

A novel role for P-glycoprotein in regulating the interaction between the colonic epithelium and commensal gut bacteria: implications for the pathogenesis of inflammatory bowel disease

Geoffrey Warhurst, Gordon Carlson, Gordon Armstrong

Gut Barrier Group, Injury Research, School of Medicine, University of Manchester and Histopathology Unit, Hope Hospital, Salford M6 8HD

Law Summary

The cells which line the colon play a vital role in maintaining our health. They not only absorb water and nutrients, but also act as a barrier to prevent the huge load of colonic bacteria and their toxic products from gaining access to our bodies. Recent studies have shown that the normal bacterial flora of the colon plays a key role in the development of colitis, and that the development of inflammation in the lining of the colon results in impairment of its barrier function. It is, however, both unclear and a source of great controversy whether this is a primary event in the cause of colitis, or a consequence of the inflammation which characterises the disease. Pilot work in our laboratories, funded by NACC, has investigated early events in the cells lining the colon of a strain of mice, which are deficient in a protein called P-glycoprotein (PGP). PGP is found in humans as well as mice. Although the normal role of PGP is unclear, it may have a role in pumping out toxic substances from the cells that line the colon. The novel finding is that mice lacking PGP develop a disease closely resembling ulcerative colitis and our early observations have shown that, **before colitis develops** in these animals, several key genes which control interactions between the colonic lining and the normal gut bacteria are switched on. The present proposal aims to build directly upon these studies to address the mechanisms by which PGP may prevent the normal gut bacteria from inducing damage in the colonic lining. We believe that these novel observations provide important information regarding the cause of ulcerative colitis and may ultimately suggest new therapies, which will allow us to treat or even prevent the disease.

Our aim is to determine how and why the loss of PGP function results in induction of inflammation and cell death when the cells that line the colon are exposed to normal colonic bacteria and their products.

We will study production of inflammatory molecules and induction of cell death (both key events in the development of colitis) in the cells lining the colon of normal mice and PGP-deficient mice, after exposing the cells to normal intestinal bacteria and their products. We aim to discover which pathways that control these responses are activated in colonic cells and the precise mechanisms by which activation occurs in the absence of PGP.

Studies will also be undertaken to determine if substances produced by these bacteria can be transported out of the cells lining the colon by PGP. As well as mouse cells, we will also use cells obtained from the colonic lining of patients undergoing bowel surgery to investigate whether the findings of our animal studies can be reproduced in human cells. To do this we will block PGP function in the human cells and determine whether their exposure to normal gut bacteria leads to cell death and/or activation of inflammation. The likely relevance of PGP to human disease is supported by recent clinical evidence that individuals with an inherited mutation that reduces the PGP in their gut appear to be at greater risk of developing ulcerative colitis. Our studies will help in understanding the reasons for this increased risk and could also suggest new therapies to control the interaction between the colonic lining and gut bacteria, aimed at PGP.