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Grant awarded £6,000 (1 Year)

Investigating the contribution and possible interaction between NF- κ B and PI-3 Kinase in the TNF- α induced signalling cascades in intestinal epithelial cells

Inflammatory Bowel Disease (IBD), comprising Crohn's Disease and Ulcerative Colitis, is a common relapsing and remitting condition whose precise cause is unknown and which is characterised by chronic uncontrolled inflammation. Medical therapies are generally based on broad, non-specific down regulation of the inflammatory response with compounds such as steroids which have side effects and variable efficacy.

Recently advances have been made in establishing a more detailed understanding of the molecular mechanisms involved in inflammation in the bowel. This information has proved crucial to establishing more specific α and effective treatments for IBD which take a more molecular approach using a variety of targets. At the forefront of these advances is treatment based on the administration of antibodies against Tumour Necrosis Factor- α (TNF- α). This pro-inflammatory molecule appears to be pivotal in Crohn's Disease and blocking its actions with antibodies against it has been shown to have a dramatic beneficial effect in people with this condition.

However, with regard to TNF- α , there are still vital pieces of information missing about this molecule and how it causes inflammation. In particular, it is not precisely known how TNF- α , once bound to cells in the bowel, sends messages or signals to that cell to tell it to behave in a pro-inflammatory way. The chain of events or reactions in the cell, stimulated by the binding of TNF- α to it, is called a signalling cascade and identifying the components of this is what this pilot study aims to do. In doing so we hope to establish targets for future therapeutic intervention.

To identify the signalling cascades used by TNF- α we will use colonic intestinal epithelial cells and laboratory models of inflammation. We will infect these cells using a virus that will deliver defective forms of enzymes and molecules which we believe to be important in the signalling process. We will then study how the inflammatory behaviour of the cells has changed and thus work out which are the key molecules involved in relaying the TNF- α message. This technique has been established by our collaborative colleagues in America who have used it to look at a molecule believed to be important in this area called Nuclear Factor kappa B (NF- κ B). In preliminary work carried out in our group in Bath we have established that another compound, phosphatidylinositol 3 kinase (P13K), also appears to be important in relaying the TNF- α message. Using a combined approach we

hope to be able to establish the viral infection method in Bath and see which of these molecules is most important, if and how they interact, and whether they can be manipulated in any way which may be therapeutically useful in the future.