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EDITORIAL

Do we really understand what the immunological disturbances in inflammatory bowel disease mean?

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Abstract

The gastrointestinal tract uses a system of tolerance and controlled inflammation to limit the response to dietary or bacteria-derived antigens in the gut. When this complex system breaks down, either by a chemical or pathogenic insult in a genetically predisposed individual the resulting immune response may lead to inflammatory bowel disease. Although the aetiopathogenesis of inflammatory bowel disease remains unsolved current evidence indicates that defective T-cell apoptosis and impairment of intestinal epithelial barrier function play important roles. In inflammatory bowel disease, it has been reported that activation of macrophages seems to be as important as increased production of the macrophage-derived cytokines such as TNF-α, IL-1 and IL-6. The triggering factor for this cascade is still to be elucidated as to whether it represents an auto-antigen or a hetero-antigen. It has been also demonstrated that a serologic anti-microbial response exists. This response includes antibodies against saccharomyces cerevisiae (ASCA), *E. coli* outer membrane porin C (Omp-C), flagelin (cBir1) and pseudomonas aeroginosa (I2). Host response to microbial pathogens includes self-defense mechanisms including defensins, pattern recognition receptors and Toll-like receptors. Neuroimmunomodulation in inflammatory bowel disease (IBD) is another interesting approach with implications on the influence of brain-gut axis on intestinal inflammation and its perpetuation. It is probable that inflammatory bowel disease represents a heterogenic group of diseases that share similar mechanisms of tissue damage but have different initiating events and immunoregulatory abnormalities. A better understanding of all these events will hopefully provide new insights into the mechanisms of epithelial responses to microorganisms and ideas for therapies.

Key words: Inflammatory bowel disease; Immunological disturbances; Serological markers; Pathogenesis

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INTRODUCTION

Although the pathogenesis of inflammatory bowel disease (IBD) still remains unexplained, its pathophysiological mechanisms have been more extensively investigated and correspond to what is known about inflammatory disease processes in general. Our understanding of these disorders has benefited enormously from the development of novel animal models and recent advances in cell and molecular biology. Nowadays, it is commonplace that in IBD, a wide diversity of immunological changes occurs, including altered populations of inflammatory cells and activation of a range of inflammatory pathways.

TOLERANCE AND CONTROL OF INFLAMMATION IN IBD

The gastrointestinal tract uses a system of tolerance and controlled inflammation to limit the response to dietary or bacteria-derived antigens in the gut[1-3]. When this complex system breaks down, either by a chemical or pathogenic insult in a genetically predisposed individual

the resulting immune response may lead to IBD[4-8]. Although the aetiopathogenesis of IBD remains unsolved, current evidence indicates that defective T-cell apoptosis and impairment of intestinal epithelial barrier function play important roles[9,10]. Differences in T-cell responses between Crohn's disease (CD) and ulcerative colitis (UC) have been identified, with mucosal T-cell apoptosis being defective in CD but not in UC[7]. In both CD and UC, it has been reported that activation of macrophages seems to be as important as increased production of the macrophage derived cytokines TNF, IL-1 and IL-6[11,12].

Chemokines play a central role in the pathogenesis of IBD as they are able to trigger multiple inflammatory actions including leukocyte activation and chemoattraction, granulae exocytosis, production of metalloproteinases for matrix degradation and upregulation of the oxidative burst[13]. Dysregulated cytokine production by mucosal lymphocytes and macrophages has been implicated in the pathogenesis of IBD. In fact, an exclusive increase of CD4+ T cells in inflammatory bowel disease and their recruitment as intraepithelial lymphocytes has been demonstrated[14,15], while a potential therapeutic effect of capthesin inhibition *via* macrophages *in vivo* has been also suggested[16,17]. Over the past few years, various murine models of chronic intestinal inflammation resembling IBD have been discovered that have provided important clues as to the nature of this dysregulation and to its possible treatment with cytokines, for example IL-10[18,19].

It is clear from various studies that nuclear factor kappa B (NF-κB) and various other regulatory proteins are very likely to play a key role and it seems that we will gain new, fundamental insights into the pathogenesis, prognosis and treatment of IBD by analyzing further transcriptional regulatory mechanisms in chronic intestinal inflammation. This allows us to understand the basis for altered cytokine gene transcription in patients with IBD. Furthermore, such studies will hopefully permit the design of new treatment strategies that will be able to add specificity but reduced toxicity compared with standard immunosuppressive therapies[20].

