CROHN'S DISEASE – A MICROBIAL DEFENSE PROBLEM OF THE INTESTINAL BARRIER?

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(Kiel, November 2007) – Crohn's disease is a chronic, relapsing inflammatory condition that mainly affects the small and large bowel. It is the paradigm of a disease of civilization with significant rises in incidence after World War II but with a clear polygenic susceptibility component (i.e. multiple disease genes interacting). It affects up to 0.5% of the population in Western industrialized nations. The main manifestation age is early adulthood and the dramatic decrease in quality of life through pain, diarrhea and severe complications is often debilitating. In 2001 the first disease gene, NOD2 (i.e. CARD15), was discovered in parallel by two international groups and in the National Genome Research Network (NGFN). Surprisingly, this gene was found to code for an intracellular, antimicrobial defense protein and not – as expected – for a molecule that would be tightly involved in the regulation of an immune cell-driven inflammatory process. The large cohorts of Crohn's disease patients that are available in the NGFN and through the BMBF competence network Inflammatory Bowel Disease allowed annotation of a well-defined sub-phenotype that is related to the genetic variants. The polygenic nature of the disease was further explained through additional disease genes discovered in Canada (OCTN1/2 – epithelial cell-based kation transporters) and in the NGFN (DLG5 – a gene responsible for mechanical barrier function in the colon epithelium). These three disease genes clearly point to a key role of the epithelial lining of the intestine in the disease process.

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New strategies to explore genetic susceptibility in polygenic disorders

Early discoveries of disease genes were made using an algorithm adapted from the exploration of monogenic diseases, i.e. the definition of susceptibility regions through linkage analysis of affected sib pairs and the subsequent association studies for fine-mapping in large sets of cases and controls using single nucleotide polymorphisms (SNPs). A new era has started with the advent of the SNP chip/array technology allowing genome-wide, systematic association studies that either use a dense coverage based on the HapMap (i.e. using 500 000–1 million SNPs per individual) or a comprehensive set of coding SNPs.

The success of systematic association studies

The first systematic association studies used a low density set of SNPs (i.e. between 100 000 and 300 000 SNPs). They already documented that the new technologies deliver a fast track to discovery by annotating a prostaglandin receptor (PTGER4), its upstream regulator NELL1 through NGFN projects and the IL-23 receptor gene as susceptibility factors for Crohn's disease. The prostaglandin system is thought to be responsible for much of the unspecific damage in the inflamed mucosa and IL-23 is both a regulator of T cell activation and an important driver for microbial defense by epithelial cells.

Further successes came through the use of a genome-wide coding SNP set that identified ATG16L1 (and confirmed the IL23R and the NOD2 signals obtained earlier). ATG16L1 is involved in the autophagy pathway that is used to dispose of microbial remnants (in particular tuberculosis) and protein debris. Together with NOD2, ATG16L1 is among the most consistently annotated disease genes in Crohn's disease. A massive experiment using 500 000 SNPs in a very large set of patient and control samples confirmed many of the previous discoveries and newly identifies IRGM, a further gene in the autophagy pathway and PTPN2, a protease that most interestingly is a disease gene for both Crohn's disease and diabetes. Finally, a three-stage experiment in Crohn's disease patients from a genetically restricted population (i.e. the Quebec French-Canadian population) followed by confirmation and fine mapping in German patients came to a comprehensive identification of a whole series of further disease genes including additional components of the IL-23R signaling cascade, further bacterial defense genes and some genes coding for proteins with yet unknown functions.

The next steps to complete understanding of disease mechanisms

Obviously, the systematic and comprehensive discovery of disease genes in a complex disease has been greatly advanced through the availability of genome-wide association studies. However, the identification of a whole series of diseases genes alone will not satisfy the need for knowledge, since the responsible disease mechanisms still remain to be identified. For this task, systematic resequencing of the disease genes and regions is needed in large numbers (i.e. thousands) of individuals. NGFN has already made investments into new technologies providing the necessary throughput for this task in Berlin, Heidelberg and Kiel.

However, the functional annotation of disease genes will remain a bottleneck. While genetic discovery allows identifying genes in an unprecedented manner, many of the cell biology techniques are still not automated. A final component will be systematic modeling of the complex disease based on the multiple genetic factors and molecular pathways, requiring a medical systems biology.

Potential benefit for patients

An important issue is the immediate benefit these discoveries may have for patients and their families. Genetic discovery will lead to a fundamental change in the therapeutic goals in Crohn's disease. While the pharmaceutical industry has focused on new therapies to suppress the adaptive immunity process in order to alleviate the inflammatory symptoms, it is now clear that future therapies will be directed towards augmenting epithelial defense.

Outlook

Inflammatory diseases of the different barrier organs (e.g. intestinal mucosa, lung, mouth, skin) are related. This is documented by increased coincidences but also a remarkable overlap of the diseases genes found thus far (e.g. NOD2 is a disease gene for Crohn's disease but also for asthma, IL23R for Crohn's disease but also for psoriasis). The simultaneous and comprehensive study of inflammatory barrier diseases in the NGFN will therefore lead to a new medical perspective on how to define and treat inflammatory barrier diseases. The medical grouping into indications that presently are determined by anatomic definitions will be replaced by functional definitions. The NGFN offers a unique platform with large patient cohorts for genome-wide studies of Crohn's disease, ulcerative colitis, atopic eczema, psoriasis, asthma, sarcoidosis and periodontitis.

In the future, we hope to gain full understanding of the genetic mechanisms and the trigger factors that are necessary in our environment to precipitate genetic susceptibility for disease. We expect that the final consequence of understanding the genetic etiology of inflammatory barrier disease will not only be new therapies but also a targeted prevention directed at maintaining health rather than treating disease.