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'The application of gene expression profiling in inflammatory bowel disease to predict disease behaviour'

Lay Summary

The inflammatory bowel diseases, Crohn's disease and Ulcerative Colitis, are chronic, relapsing and occasionally disabling conditions, which result from inflammatory cells attacking various parts of the intestinal tract. Despite recent advances in our understanding of the genetic causes of susceptibility to IBD, we do not know why two patients with an identical distribution of IBD may have very different disease courses. One patient may respond well to initial treatment and require maintenance therapy to remain in remission, whilst the other may endure frequent flares and require repeated courses of steroids. Being able to predict such behaviour would be a critical advance as this would allow early targeting of aggressive medical therapies such as anti-TNF antibodies to those destined to run a severe /refractory course without them enduring numerous relapses and complications whilst treatments are slowly escalated. Furthermore, this would also avoid the risks and cost of unnecessary immunosuppression in the 20-40% of individuals destined to run a mild course. The importance of this is emphasised by the growing recognition of the need to control inflammatory activity early to prevent the development of medically irreversible complications such as strictures and fistulae. We aim to design a tool to predict, at the time of diagnosis, how the disease will behave in the future.

The relapsing-remitting nature of both UC and CD implies that the behaviour of the inflammatory cells involved is variable. This behaviour is likely to be a consequence of the genes that are being expressed ("switched-on") by the cells in question. Although these cells contain a full complement of genes, not all of these are expressed at any one time and, furthermore, the same cell subsets from different patients with IBD will express different genes. In other diseases, which have a similar relapsing-remitting course to IBD (lupus and vasculitis), patients have been demonstrated to fall into two main subgroups based on the genes that their white blood cell subsets express. The patterns of gene expression in these two subgroups were unaffected by disease activity, and were also present in people without any disease (implying that they are not a result of, nor specific to, the diseases themselves.) From clinical follow up it was noted that patients in these subgroups had significantly different clinical courses with one subgroup having aggressive disease characterized by frequent flares and relatively short periods in remission, whilst the other had comparatively quiescent disease, remaining in remission for longer with fewer flares. Therefore, in these diseases, determination of the gene expression profile in subsets of white blood cells is able, by association, to predict the likely disease course.

We will assess whether the genes expressed by white blood cell subsets, isolated from patients with IBD, correlate with the disease activity, including the frequency of flare ups and the response to treatment. We will do this by separating subsets of white blood cells from a sample of blood and then determining which genes they are expressing using "microarrays". We aim to identify a gene expression signature which correlates with subsequent disease behaviour. If certain genes are shown to be expressed more commonly in patients who have frequently relapsing disease, we will aim to identify what those genes are, and determine, using existing data, if specific mutations within those genes also occur more commonly in such patients. Furthermore, we will also compare any group of genes that is identified with the genes that are already known to be associated with IBD susceptibility, to determine if genes which make an individual susceptible to IBD also affect the disease course.

Up until now we have had no way of predicting how Crohn's or UC will behave after they are diagnosed. This has led to both over-and under-treatment of IBD in individual cases. We hope to identify that expression and or mutation of certain genes is associated with a particular pattern of disease activity. If this is the case, it will be possible to test for these genes early in the course of the disease and, by predicting how the disease is likely to behave, assign treatment that is specifically tailored to the individual patient.