

Gordon Dent

Title of Project

Eosinophil/epithelium interactions in inflammatory bowel disease; a pilot study

Lay Summary

Eosinophils are a type of white blood cell (leukocyte) found in tissues affected by many chronic inflammatory diseases, including asthma, pulmonary and myocardial fibrosis, and inflammatory bowel diseases (IBD). The role of eosinophils in the pathology of IBD is poorly understood, although they are known to produce factors which may contribute to the scarring and intestinal narrowing in Crohn's disease. Recent research has also shown how they may affect the layer of cells (epithelium) lining the intestine to allow bacteria to pass through more easily: the infection of the underlying tissues leads to the acute, severe inflammation that characterizes ulcerative colitis (UC). This inflammatory response involves the influx of another type of leukocyte – neutrophils – which are responsible for causing pain and tissue destruction in the colon. The mechanisms by which eosinophils become activated in the colon and by which neutrophils are attracted to the tissues are important features of the understanding of how inflammation occurs in UC. Our previous research has indicated that contact with epithelial cells from the lungs increases the responsiveness of eosinophils and that the eosinophils and epithelial cells in combination produce large quantities of neutrophil-attracting substances (chemoattractants). These interactions may contribute to the episodic flare-ups (exacerbations) of asthma and, we propose, similar events may be involved in the episodic flare-ups characteristic of UC. Our hypothesis is that eosinophils and colonic epithelial cells in combination produce elevated levels of eosinophil products – which cause local tissue damage and mucus secretion – and of predominantly epithelium-derived neutrophil chemoattractants, which bring neutrophils into the colon and lead to even greater tissue damage and mucus secretion. We wish to perform experiments with colonic epithelial cells and eosinophils in the laboratory to see how the cells affect each other's secretory activity. We shall measure the output of eosinophil inflammatory products and neutrophil chemoattractants from eosinophils alone, epithelial cells alone, and eosinophils and epithelial cells in combination. We shall also determine whether the interaction between the cells depends upon direct contact between the cells or can be mimicked by exposing each cell type to substances released from the other cell type. With this knowledge we shall be able to suggest whether the eosinophil-epithelial interaction may contribute to some of the important inflammatory processes occurring in UC. By finding out whether the interaction depends upon direct contact between the cells, we shall also be able to suggest some types of molecule on or in the cells which may be targeted by novel anti-inflammatory drugs to suppress the interaction. We shall use this knowledge to design experiments to characterize the interaction in greater detail and to define specific molecular targets for therapeutic intervention.