TRIGGERING FACTORS OF THE INFLAMMATORY CASCADE IN IBD

The symptomatic phases of IBD are characterized by migration of large numbers of neutrophils and accumulation in the intestinal lumen. The triggering factor for this cascade is still to be elucidated whether it represents an auto-antigen or a hetero-antigen, i.e. a microbial component. Dysbiosis is the disturbance of intestinal microflora resulting in the breakdown in the balance between 'protective' *vs* 'harmful' intestinal bacteria[21]. Dysbiosis is implicated in many chronic diseases such IBD, which are associated with 'westernized' life style. It has been shown that enteric bacteria do not have equal capacities to induce or protect from inflammation and, interestingly, even *H pylori* infection has been implicated in CD pathogenesis[22]. It has been also demonstrated that in CD patients a serologic 'anti-microbial' response exists. In fact, granulomas in mesenteric lymph nodes from CD patients are composed of centrally located T-lymphocytes and of epithelioid cells, which are of monocyte/macrophage origin and have the characteristics of antigen presenting cells[23].

Currently available 'anti-microbial' response panel of laboratory tests includes antibodies against saccharomyces cerevisiae (ASCA), *E. coli* outer membrane porin C (Omp-C), flagelin (cBir1) and pseudomonas aeroginosa (I2)[24-26]. Of particular interest is that ASCA may develop before the obvious clinical diagnosis of CD according to a study using serum samples from the Israeli Defense Corp repository. In this study, 32% of patients were ASCA (+) 38 mo before CD clinical diagnosis was established[27]. The target antigen for pANCA is currently unknown and there is still variation regarding the inter-observer agreement with the several assays used for their determination. These serologic markers may be of great potential importance as they can provide more information on the IBD pathogenesis, the differentiation between UC and CD, the definite diagnosis of indeterminate colitis cases, the prediction of pouchitis and prediction of response to therapies. It is of importance that ASCA have a genetically modulated expression as they are found in 20%-25% of relatives of CD patients and are absent in spouses. In addition, pANCA are present in up to 20% of unaffected relatives of UC patients and they persist after colectomy indicating into two points: that the target antigen in IBD is not fully eradicated and that it is not just the colon which is immunologically targeted in UC [28-31].

It has to be emphasized that the serological markers are far from being the gold standard in IBD diagnostics and need to be combined, as they do not work separately in the clinical setting.

HOST RESPONSE TO MICROBIAL PATHOGENES

Host response to microbial pathogens includes self-defense mechanisms such as defensins, pattern recognition receptors (PRRs), pathogen-associated molecular patterns (PAMPs) and Toll-like receptors (TLRs). Toll-like receptors recognize conserved motifs on pathogens that are not found in higher eukaryotes and initiate 'innate' (rapid and non-specific) immune response. Subsequently, specific receptors recognizing chemo-attractant molecules mobilize phagocytic leukocytes and induce their migration to inflammatory sites. There, leukocytes encounter the invading microorganisms and ingest them through the activation of phagocytic receptors that mediate the uptake process. Innate immune responses are linked to the generation of corresponding adaptive immune responses and studies of genetically engineered or cellularly manipulated animal models have generated a great deal of new information[32].

Leukocyte-epithelial interactions are of special inter-

est as exposure of epithelial TLRs to microbial ligands has been shown to result in transcriptional upregulation of inflammatory mediators whereas ligation of leukocyte TLRs modulate specific antimicrobial responses[26]. It has been shown that Paneth cells play an important role in innate host defense *via* their ability to secrete antimicrobial peptides and proteins[33]. In addition, it has been shown that NOD2 mutations lead to loss of negative regulatory effects on TLR signaling while activation of the CARD domain results in activation of NF-κB[34].

THE MOLECULAR BASIS OF THE INTESTINAL IMMUNITY

Major advances in our understanding of the molecular basis of Rho guanine-triphosphatases (GTPases) function in regulating the phagocytic leukocytes that constitute the innate immune response have also been made. However, significant challenges remain. The molecular mechanisms involved in sensing chemotactic gradients, in maintaining polarized movement, and in coordinating the dynamics of the actin, myosin and microtubule cytoskeletons that are mediated by Rho GTPases remain to be worked out[32].

Matrix metalloproteinases (MMPs) seem also to play a crucial role in physiological and pathophysiological reactions such as leukocyte accumulation into inflamed tissue, cytokine production from inflammatory and epithelial cells, T lymphocyte homing to the intestine, wound healing and proliferation of epithelial cells, and intestinal innate immunity and permeability[35].

Neuroimmunomodulation in IBD remains a challenging theory with implications on the influence of brain-gut axis on intestinal inflammation and its perpetuation[36-38]. In recent years, considerable evidence has accumulated that psychological stress does indeed contribute to the risk of relapse in IBD. Furthermore, laboratory research has indicated a variety of mechanisms by which stress can affect both the systemic and gastrointestinal immune and inflammatory responses[39].

