

**RELEVANCE TO IBD**

Chronic intestinal inflammatory diseases (IBD) are multifactorial disorders involving interactions between the immune system, genetic susceptibility and the environment. Major advances in the genetic analysis of the causes of IBD have added support to the fact that both immune cells of the T cell lineages and intestinal epithelial cells play key roles in the pathophysiology of the intestinal inflammation in IBD. IBD research has led to the identification of cytokine networks involved in intestinal inflammation. This resulted in the development of a wealth of novel therapeutic strategies, including biological therapies. We believe that much more information must be gathered in order to develop targeted strategies to control IBD.

In the last few years, our research efforts have focused on determining how intestinal epithelial cells are altered in response to inflammatory processes. We have uncovered the C/EBP class of transcription factors as major regulators of acute phase protein (APP) genes in intestinal epithelial cells *in vitro* in response to cytokines and hormones and *in vivo* during inflammation. We have also developed a research program in order to understand the mechanisms involved in the action of a novel class of anti-inflammatory agents, namely histone deacetylase inhibitors (HDACi). These inhibitors affect the acetylation levels of histones, leading to modifications of chromatin structure, and of non-histone proteins, including transcription factors. We have observed that HDACi, including butyrate, a short-chain fatty acid produced by anaerobic bacterial fermentation in the colon, modulate the expression of APPs both in rat and human intestinal epithelial cells, by acting in part through C/EBPs and NF- $\kappa$ B. Butyrate is a primary energy source for colonocytes, promotes the migration of intestinal epithelial cells and affects proliferation, apoptosis and differentiation of various colon carcinoma cell lines. A defect in butyrate metabolism in the colonic epithelium of ulcerative colitis patients was observed. Furthermore, butyrate enemas may be effective in certain cases of ulcerative colitis. We finally determined that one member of the histone deacetylase family, namely HDAC1, played a major role in the regulation of C/EBP-dependent transcriptional activation of APP gene expression.

In this proposal, we will develop novel animal models of DSS colitis in order to determine the role of C/EBPs in intestinal inflammation. Indeed, we will use murine models in which the C/EBP $\beta$  isoform is deleted, or conditionally deleted in intestinal epithelial cells. These models will no doubt lead to increased knowledge of the role of C/EBP $\beta$  in the crosstalk between intestinal epithelial and immune cells, and may identify C/EBP $\beta$  as a future target for IBD therapies. We have also created a cell culture model specifically inhibiting HDAC1 expression. This model will be of utmost importance to understand the mechanisms involved in histone deacetylase-dependent regulation of C/EBP-dependent transcriptional activation, and to uncover the anti-inflammatory action of HDACi. This research program will establish necessary knowledge that will eventually be used to study the *in vivo* intestinal anti-inflammatory response of numerous HDACi now being synthesized, and showing increased specificity. Our cell culture model and our planned model of conditional HDAC1 deletion in intestinal epithelial cells will uncover the importance of HDACs in intestinal inflammation. We think that our proposed research program is highly relevant to IBD.