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The Changing Face of Inflammatory Bowel Disease: Etiology, Physiopathology, Epidemiology

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Abstract

Context: The term inflammatory bowel disease (IBD) classically includes ulcerative colitis (UC) and Crohn's disease (CD). An abnormally increased mucosal permeability seems to underlie UC, whereas CD is thought to be the result of an immune deficiency state.

Evidence Acquisition: While these phenomena may well be labeled as genetic factors, the environment has its role as well. Drugs (chiefly, antibiotics and non-steroidal anti-inflammatory molecules, with proton pump inhibitors recently joining the list) and smoking habits are all being scrutinized as IBD causative factors.

Results: Once almost unknown, the prevalence of IBD, in the Eastern World and China, is now increasing by manifold, therefore arousing warning signals.

Conclusions: A multidisciplinary approach will soon be necessary, to face the tenacious behavior of IBD, on a global perspective.

Keywords: Inflammatory Bowel Disease, Physiopathology, Microbiome, Epidemiology, Genetics

1. Context

Both ulcerative colitis (UC) and Crohn's disease (CD), unified under the inflammatory bowel disease (IBD) concept may target the human gut with their inflammatory, chronic recurrent and substantially incurable lesions. Confinement to the colonic mucosa, with an Arthus-like reaction, characterizes UC, while discontinuous transmural granuloma-like changes, often with fistula and abscess, are hallmarks of CD. Brought about by the results of recent research, novel ideas have accumulated on the pathogenesis of the two IBD entities.

2. Evidence Acquisition

2.1. Inflammatory Bowel Disease: An Updated Conceptualization

2.1.1. Evidence for an Altered Mucosal Permeability in Ulcerative Colitis

The intestinal mucosa has evolved to exert a subtly balanced function, between the need to efficiently absorb nutrients and the defense against outside invaders. Indeed, alterations of this equilibrium have long been anticipated, were searched and then found, and determined as causative factors, in both IBD phenotypes. However, it is only in more recent times that altered (increased) mucosa permeability has been studied in depth and the results of a few genome-wide association (GWA) studies have emphasized a specific link between changes of mucosal permeability and UC. The path was earlier pioneered by the Strober group (1), who using an animal model of oxazolon-induced colitis, focused on the effector role played by a particular T-cell subset, which they named natural killer T-cells (NKT-cell). Among other functions of these cells, the secretion of large amounts of IL13, capable to enhance permeability, was indicated as pivotal in the induction and maintenance of this experimental UC.

The interest in intestinal barrier functions in UC was more recently fostered by the results of studies of the genes coding for molecules that are involved with the barrier machinery, as in the two following examples, among many others. First, encoding the glycoprotein extracellular matrix protein 1 (ECM1) makes a plausible candidate for UC susceptibility: indeed, homozygous nonsense or frameshift mutations of ECM1 have been associated with a rare autosomal manifestation, characterized by skin and gut involvement. Second, mutation of the CDH1 locus, coding for E-cadherin, have been found to be linked with colitis development, in agreement with the notion that E-cadherin, along with HNF4A, effectively maintains barrier integrity (2). Intriguingly, this basic science notion seems to have received support from our

real-world clinical experience: in our office, we have recently studied a cluster of IBD patients, who either relapsed or developed de novo a severe UC, after receiving macrolide antibiotics (3). The interesting causative sequence linking these events is that macrolide molecules are known to favor *Candida* contamination of the gut (4), and *Candida* has been shown to be able to cleave E-cadherin, thereby increasing mucosal permeability (5). If, facing these issues by an in vivo approach, then the assumption must be that IL13 is upregulated in UC and can increase colon permeability by inducing apoptosis and pore-forming proteins. The IL13 signals through STAT6 and a phosphorylated tissue pSTAT6 can be taken as an indicator of exposure to IL13. To this end, the Rosen's group, at Vanderbilt (6), studied by immunohistochemistry pediatric patients undergoing their initial colonoscopy for early onset UC, comparing the results with controls and Crohn's specimens. They reached the two following results: 1) the score for tissue pSTAT6 was significantly higher in early UC, in comparison to controls and Crohn's; 2) the transepithelial resistance was partially reestablished when the activity of IL13 was mitigated, by inhibiting pSTAT6 phosphorylation, in transfection experiments. The interest in factors of increased gut permeability, as driving pathogenetic forces in UC, has dramatically been transposed onto a clinical ground, by a recent paper, followed by the publication of its ancillary review (7, 8). This paper's topic was *Campylobacter* concisus (*C. concisus*), a bacterial species that normally colonizes the human oral cavity, and, transported by saliva, might indwell the distal gut sections. The authors found that several subsets of this *Campylobacter* may become vectors of the gene zot, if infected by a specific phage that becomes chromosomally integrated; the gene zot, in turn, can upset intestinal permeability by damaging tight junctions. Subsequent finding of an increased frequency of *C. concisus* colonization in IBD patients and the demonstration of a high rate of zot positivity in these colonies has permitted to claim the evidence that, at least several cases of IBD might be driven by an indwelling commensal, if mutated to carry a virus-sourced gene specifically capable to increase intestine permeability.

