

Professor Subrata Ghosh

Title of Project

Control of adaptive immune responses via Crohn's-associated NOD2 signalling and bacterial sensing in human dendritic cells: a paradigm of innate immune response defect leading to adaptive immune response overdrive.

Lay Summary

Inflammatory bowel diseases, such as Crohn's diseases, are believed to result from abnormal immune responses towards commensal bacteria which are present in all healthy individuals. However, recent research in mice suggests interactions between the intestinal flora and the immune system, are actually *necessary* to maintain the health of the gastrointestinal system. The immune system uses many receptors to sense the presence of microorganisms. Recently, researchers have isolated a gene called NOD2 (CARD15) which is defective in many patients with Crohn's disease. In healthy individuals this gene produces a protein which enables cells to sense a bacterial cell wall component called peptidoglycan. In those carrying NOD2 mutations this ability is reduced or lost altogether. However considerable controversy exists regarding how loss of function NOD2 mutations lead to Crohn's disease, and most work come from NOD2 knockout mice models, which may not mimic the functional consequences of human NOD2 mutations affecting selectively the bacterial sensor end of the molecule. Our recent published work in this area show cross-talk between NOD2 and other bacterial sensors called toll-like receptors (TLRs).

We believe NOD2 defects alter the way particular cells of the immune system – dendritic cells (DCs) – detect and respond to bacteria in the gut. These cells are key since they essentially decide what type of immune response we mount – either a protective response (maintaining the health of the gastrointestinal tract), or an inflammatory response possibly leading to Crohn's disease. Utilising a group of Crohn's disease patients with well defined NOD2 mutations, we aim to show that normal NOD2 function enables DCs to mount a protective immune response while defective NOD2 results in DCs that promote inflammation. Currently, key therapeutic strategies are directed against important cytokines driving the adaptive immune response (anti-TNF antibodies), preventing trafficking of lymphocytes to the intestine (α_4 integrin antibodies) or inducing apoptosis of lymphocytes (several biologicals). However, 'permanent' tolerance to commensal microorganisms is not restored and relapses are virtually inevitable when therapy is withdrawn. Understanding normal NOD2 function could allow us to devise ways of circumventing the genetic defects which lead to disease development thus permanently restoring healthy gut function in those with Crohn's disease.

Currently, therapeutic strategies harnessing the innate immune response are in their infancy and involve the use of probiotics and helminthes. Understanding the molecular mechanism by which breakdown of tolerance to bacterial flora results from defects in the innate immune response would potentially permit development of novel more specific therapeutic strategies using key molecules interacting with the innate immune system. Our department is well placed to carry out this work, as we have identified patients with appropriate genotypes, methods proposed are all available and being used in our laboratory and we have well trained postdoctoral scientists and clinical research fellows. The findings from the proposed study may not be limited to just those patients carrying NOD2 mutations. Bacterial immune-regulatory molecules may be beneficial for all patients, those carrying normal (wild-type) NOD2 may benefit from molecules signalling via NOD2 (such as RIP2). Our preliminary pilot work supports such a hypothesis.

Our proposed work may also provide explanation for the changing epidemiology of Crohn's disease – the increasing incidence in the East (including Indian subcontinent, Eastern Europe) as well as the association with affluence demonstrated by our work in Scottish Children (Armitage *et al* 2004, Gastroenterology). Lack of key bacterial/helminth derived immuno-regulatory molecules as a result to improving hygiene may permit development of inflammatory adaptive immune responses as a result of specific triggers.