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Conference Details

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Communication Title: Glial Cx43 regulates neuro-immune interactions in the mouse colon

ABSTRACT

The enteric nervous system is a network of neurons and glial cells that provides local regulation of gut reflexes. Our prior data show that enteric glia regulate the activity and survival of enteric neurons in health and disease through mechanisms that involve the release of mediators through connexin-43 (Cx43) hemichannels [reviewed in (1)]. Given that immune cells express receptors for glial mediators released via Cx43, we hypothesized that enteroglial signaling involving Cx43 contributes to immune cell recruitment. Cx43 was ablated in glial cells in hGFAP::CreERT2+/–/ Cx43f/f transgenic mice (TG) and we assessed the effect of acute and chronic inflammation driven by dextran sodium sulfate (DSS). Acute colitis (aDSS) was induced by 2% DSS in drinking water for 1 week while chronic colitis (cDSS) was driven by intermittent exposure to DSS (1 week on/ 1 off) for 3 weeks. Body weight and macroscopic damage were used to assess the inflammation, and immunohisto-chemistry was used to determine numbers of neurons, glia and immune cells. Cytokine profiles were assayed by plate array. Our results show that DSS caused weight loss and macroscopic tissue damage, but not significant neurodegeneration in the myenteric plexus of either TG mice or littermate controls (wt). cDSS drove a significant increase in CD45+ and CD68+ immune cells in wt mice ($P = 0.013$ and 0.013, 2-way ANOVA, water-DSS comparison) that was not observed in TG animals ($P = 0.127$ and 0.982, 2-way ANOVA, water-DSS comparison). In addition, loss of enteroglial Cx43 affected the colonic production of cytokines: about 2-fold reduction of IL-2, IL-7, IL-9, and MIP-1a ($P < 0.05$, 2-way ANOVA, genotype comparison), and protected against the aDSS-induced increase of M-CSF in the transgenic animals [$P = 0.030$ (wt) vs 0.904 (TG), 2-way ANOVA, water-DSS comparison]. Together, our findings show that enteric glia contribute to immune cell recruitment during the chronic phase of inflammation through mechanisms that involve Cx43. These novel findings could be used to design novel therapeutics for inflammatory bowel disease.

REFERENCE: (1) Grubišić V, Gulbransen BD. Enteric glia: the most alimentary of all glia. J Physiol. 595(2): 557-570 (2017).

COMMUNICATION OUTCOMES

Crohn's and colitis, collectively known as inflammatory bowel disease (IBD), are characterized by interchanging periods of active inflammation and improvement. IBD patients in remission, however, still suffer from the persistent functional bowel deficits that underlie ongoing symptoms including diarrhea and abdominal pain. Ultimately 75% of IBD patients undergo palliative surgery to remove non-functional bowel segments. Since surgery does not treat IBD, most patients experience disease reoccurrence and additional resections. Therefore, new targeted therapies are needed for protection of gut function in IBD.

Gut function is controlled by the enteric nervous system, often called "the brain in the gut", an intricate network of neurons and glial cells residing in the gut wall. Normally enteric glial cells promote the stability of the intestinal lining, regulate gut motility and secretomotor function. In disease, however, these glial cells are transformed and intensify tissue damage. This project is aimed to identify specific cell and molecular pathways necessary to develop new and more effective IBD treatments. Specifically, I am investigating the role of enteric glia in the regulation of neuro-immune interactions in the gut, as described in the abstract. The findings of my studies are of general interest to the fields of neurogastroenterology and neuroscience as a whole. More importantly, the outcomes of my research will lead to novel and more specific therapeutic venues to improve the quality of life in patients suffering from IBD.

The inaugural Crohn's & Colitis Congress (January 18-20, 2018 in Las Vegas), organized by the Crohn's & Colitis Foundation and the American Gastroenterological Association, will allow me to learn about novel studies such as the experimental models of colitis, enteric neuro-immune signaling, visceral pain, as well as recent clinical breakthroughs in treating IBD. The congress will bring me closer to my long-range career objective of becoming an independent researcher at a top-tier academic institution. Attending this meeting is a special opportunity to meet new colleagues, discuss exciting research findings, and establish new professional contacts/ collaborations that will further advance my career and the IBD field.