Interaction of Genetic, Environmental and Immune Factors in the Pathogenesis of Inflammatory Bowel Diseases

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Ulcerative colitis and Crohn’s disease are heterogeneous chronic inflammatory disorders of the intestine. Despite intensive research, the etiology of UC and CD is still illusive. However, the clinical and epidemiologic characteristics, as well as experimental studies in humans and animal models have allowed for the development of a paradigm of factors that might be involved in the development of chronic intestinal inflammation. For example, a number of animal models were described in which genes involved in the regulation of the immune response were knocked out. These included genes of either pro-inflammatory cytokines such as interleukin-2 [1] or an anti-inflammatory cytokine such as IL-10 [2] (for review see ref. 3).

Regardless of the specific gene that was knocked out, the intestinal inflammation developed only in animals whose intestine was populated with the normal indigenous mouse flora. No inflammation developed in germ-free animals [3]. These observations suggest that an uncontrolled immune response towards the normal gut flora may play a role in intestinal inflammation in these animal models. A number of observations support the role of intestinal bacteria in the pathogenesis of CD as well. These include the efficacy of antibiotic treatment in CD [4], the beneficial clinical response following surgical fecal diversion [5,6], the presence of cellular immune response against resident flora [7], and the induction of mucosal lesions following exposure of healed mucosa to fecal extracts [8,9]. Based on these different studies, it is hypothesized that chronic intestinal inflammation may develop as the result of a combination of genetic factors that predispose carriers to environmental factors, particularly intestinal bacteria, which elicit an aggressive inflammatory response that causes the tissue damage.

In this issue of IMJ, Karban et al. [10] provide a comprehensive review of genetic components that are thought to be involved in inflammatory bowel disease. The authors reviewed the epidemiologic studies that suggest a significant role for the genetic background as a factor in the etiology of IBD, as well as studies related to specific genetic loci that are linked to either UC or CD. Special emphasis was placed on the recent finding of an association between mutations within the NOD2/CARD15 locus and CD. This finding is of particular interest since it may provide a long-sort linkage between a specific genetic background and bacterial factors that contribute to the pathogenesis of CD. The NOD2/CARD15 protein is expressed selectively in monocytes and belongs to a family of proteins that are homologous to the mammalian apoptotic activating factor 1 and the C. elegans Ced-4 proteins. These proteins share structural homology with each other and are regulators of cell apoptosis that may be induced by external stimuli such as stress [11]. The NOD proteins are composed of an N-terminal domain, which is responsible for downstream activation of signal transduction pathways, a central nucleotide-binding oligomerization domain (NOD), and a C-terminal domain that contains a leucine-rich repeat [12]. This part of the NOD2/CARD15 protein binds lipopolysaccharide, an event that leads to the formation of a dimer and subsequent activation of the nuclear factor kappa-B pathway. The activation of NFKB is a central cellular event for inducing the transcription and secretion of multiple pro-inflammatory cytokines that are thought to mediate the tissue damage in CD. Importantly, the mutations within the NOD2/CARD15 protein were described within the leucine rich repeat, i.e., the LPS-binding domain of the protein [13,14]. Indeed, when functional studies were performed, COS cells transfected with mutated NOD2/CARD15 constructs failed to activate NFKB in response to LPS as compared to cells that were transfected with control wild-type NOD2/CARD15 protein [14]. However, the current paradigm suggests that CD patients have an increased immune response to intestinal bacteria. How could these findings be reconciled with each other? One possibility is that the lack of an efficient innate immune response by the monocytes that express a mutated NOD2/CARD15 protein towards intestinal bacteria may stimulate an exaggerated adapted immune response by intestinal T cells. Alternatively, the mutation may result in gain of function that can potentially induce inflammation despite the inability of the protein to bind LPS [14]. Finally, the NOD2/CARD15 protein may perform a yet undefined cellular function whose absence leads to a defect in the control of the inflammatory process. Further studies are needed to explain this apparent paradox.

UC = ulcerative colitis
CD = Crohn’s disease
IL = interleukin

IBD = inflammatory bowel disease
NFKB = nuclear factor kappa-B
LPS = lipopolysaccharide
Despite the potential association between NOD2/CARD15 and the pathogenesis of CD, the puzzle is far from complete. As the authors noted, both in the two initial studies in which the mutations were initially described [13,14] and in a subsequent study that evaluated the frequency of the frameshift mutation 3020insC [15], it is clear that the mutations within the NOD2/CARD15 gene do not account for the entire genetic predisposition for CD. The relative low frequency of the mutations in the patient population and the calculated low penetrance of the gene suggest that other genetic loci are involved as well. Furthermore, the NOD2/CARD15 mutation may be of different importance in different patient populations. For example, conflicting results were obtained in other studies in which the frequency of the mutation was correlated with different phenotypes of CD. Thus, whereas one group of investigators found no correlation between the presence of mutation within the NOD2/CARD15 gene and specific disease phenotypes [16], two other groups noted a specific association between such phenotypes and mutations within the NOD2/CARD15 locus. Both in a British cohort and in a European cohort, mutations within the NOD2/CARD15 locus were associated with ileal but not colonic disease [17,18]. Furthermore, in the UK study, patients with frameshift mutations or compound heterozygotes/homozygotes presented at an earlier age [17]. Taken together, additional functional and epidemiologic studies are needed to evaluate the role of NOD2/CARD15 in the pathogenesis of CD in different ethnic groups and in patient populations with different disease characteristics.