UNDERSTANDING THE MULTIFACTORIAL CHARACTER OF IBD

Despite decades of research the etiology of IBD remains largely unexplained, even though there is agreement with regard to these disorders' multifactorial character. Considering the epidemiological, genetic and immunological data, we can conclude that IBD are heterogeneous disorders of multifactorial etiology in which hereditary (genetic) and environmental (microbial, behavior) factors interact to produce the disease. It is probable that patients have a genetic predisposition for the development of the disease coupled with disturbances in immunoregulation. The disease can then be triggered by any of a number of different unknown environmental factors and sustained by an abnormal immune response to these factors. Rather, the intensive interaction between intestinal epithelial cells and immune competent cells is critical to maintain and perpetuate the chronic inflammatory process characteristic for IBD.

Once the role of genetic determinants is fully understood, early interventions can be designed to prevent disease in predisposed individuals. Gene therapy or modification of bacterial flora with probiotics or antibiotics or both for specific pathogens is expected to be central to this approach. From population-based data, important hypotheses for more specialised studies can be created. Especially if environmental influences are suspected in the onset and/or cause of a disease, population-based studies are indispensable[40]. However, good population-based studies are rare, probably because of the difficulties in organization and the long-term engagement needed[41].

Regarding the role of environmental factors, Hippocrates wrote in his "Epidemics"[42] that "patients with abscesses without fever, as well as patients with bloody stools became sick because of the same reason: at younger age they used to live under very difficult conditions and they were forced to use their body energy and muscular power to survive. However, later on, by becoming older they turned to work less harder, their body weight increased dramatically and their flesh became soft and vulnerable."

Parallel to Hippocratic skepticism, forty years ago Burrill B. Crohn[43] asked himself a rhetoric question: "Are these inflammatory bowel diseases the product of our modern civilization, the end product of industrial revolution? The answer is not evident."

THE PRESENT AND THE FUTURE OF THERAPY IN IBD

Today we target different immunological mechanisms and we use basically two groups of treatment: immunosuppressives and anti-inflammatory molecules.

The target point(s) of the currently used immunosuppressives is still unclear. However it has been suggested that azathioprine has a direct effect on the leukocyte nucleus and migration ability towards the site of inflammation[44] while methotrexate acts as an antimetabolite of the folic acid[45].

The anti-inflammatory therapies are various depending on the mechanism designed to hit: proinflammatory cytokines inhibitors (i.e. anti-TNF-α therapies), anti-inflammatory cytokine mediators (IL-10, IL-11), adhesion molecule inhibitors (i.e. anti-a4 integrin monoclonal antibody), T-cell inhibitors (anti-CD3 monoclonal antibody), cell based therapies (i.e. absorption aphaeresis), signal transduction inhibitors, transcription factor inhibitors and hematopoietic growth factors[46].

All physicians caring for patients with inflammatory bowel disease have an expanding arsenal of medications that can achieve symptomatic remission and mucosal healing. Adding biologics to existing immunomodulators improves our rates of sustained remission and healing of mucosal ulcerations. However, further studies are

needed to help determine what our final therapeutic endpoint should be.

