ANNALS OF GASTROENTEROLOGY 2009, 22(4):239-241

Editorial

The role of intestinal microbial/immune cell interactions in patients with Inflammatory Bowel Disease

Aik. Chairakaki

Inflammatory Bowel Disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract (GI) and is divided into two primary forms, Crohn's Disease (CD) and Ulcerative Colitis (UC). There are numerous hypotheses as to the cause of IBD but as yet its aetiology remains unclear. It is generally accepted however that the pathogenesis of IBD involves the interaction of environmental, genetic and immunological factors with the complexity and diversity of both the CD and UC clinical pictures reflecting their multifactorial aetiology[1]. Accumulating research data supports the evidence that interactions between gut flora and commensal bacteria along with the host's immune system are responsible for the induction of IBD. Hence, a series of observations have led to the hypothesis that there is a strong relationship between human microflora and the mechanisms of the initiation and the progression of the disease.[2]

In search of the principle functions of the gastrointestinal tract, two main features come to mind. It is essential for digestion and absorption of the nutrients of the food and, predominant in the participation of the mucosal immune response. The latter function is considered to reflect a physical barrier –the intestinal barrier- for the invasion of pathogenic organisms into the host.

Primarily, the gut barrier is the first obstacle that bacteria face and is considered to be part of the mucosal immune system (MALT), consisting of three major components[3,4] namely; the mucus epithelia ("mechanical barrier"), the secreting immunoglobulin and the gut-associated lymphoid tissue (GALT) ("immune barrier"), and the intestinal flora ("biological barrier").

The mechanical barrier involves tight junctions between epithelial cells in order to induce a specialised permeability of certain molecules into the lumen. The immune barrier comprises intra-epithelial lymphocytes, (Peyer's patches), secreted IgAs, lymphatic follicles and mesenteric lymph nodes (GALT). The biological barrier consists of commensal flora, the normal inhabitants of the gastrointestinal tract which reside in colonic mucus and under normal circumstances inhibit exogenous and harmful bacteria from reaching the gut mucosa. Within the bacterial population, 600 different species have been identified and are considered to be of importance *Bacteroides, Eubacterium, Bifidobacterium, Fusobacterium, Methanogens, Peptostreptococcus, Enterobacter, Lactobacillus* and *Escherichia coli*.[5,6]

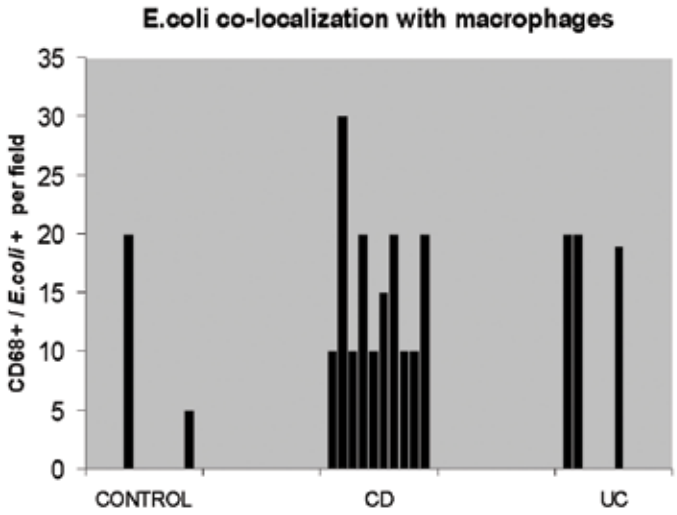
Under normal "symbiotic circumstances", the presence of luminal bacteria is beneficial to the host as not only do they maintain gut homeostasis but also induce tolerance by "educating" the human body to reduce allergic responses to food and invading environmental antigens. Noticeably, the residential microbiota, do not evoke an immune response in healthy people, contrary to the pathogenic non-commensal microbes that have evolved numerous strategies to hijack the host immune cells in patients.[7]

What distinguishes IBD among the vast spectrum of inflammatory diseases? The answer is still controversial; therefore, much attention has been given to the understanding of the mechanisms of inflammation seen in IBD patients.

During the progression of the disease, tolerance to commensal flora appears to fail and exposure to bacterial strains initiates an inflammatory response in the mucosal epithelial layer. Clinical observations support the

Author for correspondence:

A.D Chairakaki, Research Associate, Systems Biology & Bioengineering, Department of Mechanical Engineering, National Technical University of Athens. 9 Heroon Polytexneiou, 15780 Zografou, Athens, Greece, Tel 2107721516 e-mail: aikaterini.chairakaki@gmail.com



PATIENTS	Co-localization of *E.coli* with intestinal macrophages (E.coli + / CD68 +)
CROHN'S DISEASE	+/++
ULCERATIVE COLITIS	+/-
CONTROL	-

+/- => 5 cells per field, + => 10 cells per field,
++ = 10-20 cells per field, +++ = 20-30 cells per field

Figure 1. Co-expression of E.coli with macrophages in the study group. Graph shows individual patients' co-localization. Table expresses collective semi-quantitative data. ***Controls***: a minority of control individuals had bacteria in their macrophages. ***Crohn's disease***: all patients examined had E.coli-associated macrophages. ***Ulcerative colitis:*** Three out of ten patients demonstrated E.coli within macrophages.

