Insights to the Ethiopathogenesis of the Inflammatory Bowel Disease

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Provisional chapter

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1. Introduction

Inflammatory bowel disease (IBD) is a term that refers to two very different yet in many ways related phenotypes, Crohn's disease (CD) and ulcerative colitis (UC). It is well known that both of the two primary human inflammatory bowel diseases are characterized by chronic inflammation of the intestinal tract, yet their etiology still remains unclear.

CD and UC are considered to be multifactorial diseases and the underlying pathological process seems to be a combination of genetic predisposition and immunologic disturbances. Being the largest surface in the human body and since it is constantly colonized by a highly diverse community of microbes that are in normal circumstances either commensal or beneficial to human health, the role of the intestinal microbiota in development of IBD has been thoroughly investigated over the years. It is now generally accepted that the commensal flora plays a central role in triggering and perpetuating the disease process. [1] Even though there are several logical arguments contributing to the theory that the intestinal microbiota plays a major role in the IBD development, the types of microbes involved have not been adequately described. Studies of experimental animal models of IBD uncover that the presence of gut bacteria is essential in inflammation initiation and there is no disease onset in germ-free mice [2]. Furthermore, decreasing bacterial numbers in the intestine by using antibiotics, can lead to clinical improvement and decreased inflammation in both humans [3] and animal models of IBD [4, 5].

Pathogenesis of the IBD is characterized by various genetic abnormalities that lead to overly aggressive altered immune response, triggered by heterogeneous environmental factors under the influence of the commensal intestinal microbiota. There is no single abnormality of the gastro intestinal tract that would lead to development of CD or UC. Only in correlation of those four mentioned main factors a dysbalance of the gastrointestinal tract develops,

leading to chronic inflammation with all its consequences and complications. Schematized and simplified pathogenesis involving correlation between environmental factors, genetic predisposition, host immune response and intestinal microbiota is shown in Figure 1.

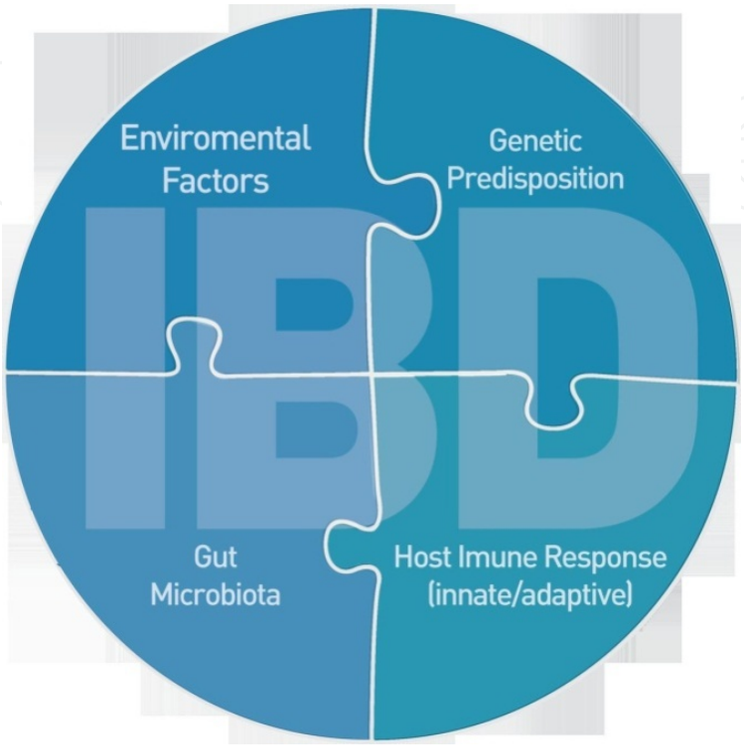

Figure 1. Schematized correlation of main factors involved in the IBD pathogenesis. Each of the mentioned factors fit together as separate pieces of puzzle, together creating a complex clinical and pathological image of the IBD.

In this review, we discuss recent insights in the ethiopathogenesis of the inflammatory bowel diseases.

2. Etiology and pathophysiology

2.1. Environmental factors

Epidemiological studies show that the prevalence of IBD dramatically increased in northern Europe, the United Kingdom and North America in the second half of the twentieth century and is also increasing in the rest of the world, proportionally to the adoption of western lifestyle [6]. This process, known as "westernization" of lifestyle [7], includes environmental triggers such as smoking (shown to be protective in UC but detrimental in CD), use of antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), stress, infection and diet. Studies have also reported an association between early life exposure to antibiotics (in the first year of subject's life) and CD development due to early childhood dysbiosis [8].

The mechanisms by which these factors initiate the onset of IBD are still not well understood. There is some evidence that infection and NSAIDs can transiently initiate nonspecific inflammation, break the mucosal barrier and activate innate immune response [9]. This process may lead to enhanced uptake of commensal bacterial antigens and in combination with genetic susceptibility, in this way stimulate protracted T-cell mediated inflammation. Up until now, only smoking and appendectomy have been clearly linked with the risk of developing IBD. A recent cohort study concerning autophagy-related genes and granuloma formation in surgically treated CD patients has showed that there is a significant association between smoking and granuloma formation [10]. This observation could be a result of inflammation promoting effects of smoking, resulting in more severe inflammation with granulomas in smokers with CD [10]. Appendectomy and smoking reduce risk for UC but on the other hand, active smoking increases risk for CD [11]. Even though proven to be valid, these facts cannot be held answerable for all variations in IBD incidence and prevalence.

