Technical update

The operating grant entitled “Sympathetic neuropathy in IBD: causes and consequences” has been funded for one full year to date. This proposal aimed to address 1) how inflammation inhibits sympathetic neurotransmitter access to its receptors and 2) how the immune system is modulated by the SNS. Using mouse models of IBD, substantial progress has been made towards each of these aims as is detailed below.

1) We have uncovered dramatic effects of colitis and a cytokine associated with IBD, interleukin 17, on the structure of the sympathetic innervation of both the gut and the immune system. Essentially, there is a significant ingrowth of sympathetic axons into the inflamed colon and into the spleen. We have developed several novel in vitro assays to examine how inflammation alters sympathetic neuroanatomy and have gained insight into the underlying mechanisms. In particular, we have identified roles for the activation of nuclear factor kappa B pathway signalling and the inhibition of Ca2+ influx through ion channels in neurite outgrowth in response to interleukin 17.

We have also examined whether the major source of circulating catecholamines, the adrenal medulla, is affected by colitis. We used electrophysiological and imaging techniques to examine whether catecholamine release mechanisms in adrenal chromaffin cells were altered in three distinct models of colitis. Similar to what we observed in sympathetic neurons that innervate the colon, colitis inhibited voltage-gated Ca2+ current in adrenal chromaffin cells, which is predicted to reduce catecholamine release. Since these endocrine cells are located outside of the gut and have no axons, these data strongly support the idea that localised gastrointestinal inflammation can have remarkably widespread effects on the nervous system.

2) We have developed several techniques to examine whether receptors for sympathetic catecholamines, adrenergic receptors, are present on and can modify the activity of, immune cells. We have begun this work by examining whether adrenergic receptor agonists can alter peritoneal macrophage activation by lipopolysaccharide (LPS). This was done by assaying mRNA levels of several important cytokines or inducible nitric oxide and my ELISA measurements of cytokine secretion. We have found that β2 and β3 receptor activation was almost as effective as the steroid dexamethosone at inhibiting the secretion of the proinflammatory cytokine TNFα and enhancing the secretion of the anti-inflammatory cytokine IL-10 in response to LPS. Interestingly, adrenergic receptor agonists had interesting differences in their effects of iNOS upregulation
and IL-6 secretion compared to their effects on TNFα, suggesting that the effects of adrenergic receptor activation are not due to a global shutting down of the inflammasome. We have developed a collaboration with Dr. Cecilia Berin, an expert in mucosal immunology at the Institute of Immunology at Mt Sinai School of Medicine in New York to examine how the function of lamina propria immune cells, in particular CD4+ve T cells, are affected by adrenergic receptor activation.

Lay translation

Our laboratory studies how inflammatory bowel diseases (IBD) alter the function of the nervous system and whether the nervous system can suppress inflammation in IBD. We focus on a particular branch of the nervous system, the sympathetic nervous system (SNS). The SNS resides outside the gut but sends axons into the gut where they regulate gut functions including motility, blood flow and secretion. Importantly, recent evidence suggests that the SNS can also modulate the immune system and change the severity of inflammation in mouse models of IBD.

In the past year, we have discovered that the structure of the SNS is profoundly affected in models of IBD. Sympathetic neurons are much more numerous in the guts on animals with colitis and we have evidence that this may be due to a specific molecule secreted by activated immune cells, interleukin 17. We have worked out how this molecule has this effect and are continuing with this work to see what the functional consequence of this rewiring of the nervous system might be. Our laboratory has also made good progress towards understanding what molecules the SNS releases to control inflammation. We have found that immune cells express receptors for SNS neurotransmitters, and that some of these receptors suppress the release of damaging molecules, including tumour necrosis factor alpha, the molecule targeted by infliximab, from activated immune cells. To date we have focussed on a single type of immune cell. Our ongoing work will determine how SNS neurotransmitters signal to reduce inflammation and whether SNS transmitters can suppress other immune cell types.

A list of abstracts and papers presented, published and/or submitted for publication related to the project or other work facilitated by CCFC funding during the year.

Original Research (Trainees in italics; * indicates author for correspondence)


Review articles


Submitted article

Abstracts


Supplementary funding
- A New Investigator Salary Award from the Canadian Association for Gastroenterology
- An Early Researcher Award from the Ontario Ministry for Research and Innovation
- A Master’s Award for Outstanding Achievement in Basic or Clinical Digestive Sciences from the American Gastroenterology Association
- A CIHR graduate scholarship awarded to Mr. Mark Lukewich
- An NSERC graduate scholarship awarded to Ms. Andrea Cervi
- A CAG/CCFC undergraduate summer studentship awarded to Mr. Jovian Wat.

The number of research assistants and other staff members (including their roles and level of education) supported by CCFC funding.
- One research assistant
- Three MSc students
- Two undergraduate summer students