

Crohn disease (CD) is a chronic debilitating inflammatory bowel disease. While the pathogenesis of CD remains ill-defined, compelling evidence indicates that in the genetically susceptible host there is an inappropriate response to intestinal microorganisms. Genome wide association studies published this past year identified an entirely new and unexpected potential pathophysiologic mechanism involved in CD. Indeed, variants in the autophagy dependent gene, ATG16L1, are associated with CD, thereby implicating autophagy in disease pathogenesis. The mechanisms by which variants in ATG16L1 promote intestinal inflammation are unknown. However, considering the role of autophagy in innate defense and immunity and the current hypothesis that inflammatory bowel disease is due to an inappropriate host response to infection with commensal or pathogenic luminal bacteria, there is considerable biologic plausibility for its role in inflammatory bowel disease. In support of the idea that autophagy might be important for controlling infection and regulating immune responses, our preliminary studies have determined that autophagy restricts the growth of the gastric pathogen *Helicobacter pylori*. Furthermore, employing genetic association studies, we identified that the ATG16L1 CD variant also increases susceptibility to *H. pylori* infection. Based on these findings, we now propose to specifically examine the role of ATG16L1 CD variant in the possible dysregulation of autophagy and its link with the development of inflammation. Accordingly, we hypothesize that the ATG16L1 variant reduces the efficiency of autophagy in response to intracellular bacteria, thereby promoting persistent infection and intestinal inflammation. In order to address this overall aim, we have brought together experts in the fields of autophagy, bacterial-host interactions and CD pathogenesis. Through this interdisciplinary approach involving myself and three other scientists, namely Drs. John Brumell, Mark Silverberg and Dana Philpott, the overall goal of this proposal is to determine the functional relevance of the ATG16L1 CD variant during autophagy and its role in CD pathogenesis. Our findings will have important implications for understanding CD pathogenesis and should lead to the development of novel treatment strategies for inflammatory bowel disease.