The role of Notch signalling in restitution, regeneration and remission in inflammatory bowel disease. -Lay Summary

Aims: The aim of this pilot study is to deduce the impact of the Notch signalling pathway on inflammatory bowel disease. Although a potent regulator of cell behaviour in a diverse range of biological systems, nothing is known of Notch's role in either the pathology or remission of IBD. We propose that these investigations will increase our knowledge of the underlying mechanisms governing tissue repair and therefore clinical remission following inflammatory damage in IBD sufferers.

Background and research plan: Inflammatory bowel disease (IBD) is a chronic, debilitating, and incurable condition affecting the epithelial lining of gut. Disease remission requires not only a reduction in inflammation but the damaged tissue must also restore its functional capacity through the processes of restitution and regeneration. The mechanisms regulating these reparative processes are not well understood but inadequate repair of the epithelium compromises this important barrier to gut content and can result in persistent symptoms, infection and chronic inflammation.

The Notch signalling pathway functions during embryogenesis but also in regulating homeostasis in adult tissues. In the mouse intestine, Notch has been shown to regulate the proliferation of the epithelial stem cells and also the fate of differentiating cells into their functional types. Nothing is currently known about the role of Notch in IBD yet its role in homeostasis makes it a strong candidate for a key role in intestinal restitution and repair. Our preliminary data shows that Notch is overexpressed in IBD compared with normal tissue and becomes visibly activated at the edge of ulcers. The epithelial cells at these edges take on a flattened shape and move across the denuded area in order to restore the epithelial barrier. We have also found that Notch can induce changes in cell shape in colorectal epithelial cells *in vitro.* These data, along with similar roles for Notch during embryogenesis, suggest that Notch could control this alteration in cell behaviour and therefore facilitate this important process in IBD. Using colorectal cell lines we will determine the role of Notch in restitution *in vitro* through cell motility and wounding assays. We will determine the affect of Notch on cell polarity and cytoskeletal reorganisation as these are also altered during restitution. Following restitution, widespread cell division is required to allow the reconstruction of the architecture of the mucosa into the characteristic glandular crypt structures. The known role of Notch in epithelial stem cell maintenance and cell fate specification also imply it's importance for this regenerative process. Using our model we will determine the role of Notch signalling in regulating cell growth and also in gland formation using colony growth in collagen gels.

The final aim of this project will be to determine whether dietary factors such as sodium butyrate and drugs such as 5-aminosalicylate (used to treat IBD) can influence Notch expression and activity and therefore its role in restitution and repair.

This study will increase our understanding of the key processes that determine satisfactory remission in IBD and will give us an insight into the ways in which the clinical management of these debilitating diseases could be improved through increased knowledge of the effects of diet and therapeutics on restitution, regeneration and therefore remission.

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