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EDITORIAL

Inflammatory bowel disease: Traditional knowledge holds the seeds for the future

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Abstract

Despite the level of sophistication they have reached nowadays, the available tools for treatment of inflammatory bowel disease (IBD) can at best chronicize the disease but not cure it. Chances to make leap forward from this hold-back may include designs to reach personalized treatment strategies taking advantage of modern genome associated studies, and shift resources towards unfolding inciting pathogenetic steps rather than continuing to develop drugs that address down-stream phenomena. We have arbitrarily chosen to scrutinize a few projects that may make their way in 2015 and mark the history of IBD research. The list includes: the role of appendix as a regulating factor in pathogenesis of ulcerative colitis/proctitis; the reappraisal of (auto)immune phenomena in the era of microbiome; projects to treat IBD by stem cell infusion; recognition of the crucial pathogenetic role of gut microbiome, and attempts to modify it to treat enteric diseases, from clostridium difficile infection to IBD.

Key words: Inflammatory bowel disease; Microbiome; Stem cells; Future treatments; Curative appendectomy

Core tip: The inflammatory diseases of the gut (inflammatory bowel disease) continue to both constitute a medical challenge, and a formidable intellectual stimulus. The latter statement is based on the accumulating evidence that the IBDS are indeed syndromes whereby a few poorly penetrating polymorphic genes can affect at once the inflammatory balance in the barrier systems of the gut, the skin, and the airways. The former statement reflects the very fact that, though described in the 19th century, IBD continues to defeat our struggle to cure it, invading yet the hitherto unaffected landscapes of the Eastern World, almost as it was a response to our efforts. We deem that the address of the initiating factors, rather than the downstream phenomena, may be a strategy to wriggle out of the hold-up. The description of interventions such as appendectomy or microbiome replacement, among other options, witnesses our own way to interpret this need in the present editorial.

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INTRODUCTION

Inflammatory bowel disease (IBD) is now understood as a dysfunction of a barrier organ, whereby the antigenic gut luminal contents (from diet and autochthonous flora) come in an undue contact with the reactive sub-mucosal tissue. The players in this event include: polymorphisms of the genes governing cytokine networks; passive defense devices (defensins and epithelial sealings); inborn errors of functional structures of innate immunity (the NOD system *e.g.*); inborn knock-out of genes coding for down-regulatory circuits [es interleukin (IL)$10^{-/-}$); the polyfunctional microbiome. From a general prospective, this universe is ruled by a plethora of low-penetrance genes, needing to come about in a critical mass to induce disease phenotypically. Needless to say, various treatment attempts at impacting this scenario have often proven deceptive, calling for a shifted frame of mind bound to overcome the simple search for the next biological formulation following failure of the former. We have arbitrarily chosen to describe a few examples whereby the authors have essayed to see the matters from a different angle.

In one of these attempts, the authors were inspired by the observation that the gut inflammation that develops in IL-10 knock-out mice seems to have an appendiceal origin; based on this, they pursued the study of the consequences of appendectomy, finding that appendectomy tends to exert a prevalent down-regulatory modulation. Back in 2009, a large clinical study enrolled humans to receive appendectomy for their ulcerative proctitis, achieving at least clinical remission in a patient subset. It is hoped that basic and clinical research in this field will march at the same pace to identify a revolutionary strategy to tackle the problem of gut inflammation and proctitis specifically.

Cutting edge research has recently confirmed that tissues and body fluids can no longer be considered "conventionally" sterile, insofar as containg a myriad of genomic (bacterial and virologic) messages. Since these determinants are reasonably able to elicit strong immune reactions against themselves inciting inflammation, the authors argue that a few chronically inflamed patients (including Crohn's) should be immune stimulated to wipe out the indwellers, rather than immune suppress them.

Some years ago, the early claim of "cure" of a few cases of Crohn's disease after bone marrow transplant had paved the way towards the strategy of reprogramming progenitor cell lineage to terminate IBD. Programs of stem cell transplant are now very active and the clinical harvest seems promising so far.

