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Grant awarded £5,920 (1 Year)

Colonic gene expression in a novel model of colitis: preliminary evaluation of the molecular mechanisms by which a primary defect in the mucosal barrier leads to IBD

Despite a great deal of research, we still have a very poor understanding of how and why ulcerative colitis (UC) develops. One theory is that UC develops because of a failure in the gut epithelium, the layer of cells that line the intestine. These are special cells that form a barrier between the bowel contents and the rest of the body. They are special cells that under normal circumstances allow water and food to be absorbed from the intestine but stop harmful substances such as bacteria or environmental toxins from entering the body. It is possible that gut inflammation develops in the first place because, for some reason, this layer of cells becomes defective and allows bacteria to enter the body. This causes inflammation which further damages the cell layer leading to more inflammation. Eventually this cycle of events leads to fully developed UC.

Unfortunately, this interesting theory has been difficult to prove. It is possible to show that UC develops in animals when gut cells are severely damaged by chemicals but this extreme situation is unlikely to occur in humans. To prove that defects in the gut lining are important in causing UC, we need to show that subtle changes of the sort that we might expect to see in man can cause disease.

The current application seeks preliminary funding to study a new model of UC that may allow us to prove this theory. This work is based on mice that have been genetically engineered so that they no longer make a protein called P-glycoprotein (PGP). PGP is a very important protein which helps to protect us from harmful chemicals. It is present in the gut of man and other animals and works by pumping harmful substances back into the gut lumen ensuring that they do not enter the body. Mice that do not make this protein appear healthy but a large proportion of them (>75%) develop a UC in adulthood that is almost identical to the human disease. This model is unique because it is the first one in which a defect in a specific “barrier” protein in the gut has been linked to the development of UC.

At the moment we do not know what changes occur in the cells lining the gut in animals lacking PGP and the studies outlined in this proposal are a first attempt to do this. We intend to take intestine from PGP KO mice before and after they develop colitis and look at whether genes which we believe may be involved in maintaining an intact gut barrier are changed (ie either switched on or off). By comparing this with normal animals we will begin to understand what changes in gut cells predispose to developing colitis.

These studies should offer us a much clearer understanding of how a simple defect in the intestinal barrier can lead to IBD and will provide preliminary data for further more extensive studies. We believe this model is particularly relevant to the human disease because scientists have recently shown that a significant proportion of the human population may have defective PGP in their intestine. Of course, we do not know whether this will make them more likely to develop IBD but it is an intriguing possibility.