

EDITORIAL

Contribution of genetics to a new vision in the understanding of inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory autoimmune conditions of the gastrointestinal tract. Other organs, such as the eyes, skin and articulations, are often affected and IBD may be accompanied by other diseases of autoimmune origin. There is no single etiological factor responsible for the onset of IBD. Recent advances in genetics and in the molecular mechanisms of the proteins coded by these genes have given rise to a new vision in understanding these complex diseases. Activation of specific genes that affect antigen presentation and the handling of cells by innate immunity may lead to autoimmunity with the consequent activation of the major histocompatibility complex (MHC) and multiple cytokines involved in the regulation of acquired immunity. In this review IBD is described as a constellation of diseases that can best be classified as barrier diseases. This vision, developed by Kiel in Germany, includes the idea that changes in our environment due to the westernization of civilization have not been met with adaptation of the innate immune system, and this has given rise to autoimmune diseases. These diseases affect 1-5 of 1000 individuals and represent a major burden on the national health systems of many countries on different continents. On a world scale, a major challenge is to generate interventions to prevent the development of these diseases in Asia, Latin America and Africa.

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Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Genetics; Autoimmunity; Major histocompatibility complex

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INTRODUCTION

In less than five years after the discovery of the first gene involved in susceptibility to Crohn's disease (CD), the initial concept that CD is a multifactorial and polygenic disease has been consolidated^[1,2].

Although the detailed functions of the *NOD2* or *CARD15* gene of chromosome 16 is not entirely clear, their relationship to intestinal flora, Toll receptors (TLR), and other intra-cytoplasmatic receptors of the NOD family together with their relation with NF- κ B, has made clear that the innate immune response is of paramount importance in the pathogenesis of CD^[3-5].

Two years ago it was suggested that the relationship between *TLR-2* and *NOD2* genes could explain the balance between activation of superficial receptors of the epithelial and dendritic cells to stimulate the production of NF- κ B and *NOD2* as inhibitors in order to prevent chronic disease^[6-8]. According to this concept, individuals with mutations in the *CARD15* gene are not able to control the intestinal inflammation and this induces a TH1 immune response^[9]. Recently, however, mutations in the terminal N of the gene in a region rich with leucine repeats have been transfected into the *NOD2* region of mice^[10]. Surprisingly, when these mice are challenged with muramyl dipeptide (MDP) they generate considerable production of NF- κ B and IL-1 β ^[10]. Also the transfection of these mutations in HEK293 cells results in increased transcription of TNF- α , which suggests that different genes contribute to susceptibility to the disease and differences in manifestations of CD^[11].

The fact that *NOD2* is preferentially expressed in Paneth cells in the ileocaecal region probably explains the strong association between these mutations and this disease localization^[12,13]. This region is rich in defensins, which are natural antibiotics that contribute to the mucosal barrier and innate immunity^[14]. It is also now known that patients with mutations in the *CARD15* gene also have less α -defensins. This defect probably contributes to the role of intestinal flora in inducing and/or maintaining inflammation^[15]. Preliminary results of a study carried out by the Stange group in Germany suggest that defensin deficiency is genetically determined. The defensin family is more complex and richer than originally described and its distribution varies within the gastrointestinal tract. The β -defensins are localized in the colon and defective β -defensins could contribute to the colonic localization of IBD^[16]. It is also possible that different defensins may be specific to CD and UC variations^[17].

These observations demonstrate the fine-tuning of

molecular biological responses of the gastrointestinal tract and the complexity of interactions among different genes on different chromosomes. Another example of complexity is gene polymorphisms of the gene inhibitor of plasminogen (PAI-1) in combination with *CARD15* mutations have an influence in the development of CD. Those patients who have mutations of *CARD15* and carry the *PAI-14G/4G* genotype develop a stricturing phenotype (OR, 4.64; 95% CI, 1.26-17.05)^[18].