REFERENCES

1 **Geboes K**. From inflammation to lesion. *Acta Gastroenterol Belg* 1994; **57**: 273-284
2 **Kraus TA**, Mayer L. Oral tolerance and inflammatory bowel disease. *Curr Opin Gastroenterol* 2005; **21**: 692-696
3 **Sartor RB**. Current concepts of the etiology and pathogenesis of ulcerative colitis and Crohn's disease. *Gastroenterol Clin North Am* 1995; **24**: 475-507
4 **Sartor RB**. Pathogenesis and immune mechanisms of chronic inflammatory bowel diseases. *Am J Gastroenterol* 1997; **92**: 5S-11S
5 **Shanahan F**. Crohn's disease. *Lancet* 2002; **359**: 62-69
6 **Holtmann MH**, Galle PR. Current concept of pathophysiological understanding and natural course of ulcerative colitis. *Langenbecks Arch Surg* 2004; **389**: 341-349
7 **Dignass AU**, Baumgart DC, Sturm A. Review article: the aetiopathogenesis of inflammatory bowel disease--immunology and repair mechanisms. *Aliment Pharmacol Ther* 2004; **20** Suppl 4: 9-17
8 **Brandtzaeg P**. Inflammatory bowel disease: clinics and pathology. Do inflammatory bowel disease and periodontal disease have similar immunopathogeneses? *Acta Odontol Scand* 2001; **59**: 235-243
9 **Gordon JN**, Di Sabatino A, Macdonald TT. The pathophysiologic rationale for biological therapies in inflammatory bowel disease. *Curr Opin Gastroenterol* 2005; **21**: 431-437
10 **Holtmann MH**, Galle PR, Neurath MF. Immunotherapeutic approaches to inflammatory bowel diseases. *Expert Opin Biol Ther* 2001; **1**: 455-466
11 **Kolios G**, Petoumenos C, Nakos A. Mediators of inflammation: production and implication in inflammatory bowel disease. *Hepatogastroenterology* 1998; **45**: 1601-1609
12 **Pallone F**, Monteleone G. Regulatory cytokines in inflammatory bowel disease. *Aliment Pharmacol Ther* 1996; **10** Suppl 2: 75-79; discussion 80
13 **Danese S**, Gasbarrini A. Chemokines in inflammatory bowel disease. *J Clin Pathol* 2005; **58**: 1025-1027
14 **Kobayashi T**, Okamoto S, Iwakami Y, Nakazawa A, Hisamatsu T, Chinen H, Kamada N, Imai T, Goto H, Hibi T. Exclusive increase of CX3CR1+CD28-CD4+ T cells in inflammatory bowel disease and their recruitment as intraepithelial lymphocytes. *Inflamm Bowel Dis* 2007; **13**: 837-846
15 **Papadakis KA**, Prehn J, Zhu D, Landers C, Gaiennie J, Fleshner PR, Targan SR. Expression and regulation of the chemokine receptor CXCR3 on lymphocytes from normal and inflammatory bowel disease mucosa. *Inflamm Bowel Dis* 2004; **10**: 778-788
16 **Menzel K**, Hausmann M, Obermeier F, Schreiter K, Dunger N, Bataille F, Falk W, Scholmerich J, Herfarth H, Rogler G. Cathepsins B, L and D in inflammatory bowel disease macrophages and potential therapeutic effects of cathepsin inhibition in vivo. *Clin Exp Immunol* 2006; **146**: 169-180
17 **Mahida YR**. The key role of macrophages in the immunopathogenesis of inflammatory bowel disease. *Inflamm Bowel Dis* 2000; **6**: 21-33
18 **Bhavsar MD**, Amiji MM. Oral IL-10 gene delivery in a microsphere-based formulation for local transfection and therapeutic efficacy in inflammatory bowel disease. *Gene Ther* 2008; **15**: 1200-1209
19 **Li MC**, He SH. IL-10 and its related cytokines for treatment of inflammatory bowel disease. *World J Gastroenterol* 2004; **10**: 620-625
20 **Neurath MF**, Pettersson S, Meyer zum Buschenfelde KH, Strober W. Local administration of antisense phosphorothioate oligonucleotides to the p65 subunit of NF-kappa B abrogates established experimental colitis in mice. *Nat Med* 1996; **2**: 998-1004
21 **Fedorak RN**, Madsen KL. Probiotics and the management of inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 286-299
22 **Jovanovic IR**, Milosavjevic TN, Jankovic GP, Micev MM, Dugalic PD, Saranovic D, Ugljesic MM, Popovic DV, Bulajic MM. Clinical onset of the Crohn's disease after eradication therapy of Helicobacter pylori infection. Does Helicobacter pylori infection interact with natural history of inflammatory bowel diseases? *Med Sci Monit* 2001; **7**: 137-141
23 **Geboes K**, van den Oord J, De Wolf-Peeters C, Desmet V, Rutgeerts P, Janssens J, Vantrappen G, Penninckx F, Kerremans R. The cellular composition of granulomas in mesenteric lymph nodes from patients with Crohn's disease. *Virchows Arch A Pathol Anat Histopathol* 1986; **409**: 679-692
24 **Mow WS**, Vasiliauskas EA, Lin YC, Fleshner PR, Papadakis KA, Taylor KD, Landers CJ, Abreu-Martin MT, Rotter JI, Yang H, Targan SR. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology* 2004; **126**: 414-424
25 **Targan SR**, Landers CJ, Yang H, Lodes MJ, Cong Y, Papadakis KA, Vasiliauskas E, Elson CO, Hershberg RM. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. *Gastroenterology* 2005; **128**: 2020-2028
26 **Liew FY**, Xu D, Brint EK, O'Neill LA. Negative regulation of toll-like receptor-mediated immune responses. *Nat Rev Immunol* 2005; **5**: 446-458
27 **Israeli E**, Grotto I, Gilburd B, Balicer RD, Goldin E, Wiik A, Shoenfeld Y. Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease. *Gut* 2005; **54**: 1232-1236
28 **Vermeire S**, Peeters M, Vlietinck R, Joossens S, Den Hond E, Bulteel V, Bossuyt X, Geypens B, Rutgeerts P. Anti-Saccharomyces cerevisiae antibodies (ASCA), phenotypes of IBD, and intestinal permeability: a study in IBD families. *Inflamm Bowel Dis* 2001; **7**: 8-15
29 **Vermeire S**, Joossens S, Peeters M, Monsuur F, Marien G, Bossuyt X, Groenen P, Vlietinck R, Rutgeerts P. Comparative study of ASCA (Anti-Saccharomyces cerevisiae antibody) assays in inflammatory bowel disease. *Gastroenterology* 2001; **120**: 827-833
30 **Joossens S**, Reinisch W, Vermeire S, Sendid B, Poulain D, Peeters M, Geboes K, Bossuyt X, Vandewalle P, Oberhuber G, Vogelsang H, Rutgeerts P, Colombel JF. The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology* 2002; **122**: 1242-1247
31 **Joossens S**, Daperno M, Shums Z, Van Steen K, Goeken JA, Trapani C, Norman GL, Godefridis G, Claessens G, Pera A, Pierik M, Vermeire S, Rutgeerts P, Bossuyt X. Interassay and interobserver variability in the detection of anti-neutrophil cytoplasmic antibodies in patients with ulcerative colitis. *Clin Chem* 2004; **50**: 1422-1425
32 **Bokoch GM**. Regulation of innate immunity by Rho GTPases. *Trends Cell Biol* 2005; **15**: 163-171
33 **Elphick DA**, Mahida YR. Paneth cells: their role in innate immunity and inflammatory disease. *Gut* 2005; **54**: 1802-1809
34 **Watanabe T**, Kitani A, Strober W. NOD2 regulation of Toll-like receptor responses and the pathogenesis of Crohn's disease. *Gut* 2005; **54**: 1515-1518
35 **Naito Y**, Yoshikawa T. Role of matrix metalloproteinases in inflammatory bowel disease. *Mol Aspects Med* 2005; **26**: 379-390
36 **Anton PA**. Stress and mind-body impact on the course of inflammatory bowel diseases. *Semin Gastrointest Dis* 1999; **10**: 14-19
37 **Anton PA**, Shanahan F. Neuroimmunomodulation in inflammatory bowel disease. How far from "bench" to "bedside"? *Ann N Y Acad Sci* 1998; **840**: 723-734
38 **Webster EL**, Torpy DJ, Elenkov IJ, Chrousos GP. Corticotropin-releasing hormone and inflammation. *Ann N Y Acad Sci*

