

RESEARCH HIGHLIGHT

Epigenetics: filling in the 'heritability gap' and identifying gene-environment interactions in ulcerative colitis

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Abstract

Ulcerative colitis is a common inflammatory bowel disorder associated with considerable morbidity. Its incidence is increasing worldwide. While familial aggregation of ulcerative colitis is a common phenomenon, genome-wide association studies, identifying a plethora of associated genes, have failed to reveal a unifying causative pathway. The well-documented impact of a number of environmental factors on disease occurrence and natural history suggests a major role for epigenetic events. The epigenome-wide association study discussed in this highlight has revealed novel loci linked to colitis and has provided unique insights into the pathophysiology of this disorder information that could translate into new therapeutic approaches.

Ulcerative colitis (UC), one of the principal clinical phenotypes of inflammatory bowel disease (IBD), is common in the West and is increasing in incidence and prevalence in the rest of the world (in Asia, Eastern Europe and Latin America, in particular) [1]. For decades, familial aggregation of IBD, both UC and Crohn's disease, has been recognized as a common phenomenon, and a search for a genetic basis for IBD began over the past decade. In a study based on the IBD registry at the University of Chicago, for example, 22% of probands had a family history of IBD - a rate that is significantly less than the 1% for non-related close household contacts [2]. Russell and Satsangi, in reviewing the literature on familial IBD, found that risk was higher for relatives of a person with Crohn's disease than for a UC proband, was highest for siblings and, interestingly, was influenced by

ethnicity (higher for Jews than non-Jews) and cigarette smoking [3]. Though such observations supported a potent genetic contribution, the limitations of a purely genetic approach to IBD, in general, and UC, in particular, were evident from early on. Thus, concordance rates for UC among identical twins were as low as 10% and detailed examinations of families failed to reveal an obvious pattern of inheritance [3,4].

More recently, the advent of a variety of technologies has permitted detailed interrogations of the genetics of IBD; while such investigations have revealed a host of genes associated with an increased risk for UC or Crohn's disease, such approaches including genome-wide association studies (GWAS) and candidate gene studies have not, as yet, provided the answers that were anticipated. Thus, a recent meta-analysis of GWAS studies, though identifying 47 susceptibility loci for UC, estimated that these loci explained only 16% of UC heritability [5]. Furthermore, some of these loci were not specific for IBD but were associated with other inflammatory disorders, such as celiac disease and primary biliary cirrhosis, suggesting that they conveyed a predisposition to chronic inflammation and that the ultimate clinical phenotype was determined by other, perhaps environmental, factors [5]. Other loci are common to both UC and Crohn's disease [4] and some appear specific to either Crohn's disease or UC. GWAS have provided valuable insights into pathophysiological mechanisms by highlighting the potential contributions of disturbed immune responses, impaired intestinal barrier function and dysfunctional microbe-host interactions; however, neither a unifying hypothesis regarding causation nor an all-encompassing pathogenetic mechanism has emerged.

The role of environmental factors

From the outset, those who suggested a role for environmental factors in the pathophysiology of IBD have been able to call on a considerable body of evidence [6]. The changing prevalence rates of IBD in many countries over time, as well as the different patterns of emergence of UC and Crohn's in a given country, speak volumes regarding

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the potential contributions of factors in the personal or general environment. The observation of similar trends for allergic disorders, such as asthma, led to the development of the 'hygiene hypothesis,' whereby a lack of exposure to infectious agents and microbes early in life suppresses the immune system and increases susceptibility to allergic diseases; at the very least, this concept has brought much deserved attention to interactions between the gut and its most immediate environment - the microbiota. What about more specific environmental influences?

The identification of environmental triggers for UC onset or relapse has presented formidable methodological challenges [7]. Nevertheless, some trends have emerged. While the contribution of stress to UC was probably overestimated and the identification of dietary triggers has proven elusive, some environmental influences have proven more enduring, such as cigarette smoking, exposure to enteric infection and, possibly, a history of appendectomy [6,7]. In contrast to its role in Crohn's disease, cigarette smoking seems protective in UC - a phenomenon that has not been satisfactorily explained. Clinicians have recognized for decades the induction of relapse in UC on exposure to enteric pathogens such as *Clostridium difficile*. More recently, enteric infections, such as salmonella and campylobacter, have been linked to the *de novo* onset of IBD [6]. That more subtle modifications of the gut microbiota might be relevant is suggested by a report of an association between childhood exposure to antibiotics and the development of IBD in later childhood [8].

The epigenetics of ulcerative colitis

How then can one integrate what is clearly a genetic predisposition with convincing evidence of an important role for environmental factors? The study of epigenetics, defined by Tang and Ho [9] as 'heritable changes in gene expression that occur without alterations in DNA sequence,' focuses on the complex and dynamic interaction between the DNA sequence, DNA modifications and environmental factors, all of which combine to produce the phenotype. In this manner, epigenetic studies provide a vehicle for the integration of genetic and environmental factors. The most widely studied epigenetic mechanisms are DNA methylation and histone modification. DNA methylation involves the addition of methyl groups to nucleotides, which usually silences gene expression.

In the first detailed study of the epigenomics of UC, Hasler and colleagues devised a functional methylome map of UC, representing a major contribution to the understanding of this common and potentially debilitating disorder [10]. Using genome-wide transcriptome analysis, genome-wide quantification of methylation

variable positions (MVPs), and genome-wide assessment of differentially methylated regions (DMRs) in combination, the authors generated a genome-wide functional epigenetic map from 20 monozygotic twins. The results from the study were then validated in a large cohort of unrelated individuals with UC.

Transcriptome analysis of mucosal biopsies from the 20 monozygotic twins identified 361 significantly differentially expressed transcripts, 356 of which were identified in close proximity of at least one MVP or DMR. Subsequent analysis identified 703 MVPs and 345 DMRs between healthy and diseased individuals. Collectively, these three methods of analysis identified 61 disease-associated genes, defined by differential expression and at least one MVP or DMR in close proximity. Interestingly, none of the previously identified loci exhibited significant alterations using this three-layer analysis.

The majority of loci identified by Hasler and colleagues function in immune processes, consistent with previous genetic studies of UC. They included loci such as those associated with complement activation, positive regulation of I- κ B, the immune response, regulation of T cell activation and regulation of cell proliferation.

The results presented illustrate the power of combining transcriptome and methylome analysis to reveal disease mechanisms for UC. The design of this study was key to its success. Not only did they avail of access to tissue from a unique data bank, identical twins discordant for UC, but they also went on to verify their findings in a much larger patient cohort comprising 135 unrelated individuals. In so doing, they incorporated not just normal controls, but disease controls, that is, individuals with colonic inflammation not due to UC or IBD. The latter was an important inclusion - addressing the potential impact of inflammation *per se* on observed changes.

Implications

These first insights into the epigenetics of UC have provided novel and exciting findings that could go some way towards closing the 'heritability gap' (that is, those instances of familial UC not explained, to date, by genetic variation) in UC and also appear to provide real substance to the oft-repeated mantra that IBD reflects the interaction between genetic predisposition and environmental factors. Future studies will undoubtedly define relationships between epigenomic patterns and disease phenotype and natural history, as well as facilitating a better understanding of interactions between genotype and specific environmental factors, such as cigarette smoking (known to alter DNA methylation [11]). The ultimate goal, of course, will be to translate such findings into valid biomarkers of the disease as well as effective therapeutic strategies.

Abbreviations

DMR, differentially methylated region; GWAS, genome-wide association studies; IBD, inflammatory bowel disease; MVP, methylation variable position; UC, ulcerative colitis.

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