Despite the well-demonstrated and replicated role of *CARD15* mutations in the susceptibility for CD in the majority of Caucasian populations^[19-23], no mutations have been found in Asian^[24-27] and in several European populations. In Scotland, Ireland, Galicia, Sweden and Finland the carriership of mutations in the *CARD15* gene is less frequent^[28-32]. An interesting phenomenon was recently reported in monozygotic twins. In Sweden, the number of carriers of these mutations was as low as in the general population^[32]. However, in Denmark 40% of the monozygotic twins carried *CARD15* mutations, which was a higher rate than in the Danish population with CD^[33]. This corroborates the observations in Finland where the 1007fs allele frequency was higher in familial CD than in non-familial cases with CD (10.9% vs 3.5%; $P < 0.01$)^[30]. These observations underscore the incidence of genetic variability and the importance of studying healthy controls in the general population.

RELEVANCE OF OTHER GENES

Several other genes on other chromosomes are involved in determining susceptibility to CD. Two interesting genes, one on chromosome 5 and one on chromosome 10, contribute to the new vision of the genetics of CD. On chromosome 5, the *SLC22A4/SLC22A5* haplotype codes for molecules involved in cationic transport, other solutes and carnitine (OCT-1 y OCT2)^[34-36]. In some populations, an epistatic interaction has been found to exist between the *CARD15* mutations and the 250 KB region of 5q31^[37,38]. The other interesting gene in this context is the *DLG5* on chromosome 10, which is a gene that is important in the scaffolding of the epithelial cell^[39,40].

The 250 KB region of 5q31 and the HLA region of 6p21 contain several genes that are of paramount importance in the regulation of the immune response and probably contribute to the phenotype of the patient with IBD. The *HLA-DRB1*0103* allele is associated with UC and with the colonic localization of CD^[41,42].

Carriers of *HLA-DRB1*0103*, *B*35* and *B*27* have higher risk for arthralgias/arthritis in some of the greater articulations and *HLA-B*44* carriers are at higher risk for symmetric poly-arthritis^[43,44].

A meta-analysis of 1068 CD patients has also implicated the genes described above in the development of CD and this study identified other regions of potential relevance on chromosomes 2q, 3q, 17q and 19q^[45].

THE CONTRIBUTION OF GENETICS TO A NEW VISION

In the new vision of CD, several genes are involved in the

maintenance of the intestinal barrier, such as scaffolding genes (*DLG5*^[46]), genes involved in the transport of key molecules for the homeostasis or exclusion of toxins (*SLC*^[47] and *MDR1*^[48,49]), genes involving the sensing of bacteria, both on the surface (TLR, CD14) and intracytoplasmatically (*CARD15*, *CARD4* and *CARD8*^[50-52]). Whether a specific gene for regulating permeability exists, as has been suggested on chromosome 19, remains to be demonstrated. The combination of gene rich regions of chromosome 5 and 6 involved in regulating the immune response may contribute to the phenotype of the disease.

In summary, in less than a decade the genetics of IBD has evolved from epidemiology to molecular biology, and from observational studies to functional studies. The challenge for the coming years is the discovery of gene-gene interactions and gene-environment interactions.

A delineation of phenotypes based on genetic and molecular mechanisms will improve diagnoses and more accurate prognoses. This knowledge, together with advances in the understanding of the phenomenon of tolerance and the disruption of this mechanism in the understanding of chronic inflammation of the gastrointestinal tract, will lead to the design of better and novel therapeutic strategies. This should be the basis for effective drug development in addition to increasing knowledge generated by pharmacogenetics and pharmacogenomics.

Regarding the role of the environment in those individuals with a genetic susceptibility, new findings on epigenetic effects from long-term follow-up in monozygotic twins will open a new area of investigation. Investigators at the Spanish National Cancer Centre (CNIO) in Madrid have shown that older monozygotic twins exhibited differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation. These epigenetic changes affect their gene-expression patterns and may explain the well-known disease discordance in these cases of monozygotic twins^[53].

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