2.1.2. Crohn's Disease

Crohn's Disease (CD) has traditionally been considered a hyperimmune state, and a tremendous variety of immune suppressors, recently including tumor necrosis factor-alpha (TNF-alpha) blockers, have been released and indicated for its treatment. However, several orders of observations, including an erratic, although convincing, response of the disease to antibiotics (9) and the fact that CD has, so far, proven medically incurable, have never ceased to fuel scrutiny of these tenets in search for other options. Recently, the efforts of several groups (10, 11) have converged into the view that CD is, in fact, a disorder of immune deficiency, wherein the basic defect is an inappropriate dealing with bacterial antigenic loads. Such an original failure of the innate immunologic arm, with time, would involve the adaptive immune system into the battleground. With a substantial inability to affect immune clearance of the invaders, the disease would run a waxing-and-waning course of quiescence and reactivations. Due to the active release of inflammatory mediators, including the TNFs, only the latter phases would prove responsive to immune suppressors and biologics, therefore yielding the tantalizing, yet elusive, mirage of being able to terminate the disease. At the subcellular level, the abnormalities have been clarified as not being dependent on a wrong cytokine transcription. In contrast, they have been explained by their wrong trafficking to degradation, via the lysosomal pathway, instead of being stored in secretory vesicles (12). The gene counterpart of this subcellular scenario has proven not less interesting. The continuous refinement and extension of the pioneering studies of a decade ago have now shown a complex synergic scenario. Briefly, the actors [Nod1 (in epithelial cells) and Nod2 (in macrophage/dendritic cells)] are encoded for by the CARD15 gene, and function as sensors for bacterial polysaccharide motifs. Of equal importance, is the ATG16L1 gene, an autophagy regulator, with the specific mission of disposing subcellular organelle debris and intracellular bacteria. Upon stimulation in normal conditions, Nod1, Nod2 and ATG are supposed to coalesce at the cell membrane, therefore opening the well-known inflammatory cascade, dominated by Nuclear Factor-kappaB (NF-Kb) activation (12). Such chain of events seems to be particularly prone to be hampered by mutations in the CARD 15 gene. The view of CD, as an immune deficiency state, has been very recently fostered by the publication of a paper dealing with the epoxygenase CYP2J2 (13). The results of this study demonstrated that CYP2J2 mediates bacterial phagocytosis, in macrophages, and implicated that a CYP2J2 defect may negatively regulate bacterial clearance in CD. The ability of Nod2 functions to influence granuloma formation stems clear from its role in the genesis of CD. However, it seems not to be limited to this condition. Recent evidence indicates that Nod2 variants, may participate in the genesis of early onset sarcoidosis and, also, other non-granulomatous conditions are being added to the list of the abnormalities that might be prompted by polymorphisms of the Nod sensors (14), including: *Helicobacter Pylori* infection and malignancy, allergic disorders and atopy, as favored by an exaggerated Nod2 dependent response of the Th2 type.

3. Results

3.1. Etiology

3.1.1. Congenital Abnormalities of the Immune Response

The IBD may present accompanied by defects of either the innate, or the acquired immune response, and have

been reviewed recently (15). Chronic granulomatous disease may be an example of the former instance, whereas Wiskott-Aldrich syndrome may exemplify the latter. We have recently described a young patient presenting with co-morbid Bruton's agammaglobulinemia and Crohn's disease (16), bringing about an example of association of IBD with a defective acquired immunity.

3.1.2. Drugs

3.1.2.1 Micophenolate

Introduced in the immune suppression regimes for solid organ transplantation, in the mid-'90s, mycophenolate was soon indicated as the cause for the gastrointestinal symptoms complained by the treated patients, including nausea and diarrhea. Recent use of colonoscopy, to investigate these symptoms, has yielded useful information in identifying at least two patterns of pathologic changes. In several patients, aspects amenable to graft-vs-host-disease were detected. However, not less importantly, a Crohn's-like disease was also consistently observed (17). The causal involvement of mycophenolate in these changes was suggested by repair upon withdrawal.