The association between NOD2/CARD15 proteins and CD was demonstrated using both the candidate gene approach and genome-wide scanning. Although the association between bacteria and the genetic factor received substantial attention due to the aforementioned findings, other environmental factors were noted and are unexplained at this point. Such factors include, among others, the protective effect of smoking [19] and appendectomy [20] in UC, and the potential association of oral contraceptives with the development of IBD [21]. Results of therapeutic trials may provide mechanistic insight into disease pathogenesis as well. Examples from such studies are the beneficial effect of nicotine in UC [22] and probiotic treatment in pouchitis [23]. These observations may serve as the starting point for research of additional genetic loci based on the target gene approach and hypothetical pathogenic mechanisms by which these specific factors can be linked to inflammation or its down-regulation.

The final damage to the intestine is caused by the immune response, which is hypothesized to result from the combination of genetic and environmental factors. Although both CD and UC result from chronic uncontrolled inflammation, they differ in other aspects of the disease, such as the nature of the inflammatory process, the distribution of disease, and the associated disease complications. For example, the inflammation in Crohn’s disease is thought to be mediated mainly by Th1 type cytokines [24], whereas the Th2 type cytokine IL-5 is found in higher levels in ulcerative colitis [25]. In addition, therapeutic trials using anti-tumor necrosis factor antibodies to treat CD patients suggest that other pro-inflammatory cytokines might play an important role in intestinal inflammation. However, not all patients respond to such treatments [26], suggesting that the secretion of these cytokines may be regulated differently in different patient subpopulations. Such studies, which are based on specific immunotherapy and the fine definition of the immune response, constitute the basis for additional research that can link these observations to the different IBD patient populations.

In conclusion, in light of the lack of knowledge regarding the precise etiology of IBD, future research will be aimed at finding the link between the environmental, immunologic and genetic arms that appear to interweave in their pathogenesis.

References
Pheochromocytoma: A Disease with Many Faces

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Catecholamine-secreting tumors are frequently sought but rarely diagnosed. In many cases their presence is associated with spectacular cardiovascular disturbances. When diagnosed and treated properly, however, these tumors are mostly curable. Pheochromocytomas provide clinicians with a unique treatment opportunity since the response to either surgery or pharmacologic therapy is dramatic, but incorrect diagnosis and treatment can have catastrophic consequences.

Catecholamine-secreting tumors are extremely rare, with an incidence of 2–8 cases per million people. Despite their rarity, they should be considered in patients with hypertension, panic attacks, adrenal incidentalomas, autonomic disturbances or familial diseases with a predisposition to develop pheochromocytoma. Identification of pheochromocytomas is essential because the associated hypertension is curable upon diagnosis, localization and surgical resection of the tumor. In contrast, unidentified cases are at risk of lethal paroxysms and about 10% of cases are malignant. Patients with catecholamine-secreting tumors may be asymptomatic, however symptoms usually arise from the pharmacologic effect of excess catecholamines in the circulation. Hypertension may be sustained or paroxysmal, and spells may occur spontaneously or can be precipitated by postural change, medications, anxiety, increase in abdominal pressure, exercise, or manual compression of the tumor. A spell usually lasts from several minutes up to one hour. Clinicians usually screen patients for pheochromocytomas when paroxysmal symptoms are evident, but pheochromocytomas are usually not the most common cause of hypertension-related spells.

In their article in this issue of IMAJ, Hamdan et al. [1] report a rare manifestation of a rare disease — low back pain with vertebral lytic lesion. In another article in the current issue, Liel et al. [2] describe a confusing pheochromocytoma that appears together with meningiomas and mimics meningioma in the base of the skull. These are only two of the many faces of the diverse clinical presentations of this peculiar disease.

A ‘rule of 10’ has been described for catecholamine-secreting tumors: 10% are multiple or bilateral, 10% recur after surgical removal, 10% are familial, and 10% are malignant. Several syndromes have been associated with pheochromocytoma, such as MEN II a and II b, neurofibromatosis, and von Hippel-Lindau disease [3]. It is obvious that before any attempt to localize the pheochromocytoma, excess of catecholamine levels in the plasma or urine should be sought.

The diagnostic approach, which in the 1940s was based on clinical impression, exploratory laparotomy, histamine stimulation and phentolamine suppression tests, progressed to catecholamine measurements and intravenous pyelograms in the 1960s. In most laboratories today, plasma or urinary catecholamines are measured by high pressure liquid chromatography, usually with electrochemical detection. However, despite these developments, the...