, molecular biology, physiology, pathophysiology, immunology, and research methods, from which she drew much of her interest in scientific research. She received her MD degree 2013. During her residency training from 2013-2016 at Shanghai 10th People's Hospital, Tongji University, she grasped the diagnosis and treatment of IBD, and gained interest in it. She was able to conduct research on IBD with Dr. Zhanju Liu, a renowned physician scientist specialized in IBD research and clinic care in Tongji University. In 2016, she was enrolled to the PhD graduate program of Tongji University in Dr. Liu's laboratory. Her research focused on the roles of Rho-associated kinase (ROCK)2 in CD4+ T cell differentiation and the development of inflammatory bowel disease (IBD). In addition, she also took part in other projects closely related with the basic research of mucosal immunology and the pathogenesis of IBD. These works helped her to gain key knowledge on mucosal immunology and related techniques. Since 2017, she chose to further her research as a predoctoral fellow with Dr. Yingzi Cong, a professor at UTMB as well as a renowned expert in the mucosal immunology and immune regulation of IBD, on the roles of microbiota metabolites in regulating innate and adaptive immune responses. This position has broadened her perspectives on research and helped to equip herself with important professional skills. After she received her PhD degree, she continues to work with Dr. Cong as a postdoctoral fellow. During these four years in UTMB, she was actively involved in several projects related with IBD and mucosal immunology, including intestinal barrier functions and have published ten articles. Aside from these experiences, she also has a passion for investigating the mechanisms involved in the pathogenesis of colitis, so she enjoys recent work.

Abstract: Background: $CD4^+$ T cell production of IL-10 plays a critical role in maintaining intestinal homeostasis. G protein-coupled receptor (GPR) 120, a receptor for omega 3 fatty acids, has been implicated in regulating metabolic syndromes with anti-inflammatory function. However, the role of GPR120 in intestinal inflammation is unknown. In this study, we investigated whether and how GPR120 regulates $CD4^+$ T cell production of IL-10 to the maintenance of intestinal homeostasis.

Methods: Dextran sodium sulfate (DSS) induced colitis model and *Citrobacter. rodentium* induced infection model were used for comparison of intestinal inflammation between wild-type (WT) and *Gpr120*$^{-/-}$ mice, or *Cd4*^{cre} *Gpr120*$^{fl/+}$ and *Cd4*^{cre} *Gpr120*$^{fl/fl}$ mice. GPR120 expression in different cell types was measured by Western blot. $CD4^+CD45RB^{hi}$ T cell adoptive transfer model was utilized to analyze the pathogenesis of WT and GPR120-deficient $CD4^+$ T cells in inducing colitis. Mouse splenic $CD4^+$ T cells were treated with or without GPR120 agonist, CpdA, and the gene differences were analyzed by RNA sequencing and qRT-PCR. The effect of GPR120 on T cell metabolism was measured by glucose uptake assay and Seahorse metabolic assay. Chemical inhibitors, including mTOR inhibitor and glycolysis inhibitor, and Blimp1-deficient $CD4^+$ T cells isolated from *Cd4*^{cre} *Prdm1*$^{fl/fl}$ mice were used for mechanistic studies. Mice were administered GPR120 agonist for investigating the potential treatment of GPR120 agonist in treating intestinal inflammation.

Results: We demonstrated that deficiency of GPR120 resulted in more severe colitis in mice upon inflammatory insults and enteric infection. Interestingly, $CD4^+$ T cells expressed GPR120 at a high level, and mice specifically lacking GPR120 in $CD4^+$ T cells were more susceptible to colitis development. Transfer of GPR120-deficient $CD4^+$ $CD45Rb^{hi}$ T cells induced more severe colitis in *Rag*$^{-/-}$ mice with increased IL-17 and IFNγ producing $CD4^+$ T cells and decreased IL-10 producing $CD4^+$ T cells in intestinal lamina propria than WT T cells. Treatment with GPR120 agonist, CpdA, promoted $CD4^+$ T cell production of IL-10 by upregulating Blimp1 and enhancing glycolysis, which were regulated by mTOR. Consistently, docosahexaenoic acid (DHA), a dietary long-chain fatty acid, also upregulated the IL-10 production in $CD4^+$ T cells. GPR120 agonist-treated WT but not Blimp1-deficient Th1 cells induced less severe colitis. Importantly, oral administration of CpdA protected mice against intestinal inflammation.

Conclusions: Our findings demonstrate the role of GPR120 in regulating intestinal $CD4^+$ T cell production of IL-10 to maintain intestinal homeostasis, which identifies GPR120 as a potential therapeutic target for IBD treatment.