

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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The Role of Innate Immunity in Crohn's Disease

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G&H What has been the historic understanding of the role of the immune system in Crohn's disease?

JK When steroids were introduced in the late 1950s and early 1960s as therapy for inflammatory bowel disease, particularly Crohn's disease, their immunosuppressive properties suggested that Crohn's disease is fueled by an excessive immune response. As better understanding of T-cell biology developed, studies further suggested that the T-cell was the central player in Crohn's disease pathophysiology. As a result, most experimental studies and therapies currently under investigation target the T-cell. The question that remains unclear is what provokes the T-cell to be inappropriately active in Crohn's disease.

As early as the mid-1970s, there was research done on the role of neutrophils in Crohn's disease, suggesting a deficient response. These findings were followed-up but were eclipsed by research and treatment of T-cell response. It is only recently that we have tried again to understand some of the factors, including innate immunity, that may encourage or provoke this disease.

G&H What research has led to the reignited interest in innate immunity as it relates to Crohn's disease?

JK A number of factors have led us to reconsider the role of innate immunity. In terms of my own research, Dr. Brian Dieckgraefe and I began examining innate immunity by looking at the set of genetic diseases that could be

associated with Crohn's disease. These are, for the most part, rare disorders that we do not see in routine practice, including chronic granulomatous disease, glycogen storage 1b, autoimmune cyclic neutropenia, leukocyte adhesion deficiency, and familial Mediterranean fever.

These diseases have been associated with Crohn's disease in case reports or in small series. They are also all linked through a well-described genetic defect in the innate immune system, which includes both circulating immune cells such as neutrophils and monocytes, other mucosal protective factors including mucus and the epithelial layers, and still other, more passive elements like complement.

Going through this list of diseases and matching them through the different functions of phagocytic cells, there exists an almost direct match of a genetic defect with a phagocytic cell function. Whether it is in the numbers of circulating cells, as in glycogen storage 1b, cyclic neutropenia, or autoimmune neutropenia, all of which lower phagocyte cell count, or a more severe defect such as microbial killing, all of these diseases share some characteristic. First, we needed to establish whether these were random associations among a few case reports or legitimate models that could aid in our understanding of Crohn's disease.

We did a systematic study on glycogen storage 1b, which is a rare disorder of the manner in which glycogen is stored and broken down by the liver. It is estimated that 60–100 cases of this disorder exist in the United States. We were able to locate 35 of these patients. Of the 35, 10 had what could be defined as Crohn's disease in all manners of diagnosis, including symptoms, radiologic evaluation, endoscopic evaluation, and location of disease (some ileal, some colonic, all with rectal sparing). Most of these patients had perianal disease, fistulas, and extraintestinal manifestations. Another 10 had chronic gastrointestinal

symptoms, but they had not been sufficiently investigated to say with any confidence that it was Crohn's-like. We felt these findings to be a reasonable starting point to posit the idea that a defect in the innate immune system can lead to a Crohn's-like phenotype and that this defect may be at work in at least a sizable subgroup of patients with Crohn's disease.

Soon after these findings and ideas were advanced, the *NOD2* gene was discovered. The real function of *NOD2* is uncertain, and initially there was some thought that it imparted, in T-cells, a gain of function and a loss of regulation. Subsequently, research has led to a greater consensus that there are a variety of innate immune defects associated with *NOD2*, which are much milder than what is seen with the more pronounced innate immune defects discussed above. However, *NOD2* does seem to fit into the same paradigm of innate immune defect.

More recently, studies have examined a variety of parameters, including epithelial cell function, monocyte function, and dendritic cell function that are defective in people with *NOD2*. Other studies have looked at decreased production of defensins not associated with *NOD2* exclusively, which are antimicrobial peptides produced in huge amounts by the immune system and a major component of neutrophils.

G&H Have these innate immune similarities led to new possibilities for the treatment of Crohn's disease?

JK In the early 1990s, granulocyte-colony stimulating factor (GCSF) and granulocyte-macrophage colony stimulating factor (GMCSF) were first used as a routine medical therapy in patients with glycogen storage 1b, in an attempt to prevent infections. With this therapy, there were reports of some improvement of pre-existing Crohn's-like phenotype, as well as a decreased incidence of development of Crohn's-like phenotype among pediatric patients. In contrast, the European cohort from the same study, where GCSF and GMCSF were not given, did not show the same decrease in Crohn's development. This provided further support to investigate the use of GMCSF for the treatment of Crohn's disease.

Other possible therapies that are currently in the pipeline involve augmentation of other aspects of innate immune function. Further alteration of T-cell regulatory

function or suppression of the T-cell processes are also under investigation.

G&H What are the areas of research in innate immunity that require future follow-up?

JK There are two main lines for future research. The first is a continuation of our examination of the basis of an innate immune defect as it relates to Crohn's disease. This involves the more complete description of innate immune defects and the broad role of the innate immune system in Crohn's disease and possibly in ulcerative colitis. In conjunction, factors that may influence the development of impaired innate immunity in Crohn's disease are important as well, as the central factor to investigate is the role of both the luminal and mucosal bacteria in possibly impairing or interacting with innate immunity. Environmental influences must also be further investigated. Other genes possibly associated with Crohn's disease may cause defects in barrier function but these genes are currently less well-defined, in terms of the strength of their association with Crohn's disease.

The other area to research is in understanding how these insights will culminate in therapy. The potential therapeutic uses of GMCSF and possibly GCSF or other therapies need to be further explored. In addition, biomarkers should be identified for subtypes of disease, to identify patients who are more likely to respond to these therapies rather than biologic therapies or other approaches that downregulate the T-cell.

Suggested Reading

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