The rapidly growing understanding of the microbiome could not avoid to bear significant impact on our clinical address on IBD. There is now consistent evidence that microbiome composition is profoundly altered in IBD, lending rationale to the use of fecal transplant as a treatment option. This is a rapidly growing matter that will not fail to produce results in the near future.

Conclusively, there are at least two added values attached to this novel mindframe. Firstly, it may take us even closer to the now legendary promised land of personalized medicine; Secondly, we are finally driving the coach towards understanding the roots of the disease, rather than blindly aiming at its epiphenomena.

IBD: TRADITIONAL KNOWLEDGE HOLDS THE SEEDS FOR THE FUTURE

Certain anatomic/functional structures have evolved to discern between the inner "sterile" milieu and the outer "polluted" environment. The pivotal components in such "barrier organs"[1] (the gut, skin, the airways, urinary tract) consist of a mucosal immune system (biased to tolerance) and an underneath lymphoid tissue (primed to react).

Owing to their functions, inflammation in barrier organs is constitutive; it may grow to be induced if the balance between pro- and anti-inflammatory forces is breached. Specifically, the players in this balance at the colonic level are the diet constituents, the local immune system, and the microbiome[2,3].

In 2009, we compiled a scrutiny of the elements that factor in colon pathophysiology (unpublished data). In the lines to follow, we reappraise this rather outdated paper, with the bias to uncover current and future links to research in colonic physiology and disease.

THE MAIN COMPONENTS IN THE SYSTEM

Barrier alterations

Insofar as preventing the rise of inflammation by avoiding contact between luminal antigens and the overreactive lymphoid tissue underneath the mucosa, epithelial integrity, inter-cell sealing, and production of defensive substances are essential. Chimeric mice for a defective cadherin[4] (a crucial factor in the sealing properties of tight junctions) exhibited unchecked intestinal inflammation; patients with active Crohn's disease showed a 50% reduction of secretion of defensins[5], that are Paneth cell-derived cationic peptides endowed with antibacterial activity. Noteworthy, updated research is now showing that correct production and release of beta-defensins is under the control of the vitamin D receptor (see below)[6].

Alteration of gut flora

This topic has largely been treated by others[7] and ourselves[8]. Such trillion-individual metagenomic world in our digestive tract has been shown to affect a range of conditions including diabetes[9,10], obesity[11], inflammatory disease[12], and behavioral changes[13]. Just two examples showing that microbiome components might influence inflammatory circuits are the following. Microbiome-derived free-fatty-acids might regulate size and function of regulatory T-cells (T-regs), activating SMAD 3 and 4[14,15], and ameliorating experimental

colitis; Prevotella Copri can educate T-lymphocytes to secrete IL17, a key cytokine in rheumatoid arthritis[16]. Evidence that microbiome composition can be modified by diet, has prompted intensive study programs aiming at determining the therapeutic role of fecal flora transplantation in treatment of both IBD and Clostridium difficile infection (CDI)[17].

Alteration of innate immunity

Evolution has endowed us with a number of sensors to check the outer environment for invaders[18]. The toll-like receptors (TLR)[19] are membrane confined elements, the nucleotide oligomerization domains are cytoplasmic. The NODs[20] comprise a leucine-rich repeat, a central NOD structure facilitating oligomerization, and a terminal caspase-recruitment domain. Essentially, the final common action of both TLRs and NODs leads to activation of cytoplasmic NFκB[21], which, upon nuclear translocation, will induce the genes of pro-inflammatory cytokines, as part of a defensive program. As a key-stone discovery by two independent teams in 2001, a loss-of-function NOD mutation was described in a significant proportion of Western Crohn's patients, but not in those of an oriental descent[22].

Alteration of adaptive immunity

These may encompass both B-cells and T-cells misfunctions. The B-cell products ASCA and ANCA antibodies are well-studied markers of Crohn's[23] and UC[24] respectively. On the other hand, anomalous T-cell clones may arise in IBD as a consequence of a changed dendritic cell antigen presentation, or presentation by non-professional cells[25]. Among such T-cell phenotype variants, the Th17 cells have received most of the attention recently.

