

Relevance to IBD

In the intestine, as in the central nervous system and brain, neurons that are lost are not replaced, and if enough damage occurs, there will be impairment or loss of function. Evidence that neurons are lost in the inflamed intestine in animal models suggests that the severe inflammation of IBD involves a similar pathology. However, surprisingly little is known about the effects of severe inflammation on damage to intestinal neurons, in either IBD in humans or in animal models of intestinal inflammation. The consequences include impaired motility and altered mucosal transport that may become permanent if not met by adaptive processes. Further, our recent work correlates neural loss with stricture formation as a final endpoint of inflammation-induced remodelling. This proposal addresses this issue of neural damage through use of an animal model to gain insight into IBD.

Earlier, we carried out the first thorough study of the effects of colitis on neurons, using a rat model, and showed that up to 40% of neurons die quite early in colitis, within the first 24 hr. This animal model of TH1-predominant disease is the best current approach to Crohn's disease, being well-characterized, and perhaps above all, involving sporadic stricture formation at late time points in our hands. Recently, we found that axon loss occurs (as expected) but the important finding was the subsequent axonal *proliferation* that was greatly in excess of that loss - sufficient to re-innervate the ISMC that also increased in number at that time. Therefore, this model offers an excellent opportunity to gain understanding of the effect of inflammation on the ENS and the response of the ENS to inflammatory damage.

Tissue culture studies are an important part of the proposed research. This uses primary cultures of neurons, smooth muscle and glia for the study of neuron-smooth muscle interactions and the nature and outcome of neural damage. While cell lines will be employed as needed (ie, early passage pure cultures of ISMC or glia), these primary co-cultures are the closest possible approach to events in vivo that allow precise control of cellular environment.

The animal model, and its tissue culture parallel allows study of the events at the start of inflammation that cannot otherwise be approached. This is due to the inability in IBD research to obtain useful biopsy specimens from regions below the mucosa, although it is these regions that suffer the lasting changes to innervation and smooth muscle. Tissue obtained upon resection is inevitably for severe disease, and is affected by prior and ongoing treatments as well as the usual years-long course of inflammation. The research proposed here remains close to human IBD through an animal model, and where done in vitro, uses cells that remain close to their nature in vivo.

The goals of study of damage to the enteric nervous system, its consequences to smooth muscle regulation and the processes of nerve regeneration are important to our general understanding of intestinal inflammation in animal models and IBD in two major ways. First, understanding the nature of nerve cell damage is important in finding ways to prevent it. Second, understanding the physiological processes of the repair mechanisms gives important clues to directions for extrinsic intervention to promote nerve preservation and repair.