3.1.2.2. Anti-Cytokine Biological Drugs

In 2010, the first report (18) was published of a 4-year-old boy, who, receiving regular doses of rituximab for his steroid-dependent nephritic syndrome, developed gut symptoms, at around 6 weeks after therapy was started. After excluding other causes, colonoscopy revealed a UC-like pancolitis, with histologic cryptitis. The intestinal cell infiltrate in this young patient revealed absence of CD19 + and CD20 + B-cells, activation of mature CD3 T-cells and Fox-P3 regulatory T-cells. Rituximab discontinuation and intensive conventional treatment, with high-dose prednisone and thiopurines, led this UC-like manifestation to remission. Although the gut pathology did not recur, the nephritic syndrome tended to relapse when the CD19 +/ CD20 + B populations switched to reconstitution.

So-called paradoxical reactions to the use of anti-TNF strategies have been known to develop in a minority of rheumatologic patients. The proportion of paradoxical IBDs, among this series, has been significant. The initial impression that such unwanted effects could be restricted to etanercept has required a reappraisal, due to the most recent descriptions of IBD-alikes, following prescription of either infliximab or adalimumab. We ourselves (19) have recently described a case of juvenile arthritis, which had developed a class-specific intolerance to all three of the mostly prescribed formulations of etanercept, infliximab, adalimumab, with his pancolitis ceasing only after discontinuation of all anti-TNF preparations and a long wash-out. A cooperative group of French rheumatologists has recently released the results of a 2-year observation study period (20). Sixteen patients, most of whom were on etanercept for ankylosing spondylitis, were declared to have developed an IBD-like picture.

At least at a speculative level, both the rituximab and the etanercept cases of paradoxical IBD can be explained by recalling that all of these biological formulations can favor specific lymphocyte subpopulation imbalances, at the mucosal level. Regulatory Fox-P3 has been mentioned to follow rituximab administration. The anti-TNF preparations have been shown to provoke an increased expression of the alpha-4/beta-7 integrins, on the surface of CD4 lymphocytes fluxing into the gut, therefore augmenting their gut-seeking potential, their pathogenicity then depending on the equilibrium between these integrins and the specific cell adhesion molecules, on-site (21).

3.1.2.3. Antibiotics

Through their anticipated action on microbiome composition, (see below) antibiotics are likely candidates among the factors potentially affecting gut homeostasis. During time, various studies have, in fact, addressed this point, yet with prevalently mixed results. A large epidemiological study, in the pediatric setting (22), has recently constituted a breakthrough, demonstrating that a large antibiotic utilization, early in infancy or childhood, is statistically linked with a subsequently increased risk for developing IBD. Analyzing the adult population referred to our out-patient clinic, we found that antibiotic prescription (mainly for respiratory infection) might be followed by rise of IBD, shortly. As anticipated above, we further found that the risk may be specifically linked to the use of macrolide molecules, which, favoring gut colonization by yeasts (4), might loosen tight junctions and abnormally increase gut permeability. This clinical evidence is being corroborated by cutting-edge data from experimental animal work, showing that macrolide treatment of murine gut strongly impacts microbiome, jeopardizing resiliency following a significant diet change, with such an effect lasting several months (23). Based on this laboratory and clinical evidence, it has now become our policy to recommend family physicians to carefully reconsider their macrolide prescriptions.

3.1.2.4. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Inhibiting protective prostaglandins, non-steroidal anti-inflammatory drugs (NSAIDs) can be reasonably anticipated to imbalance gut equilibrium. Ananthakrishnan's recent work has recently shed robust light on this issue (24). Enrolling a large number of hospital staff members to self-report on their NSAID use, on the long term, he found that those, who had used the drugs for longer than 15 days a month, reached a significant level of risk for developing IBD. In our own out-patient environment, we found that NSAID prescription, for orthopedic and dental surgery are those to look at, with maximal caution.

3.1.2.5. Proton Pump Inhibitors

Various proton pump inhibitors have recently been indicated as the cause of right-sided colitis (25). While most of these patients are asymptomatic, biopsy specimens of the right colon may typically show lymphocyte aggregates, in the submucosa.

3.1.3. Environment

3.1.3.1. Smoking

Cigarette smoke has classically been held to be protective factor against UC, while favoring occurrence or aggravation of CD (26). Specifically, the risk of activating UC is maximal several years after quitting smoking. The CD patients who continue to smoke have been shown to need increased doses of medication and immune suppression, to maintain remission.

3.1.3.2. Stress

Stress has long been targeted by various epidemiological studies, yet with mixed results (27). A very recent paper (28) has now claimed robust evidence that anxiety disorders may be twice as likely in IBD.