The Th-17 lymphocytes[26]. We wish to devote a deal of attention to these cells as they are destined to be further discussed below. Derived from $TCD4^+$ lymphocytes, and $CD4^+CD25^-$Foxp3 lymphocytes, can mainly release IL17, as driven by IL-23 dependent STAT-3 activation[27].

Physiologic roles

Rise of Th17 cells was initially demonstrated in fungi and bacteria infected milieus, suggesting a protective mission for these cells; klebsiella pneumonitis, Candida infection, and mycoplasma invasions were all demonstrated to constitute an arena for Th17 cells[28].

Pathophysiologic roles

In the unstable milieu of the sub-clinical intestinal inflammation, Th17 cells can easily be traced to the lamina propria; in full-blown pathologic conditions, they can easily be shown to migrate to inflamed areas[29]. The chemokine-ligand interaction CCr6-CCL20 has been found to be crucial for the homing of Th17 cells to the distal colon[29] (see below). Arthritis has long been recognized as a co-morbidity of IBD and Th17 cells have recently been reckoned to be effectors in this pathologic events[30]. Interaction of the chemokine CCR6 with its homologous synovial chemokine CCL20 have been shown to allow Th17 homing to arthritic sites, thus initiating bone resorption.

FUTURE RESEARCH SEEDS

The chain of evolution and function of Th17 cells as summarized above allows us to open the list of future endeavors with this topic. This list will therefore comprise: (1) The appendicitis/appendectomy model; (2) Metagenome and autoimmunity; (3) Bone marrow transplants; and (4) Microbiome modulation.

The T-cell receptor-α mutant mice (TCR-$\alpha^{-/-}$), obtained by gene targeting of the TCR-alpha gene in embryonic stem cells, is a popular mouse model that spontaneously develop ulcerative colitis-like inflammation of the colon[31]. In 1996, the team of Bhan published the results of experiments aiming to define the reciprocal roles of appendix associated lymphoid follicles (ALF) *vs* that of Peyer's patches (PP) in such diseased mice. They found that: (1) the proliferative index in ALF was twice that of PP; and (2) The frequency of IgG secreting B cells in ALF of mutant mice largely exceeded that of non-mutant animals. Early appendectomy in mutant strains had two orders of consequences: (1) the number of mesenteric lymph nodes got significantly reduced; and (2) appendix ablation at 1 mo of age suppressed the development of IBD[31]. The tenet that appendicectomized humans might be protected from ulcerative colitis in fact relies on these basic data of the 1990's. Specifically, a clinical paper issued in 2009[32], followed in 2011 by a short communication in a letter format[33], have shown that appendectomy might ameliorate symptoms in a limited group of patients with ulcerative proctitis. The team of Cheluvappa *et al*[34] in Sydney has recently reappraised the basic information on Th17 cells we collected above, to design an animal model. BALB/c mice were subjected to experimental appendicitis and appendectomy (AA), then distal colon samples were harvested. Results were validated using reverse-transription-polymerase chain reaction. The authors mainly found that prior AA ameliorated experimental colitis. CCL20 expression was suppressed in the most distal colon 3 and 28 d after the AA was done at the proximal colon[34]. Another piece of study from the same group[35] has suggested that suppression of a few endothelin genes may be a mechanism in these findings. The authors conclude by wishing that this expanded knowledge on the Th17 system and CCR6/CCL20 interaction can be transferred to clinical grounds before long.

The team of Amy Proall has conducted extensive basic research on the human microbiome, pushing her findings to somewhat extreme consequences[36]. The author starts out by stressing that modern techniques are now demonstrating that not only the usual sites such as the colon are dwelled by abundant

