

Title of Project

IL-13 promotes inflammation-induced gut fibrosis via a TNF- α -dependent mechanism.

Lay Summary

One of the major complications of Crohn's disease is the development of fibrosis – hardening and thickening – in the bowel wall. This causes the intestine to lose its mobility and it eventually becomes so narrow that food and faeces are unable to pass. Although there is some success in treating the inflammation in Crohn's disease, there are no current effective drugs to treat fibrosis. In severe fibrosis, therefore, the only remedy is surgical removal of the fibrosed tissue. Unfortunately, removal of this fibrosed section does not prevent fibrosis recurring in another part of the intestine and Crohn's patients frequently have to endure repeated surgery, eventually resulting in a short bowel which is no longer able to sustain adequate function. Understanding how fibrosis occurs will help us to develop new medicines to treat patients.

Fibrosis occurs when there is an over-production of the proteins which are normally involved in the tissue healing process, including collagens. Acute inflammation is normally a protective response against microbial invasion and, when the pathogen has been successfully dealt with, it normally stimulates the healing process. However, in chronic, long-lasting inflammation like Crohn's disease the mechanisms which control the normal healing process do not work properly and too much collagen is produced. This hardens the tissue and, in the case of a tubular organ like the gut, the internal channel becomes blocked.

In the tissue, the cells that produce collagen are subject to a battery of signals, some from soluble mediators and some from contact with surrounding cells and their supporting matrix. These signals allow the cells to interpret their environment. The signals change during inflammation and the cell responds accordingly. One of these responses is collagen synthesis.

Recent studies which have investigated fibrosis in the lung, liver and kidney, have shown that one soluble mediator, interleukin 13 (IL-13) is a key molecule promoting fibrosis and this has been proposed as a therapeutic target in fibrosis. IL-13 binds to cell surface receptors causing collagen synthesis.

In this project, we plan to determine the involvement of IL-13 in intestinal fibrosis, by examining normal and fibrotic intestine and by using cells derived from these tissues. The work will lead to the testing of new treatments for this debilitating complication of Crohn's disease.