1998; **840**: 21-32
39 **Mawdsley JE**, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut* 2005; **54**: 1481-1491
40 **Tsianos EV**, Katsanos KH, Christodoulou D, Dimoliatis I, Kogevinas A, Logan RF. Continuing low incidence of Crohn's disease in Northwest Greece. *Dig Liver Dis* 2003; **35**: 99-103
41 **Riis L**, Vind I, Vermeire S, Wolters F, Katsanos K, Politi P, Freitas J, Mouzas IA, O'Morain C, Ruiz-Ochoa V, Odes S, Binder V, Munkholm P, Moum B, Stockbrugger R, Langholz E. The prevalence of genetic and serologic markers in an unselected European population-based cohort of IBD patients. *Inflamm Bowel Dis* 2007; **13**: 24-32
42 **Mitropoulos K**. Glossary of the Hippocratic collection. About Epidemics, Ch. VII. Athens, 1989
43 **Crohn BB**. Granulomatous diseases of the small and large bowel. A historical survey. *Gastroenterology* 1967; **52**: 767-772
44 **Tiede I**, Fritz G, Strand S, Poppe D, Dvorsky R, Strand D, Lehr HA, Wirtz S, Becker C, Atreya R, Mudter J, Hildner K, Bartsch B, Holtmann M, Blumberg R, Walczak H, Iven H, Galle PR, Ahmadian MR, Neurath MF. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *J Clin Invest* 2003; **111**: 1133-1145
45 **Domenech E**, Manosa M, Navarro M, Masnou H, Garcia-Planella E, Zabana Y, Cabre E, Gassull MA. Long-term methotrexate for Crohn's disease: safety and efficacy in clinical practice. *J Clin Gastroenterol* 2008; **42**: 395-399
46 **Sandborn WJ**, Targan SR. Biologic therapy of inflammatory bowel disease. *Gastroenterology* 2002; **122**: 1592-1608

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