microbiome species, but virtually all tissues or fluids within our bodies harbor trillions of yet unknown bacterial and viral phila. The authors list a few of the implications of these revolutionary findings: (1) The inner milieu can no longer be considered sterile; (2) The concept itself of autoimmunity might be reduced to a concept of a reaction against antigenic determinants of this overwhelming microbiome, or against modified self-antigens; (3) Given these premises, the correct approach to treatment of inflammatory disease would be immunostimulation to get rid of the indwellers, rather than immune suppression. The latter will obviously lend symptom relief but will promote persistence of the inciting causes, whether bacterial, viral or else[37]; and (4) Worth of note, this overriding antigenemia might also be fueled by the action of active transport systems. A recent paper[38] dealing with peptide transport from the intestine, has described a carrier, pepT1, which, belonging to the superfamily of proton -coupled oligopeptide transporters, can transport oligopeptides through the cells to the bloodstream thanks to coupling with hydrogen ion. Interestingly, the authors pin-point that the activity of pep T1, can turn out to be heightened during intestinal disease such as IBD, wherein in this case bacterial flora (metagenomic) by-products may become the transported antigenic material. As a consequence of this shift, mounting of inflammatory and auto-inflammatory responses can easily be predicted. Thus, the findings of such independent work seems to lend fuel to Proall's speculation.

The authors conduct an interesting focus on the vit D receptor (VDR). Of the two recognized classes of VDR, the first, segregating to the cell nucleus, belongs to the family of the class 2 steroidal hormones receptors, and is closely linked with the retinoic acid and thyroid hormone receptors. As a protein of 427 aminoacids, the human VDR couples DNA, links the ligand, and self-activates through its three respective domains. Functionally, VDR heterodimerizes with retinoid X receptor (RXR), activating gene transcription (vit Response Elements) and protein synthesis. The other VDR is a membrane element, and as a non-genomic action, catalizes release of cellular messengers. Noteworthy, the VDR complex conditions release of a huge number of protective molecules. When thwarted by a load of bacterial ligands it may cease producing crucial protective compounds from cathelicidine to difensins[39], thus fully impacting on IBD pathophysiology; in addition also Vit D handling might be damaged, and a receptor leaking 1,25 vit D has been described in inflammatory conditions including Crohn's. Vit D itself, on the other hand, bears the structure of a secosteroid. Because exerting in fact a down-regulatory effect on various immunologic steps, it should be considered an immune suppressor. Based on this, the authors express doubts as to the indication for vit D in a few inflammatory conditions, including IBD.

Coherently with these premises, the authors declare to have studied the possibility of alternative non-suppressive regimes for immune-inflammatory conditions, including satanic derivatives.

C STEM CELL THERAPY FOR IBD

The issue has recently been addressed in an exhaustive review[40]. Stem cells characteristically undergo a process of asymmetrical cell division, giving birth to a cell with the same properties as the original cell, and another cell of multilineage differentiation potency, depending on environmental conditions. The comprehensive term "stem cells"[41] includes: (1) embryonic stem cells, *e.g.*, pluripotent cells obtained from embryos; (2) multipotent adult stem cells including hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) found in all body tissues; and (3) induced pluripotent stem cells, defined as artificial pluripotent stem cells generated from somatic cells by the introduction of reprogramming factors.

HSC and MSC are currently used and evaluated to treat therapy - resistant Crohn's disease. The only protocol that is officially accepted requires infusion of autologous HSC[42] following a program of cell mobilization and myeloablation[43]. Briefly, the patient first receives cyclophosphamide and granulocyte colony stimulating factor to stimulate production and release of stem cells from blood marrow; these cells are then collected from peripheral blood and then cryopreserved until re-infusion. The therapeutic objective of autologous HSCT[44] is the resetting of the patient's immune system thanks to the myeloablation program, which effects T-lymphocyte and memory T-cells elimination.

The first case reporting the efficacy of HSCT in the control of CD was published in 1993[45]. It is difficult to firmly evaluate the effectiveness of this technique in CD, given the relatively low number of published cases. In the series published by Burt *et al*[46] in 2010, the most updated series, all of the 24 patients entered remission after transplantation.

Most clinical studies have shown that MSCs can be obtained from bone marrow, adipose tissue, and umbilical cord. Being not significantly immunogenic, MSCs can be administered without a conditioning phase[47-49].