3.1.4. The Microbiome

Rapid progress in molecular techniques has now shown us that the so-called barrier organs (respiratory epithelia, skin, urinary tract and gut) do harbor trillions of bacterial species, outnumbering the mass of our somatic cells (29). There is now evidence that gut microbiota can influence metabolism, energy utilization from nutrients, development of type-2 diabetes, obesity, and mental health. Several microbial entities in the gut microbiome can specifically promote pathology: *C. concisus* species can influence intestinal permeability and promote IBD, while Prevotella genuses might trigger joint inflammatory lesions. An increasing interest towards the microbiome, in IBD, is no wonder. The gut flora in IBD is unstable, showing a reduced biodiversity with Firmicutes and Bacteroidetes being restraint. Diet has excitingly been shown to be able to favor growth of proinflammatory pathobiota. For example, a diet rich in saturated fat milk, promotes the thrive of Bilephila Wadsworthi (30), a bile-specific species, capable of inducing populations of TH1 positive T-cells and ensuing inflammation.

3.2. Epidemiology

3.2.1. Diffusion of Inflammatory Bowel Disease in Asia

Statistical data for IBD, in our country, indicate a prevalence of 177 - 254 cases per 105, per year, and an incidence of 2.7 - 13 annual cases, per 10^5 (31). While these figures have shown a substantially stable trend, they also roughly mirror figures from abroad. Interesting news, by contrast, do derive from the Eastern World, where it seems that IBD is on the move. The bulk of information is contained in a recently issued survey (32), regarding specifically the topic of IBD in Asia. Traditional incidence figures of 0.60 - 3.44 have recently increased by a threefold. A few of the most relevant features are listed below:

- UC prevails over CD
- A family history and extraintestinal manifestations are less impressive than in the Western cases
- By contrast, complicated and penetrating CD is more common in Asia
- Genetically, NOD2 and autophagy variants seem to be poorly associated with CD.

A multitude of factors may play in the Asian diffusion of IBD:

1) Westernization of life
2) Use of appendectomy
3) Breast feeding (impacting microbiome composition)
4) Changing diets

The study of IBD in Asia proves rewarding, because it represents a sort of rewinding of the events that accompanied IBD diffusion in the West, at the rise of the 20th century.

3.2.2. Diffusion of Inflammatory Bowel Disease Among Immigrants

Based on the reasons illustrated above, assuming that IBD is thriving in the Far East and China, taking advantage of refinement of life and the arising of sources of industrialized food, it seems reasonable to expect that IBD will not have to wait to reach the power to invade a given target country. Nevertheless, it will be keen at creeping among those who, deliberately or forcefully, have left home behind, to face an abrupt encounter with a different (westernized) pattern of life. Such a scenario has recently been described (33) for thousands of North Africans or South American people, who moved to Canada. Following them up for a relatively short time, the investigators found that, by the second generation (at the latest), the risk of these immigrants to develop IBD matched the figures of the native Canadians. The implication is that such a pace of change is not compatible with genetic mutations (obviously far slower), while strongly recalls fast epigenetic factoring, including points one and four, above. To tragically remind us that these data are real life and not fiction, swarms of hopeless inhabitants of Northern Africa and Middle East are now invading the coasts of Southern Italy, whilst aiming to and already reaching France, Germany and England. It is easy to envisage that these people's descent will soon be hit by an authentic outbreak of IBD, impacting, among all, the already staggering medical budgets of Europe. In this sense, IBD may be seen as strictly intertwining with an epochal process of re-definition of the socio-political and financial profile of Europe, Northern Africa, and Middle East, playing a protagonist role in such keystone changes.

4. Conclusions

The IBD is, nowadays, best understood as a hub (or one of the hubs) in a network of inflammatory disorders, targeting joints, liver, skin, the eyes (to name just a few). Interest in the IBDs continues now to be renovated by the results of genetic studies, the discovery of the pluripotent microbiome and by the intriguing tendency of the disease to invade the Eastern World, intertwining with massive migratory streams. A team of immunologists, rheumatologists, microbiologists, psychologists and economists, must join the gastroenterologist to best serve IBD patients. In the ultimate analysis, the IBDs may be considered a function of the way the individual copes with “the outer life”. This concept is perhaps best translated into poetry/philosophy by the aphorism of a scientist of the past century:

The states of health or disease are the expressions of the success or failure, experienced by the organism, in its efforts to respond adaptively to environmental challenges (Rene Dubos, 1965).

The history of the relationship between IBD and mankind is probably a never-ending work in progress.

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