data that the chronic inflammation clinically investigated in both CD and UC, is the result of an acute immune response against commensal luminal enteric bacteria in a genetically susceptible host.[2] One theory is that the inflammatory response in IBD patients is initiated by a yet unidentified invading pathogen(s), leading to the recruitment of inflammatory cells such as lymphocytes, macrophages and plasma cells, inducing proinflammatory cytokine and chemokine accumulation. Therefore, the mucosal immune system remains chronically active due to the inability to cease such inflammation and the loss of tolerance against commensal microflora.[5] Amongst the aforementioned commensal bacteria implicated in the disease, *E.coli,* is probably the most extensively studied. Alterations in the numbers of the luminal bacteria have been identified in IBD patients showing an increase of *E.coli* in the adherent mucosa as well as in intracellular entities.[8]

In our recent study, we hypothesised that in IBD patients there is a "functional defect" in the macrophage population which render them susceptible to infection with *E.coli*. The primary function of the sentinel macrophage which resides in the subepithelial lamina propria is to sense danger within the local microenvironment, phagocytose the potent invaders of the epithelium and secrete cytokines and chemokines that prime and amplify the immune system to abrogate any bacterial invasion. It is yet unclear whether the observed presence of the mucosal macrophage-associated *E.coli* in IBD patients is of pathogenic significance. For this reason, we tried to affiliate the monocytic lineage response to the bacterial invasion by immunohistochemically measuring its activation status aside from its cytokine/chemokine secretory capacity. Concisely, existing *in-vitro* data provided evidence that adherent invasive *E.coli* strains, isolated from Crohn's granulomas, were able to intracellularly survive within murine macrophage-like cell lines.[9]

We confirmed the *in-vivo* presence of *E.coli* in the lamina propria[l] macrophages in 100% of patients with Crohn's disease and unlike others, a 30% presence in ulcerative colitics, compared to controls. Furthermore, in all patients examined, we found an upregulation of the macrophage-associated activation status levels in comparison with normal controls. Particularly, an overall up-regulation of both chemokine and pro-inflammatory cytokines was defined in patients whose macrophages were laden with *E.coli* compared to those free of bacteria and controls: enhanced TNF-α, IL-15, IL-23, IL-8 and MCP-3 expression in macrophages correlated well with biopsies in patients' macrophages loaded with the bacteria. (Fig 1). Our data suggested that the studied monocytic lineage contributes to the chronic inflammation clinically seen in IBD. The dysfunctional macrophage profile in patients supported our hypothesis that *E.coli* uptake may be the initiative step in the disease pathogenesis. It remains uncertain albeit, whether the survival of *E.coli* within macrophages is a property of the bacteria, a defect in innate immunity or both.

Advances in our understanding of the inflammatory cascade of the disease and the possibility of the development of novel efficacious therapies to interrupt such in-

flammation via probiotics treatment, or genetically engineered bacteria administration, seems really promising. If IBD develops in response to intestinal microbiota, then shifting the targeted antigenic milieu might be of innovative therapeutic value.

REFERENCES

1. Hanauer S. Inflammatory bowel disease: Epidemiology, pathogenesis, and therapeutic opportunities. Inflamm Bowel Dis 2006,12:S3-S9
2. Sartor RB. Targeting enteric bacteria in treatment of inflammatory bowel diseases: why, how, and when. Curr Opin Gastroenterol 2003;19:358-365
3. Brandtzaeg P, Halstensen TS, Kett K, et al. Immunobiology and immunopathology of human gut mucosa: Humoral immunity and intraepithelial lymphocytes. Gastroenterology 1989;97:1562-1584
4. Ding L, Li J. Intestinal failure: Pathophysiological elements and clinical disease. World J Gastroenterol 2004; 10:930-933.
5. Green GL, Brostoff J, Hudspith B, et al. Molecular characterization of the bacteria adherent to human colorectal mucosa. J Appl Microbiol 2006; 100:460-469.
6. Tlaskalova-Hogenova H, Stepankova R, Hudcovic T, et al. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immunol Lett. 2004; 93:97-108.
7. Sartor RB. Mechanisms of Disease: pathogenesis of Crohn's Disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006; 3:390-407.
8. Mylonaki M., Rayment N.B, Rampton D.S, Hudspith B.N, Brostoff J. Molecular characterization of rectal mucosa-associated bacterial flora in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2005; 11:481-487.
9. Glasser A, Boudeau J, Barnich N, Perruchot M, Colombel J, Darfeuille-Michaud A. Adherent Invasive *Escherichia coli* strains from patients with Crohn's Disease survive and replicate within macrophages without inducing host cell death. Infect Immun 2001; 5529-5537.
10. Rayment NB, Chairakaki AD, Hudspith B, Petrovska L, Parkes G, Brostoff J, Sanderson JD. T1230 Cytokine Profiles from *E. coli* Laden Macrophages in IBD. Gastroenterology 2008; 134:P. A-511.