Systemic administration of MSCs for treatment of IBD. The results of phase 1 studies have recently been published. In 2012, Liang *et al*[50] reported the results obtained in 7 patients with IBD (4 CD and 3 UC). Remission was achieved in 5 subjects and maintained for over 24 mo in 2 of them; endoscopic improvement was demonstrated in 3 subjects. Side effects were mild

Local MSCs therapy in fistulizing CD. The initial study dates back to 2008[51] and reported remission in 7 of 9 CD patients with complex peri-anal fistula. At present, a phase 3 study is under way, involving the use of expanded MSCs from adipose tissue to treat complicated fistula.

D MICROBIOME MODULATION

The bacterial cells pertaining to the human microbiome

are estimated to attain the notable number of 10^{14}, dwarfing the few thousands of indwelling somatic cells. The protean characteristics and functions of the microbiome have been addressed in a number of reviews from others and ourselves[7,8]. Results from various studies are now accumulating to point to the astonishing variety of targets that are touched by the microbiome, including effects on immunity, determination of diabetic and overweight statuses, up to influence behavior and mental health. No wonder that a deal of efforts has concentrated onto the endeavor to modulate microbiome composition and function. The array of means and strategies that have been assayed include pre-biotics, pro-biotics, antibiotics, and fecal transplant (FT). The latter technique has received a special deal of attention, and to challenge the feasibility of its translation to clinical practice, two questions may be particularly relevant: (1) Is it effective? (2) How long does its action last.

As to the former question, FT has been convincingly shown to treat CDI[52]. A recent meta-analysis[53] has examined the role of FT as a therapy for IBD. Elaboration of the data from 18 studies including 122 patients led this study to conclude that FT may be safe and effective, but controlled trials, donor selection and standardization of microbiome analysis are strongly needed.

As to the length of effect, studies on CDI have reported encouraging results. The diseased microbiome of IBD, by contrast, has shown a deal of resiliency against the actions of FT. Most of the authors have concluded that prolonged and repeated treatments are probably needed to achieve some consistent results in these premises[54]. Last but not least, cutting-edge data from current research work[55] are showing that a number of host genes, some with known involvement with microbial handling, exhibited consistent effects on the taxonomic structure of the microbiome across multiple cohorts. Specifically, NOD mapping work showed links between NOD polymorphisms and gut colonization with Enterobacteriacee, allowing for the first time to envisage the chance of genetic transmission of IBD strains along with innate immunity sensors such as the NODs.

CONCLUDING REMARKS

The succinct lines above, stress the need to progressively move towards a mindset that sees IBD as a contextualized polyfactorial syndrome of outer environment misrecognition, whereby innumerous co-morbidities recognize shared roots and immunological circuits, the microbiome being the crucial but not the only player. Against this background, traditional immune suppression, including the novel biologics, has revealed its inadequacy to eradicate the disease. Having set this, we arbitrarily chose to gain more insight into the projects put forward by a few world leading teams in basic and clinical IBD research. Based on previously encouraging clinical hints, Cheluvappa's team has studied the immune-regulatory consequences of appendectomy in IBD patients and is actively pursuing a pathway to render the idea amenable to clinical application. Programs of stem cell infusion are probably bound to be the most rewarding ones in the future, yet intrinsic risks continue to require balance against the clinical gains. Facing this sometime chaotic wealth of evidence, Proall and her team see immune-inflamed patients including the IBD subjects as immune-depressed individuals which deserve immune reconstitution far more than immune suppression. Already successfully applied to the treatment of hepatitis B[56], this proposition is less fanciful than it appears. Despite this, the gap between conceptual refinements of these approaches, and their clinical transition is still significantly wide. FT has already shown exciting promise in the treatment of CDI. Its transition to clinical treatment of IBD will depend on the availability of pharmacological strategies to overcome the resilience of microbiome in the inflammatory intestinal states.

In terms of world-wide epidemiology, one can identify at least two opposite driving forces. Rapid "occidentalization" is providing IBD with unprecedentedly wide areas of expansion in huge landscapes like China[57]. On the other hand, one knows that life and evolution may sometimes reveal their complexity presenting as "erase-and-rewind" processes. On this line, poor or regressing life standards in certain world areas tend to make violent infection agents prevail over "sophisticated" immune inflammatory condition, threatening to absorb mental and financial energies in the future[58], perhaps distracting commitment from the programs illustrated above.

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