There is also a hypothesis known as the "hygiene hypothesis", that could be the fundamental reason for the switch from infectious to chronic inflammatory diseases. This hypothesis proposes that there has been a lifestyle change from one with high microbial exposure to one with low microbial exposure [12]. There are numerous environmental factors that could be assigned to the hygiene hypothesis, some of which being better housing, safer food, cleaner water, vaccines, dietary changes, fewer infections, improved hygiene and sanitation and widespread use of antibiotics [12].

Even though there are many firm epidemiological studies and evidence linking certain environmental factors to greater probability of developing IBD, it is still widely believed that there is no one simple environmental factor that could alone cause CD or UC. Based on the fact that differences in geographic distribution combined with changes in incidence over time within one observed area could provide insights into possible etiologic factors, a prospective population based study investigated the incidence of UC and CD in Primorsko-goranska County, Croatia (January 2000 to December 2004) was performed by the authors [13]. The study included a total of 170 patients residing a county with a stable, ethnic and racially homogeneous population and the results showed an increase in UC and CD incidence, in comparison to an earlier prospective study for the county of Zagreb, with a similar population and similar environmental circumstances [13]. It is considered that the rapid "westernization" of the country combined with the improved awareness of the disease play a role in the reported increase. Annual age-standardized incidence rate was $4{,}3/10^5$ for UC and $7{,}0/10^5$ for CD. Croatian results concerning UC were similar to those reported in Belgium, Northern France and Germany and those concerning CD reach the mean incidence value reported in European multicentric study of CD [13].

2.2. Genetic predisposition

There have recently been great advances in understanding the very complex genetics of the IBD, from studies based on single nucleotide polymorphism and candidate gene approaches to studies based on transgenic and deletion techniques [14]. It is thought that UC and CD may be heterogeneous polygenic disorders, sharing some but not all susceptibility loci and

there are most likely several factors determining the disease phenotype [15]. Presence of a mutated gene in a host does not guarantee that IBD will develop and we cannot use it as a predicting factor for later development of IBD.

In order to prove that genetic factors contribute to the pathogenesis of IBD, studies have shown that the concordance rate between twins is much lower for UC than for CD, which may indicate that the genetic penetrance in CD is much greater than in UC. Reported concordance rate for UC in monozygotic twins is 15,4% vs. 3,9% in dizygotic twins and for CD 30,3% in monozygotic vs. 3,6% in dizygotic twins [16]. These findings may be considered valuable evidence that there is genetic susceptibility for IBD, particularly CD. Also, studies have shown that there is linkage between certain genetic disorders and incidence of IBD. In infants born to consanguineous parents there is a risk of developing extremely rare autosomal recessive mutations in genes encoding interleukin (IL)-10 receptor and the IL-10 cytokine [17, 18]. IL-10 is an anti-inflammatory cytokine and its primary purpose is to limit and ultimately terminate inflammatory responses [19]. Disturbance in either IL-10 or IL-10 receptor function via autosomal, recessive mutations are sufficient to cause severe forms of CD, which have been successfully treated by bone marrow transplantation [20].

There have been over a hundred IBD genes and loci defined and one of the most important genes associated with CD is *nucleotide binding oligomerization domain protein 2* (NOD 2), also known as the *caspase recruitment domain family member 15* (CARD15) gene [21, 22]. The NOD2 gene is expressed mainly in monocyte/macrophage cell lines where it plays an important role in host-signaling pathways. One of its main effects is the activation of the NF-κB protein, a transcription factor involved in cellular inflammatory pathways and an important regulator in cell fate decisions, such as programmed cell death and proliferation control, and also a critical factor in tumorigenesis.

The NOD2 mutations have been observed in individuals of European and African-American ancestry and studies have shown that in individuals of European ancestry heterozygous carriage of one of the major risk alleles bargain a 2,4-fold increase in risk for CD while homozygous or compound heterozygous carriage bargains 17,1-fold increase in risk for CD [22]. In those of African American origin, mutations are only heterozygous with similar risk for CD among carriers as mentioned above. When it comes to Asian populations, studies show that NOD2 mutation has not been associated with CD in studies of IBD patients form Hong Kong, China, Japan and Korea [23]. Mutations in the NOD2 gene, unexpectedly, reduce macrophage activation of NF- κB protein, which is why one would expect inflammation to weaken, instead of the increase of inflammation, which can be seen in IBD. In the absence of NOD-2 expression by epithelial cells, microbial products that normally induce these cells to secrete chemokines fail to do so, leading to potential loss of barrier function [7].

It is known that in about 70% of patients suffering from CD, the disease affects the small intestine. The human intestinal epithelial wall exceeds all other tissues of the human organism in its cell-renewal rate [24]. The intestinal adult stem cells self-renew and produce daughter cells. Daughter cells form an adjacent zone of rapidly cycling progenitors and undergo 4-6 rounds of division before differentiating into multiple lineages, fabricating up to

300 cells/crypt per day [25]. In this way, post-mitotic cells covering the biggest area of the intestinal epithelium are formed.

Besides absorptive cells, there are three classes of secretory cells: goblet cells (secrete mainly mucus), enteroendocrine cells (secreting different hormones) and Paneth cells [26]. Currently, the most acceptable role of Paneth cells in the small intestine is the production of a stream of antibacterial secretions, responsible for the sterile environment of the small intestinal lumen and in this way, protection of the vital stem cells in the neighborhood. Two most frequent defensins found in Paneth cells are the α defensins, human defensin 5 and 6 (DEFA5 and DEFA6) and in addition to DEFA5 and DEFA6, Paneth cells store several other antibiotic peptides (for example regenerating islet-derived 3-γ and phospholipase A2group IIA) [27]. Investigations on human α defensins have shown that DEFA5 has a very effective antibacterial activity against *S. aureus*, while DEFA6 expressed some antibacterial potential in vitro and there are ongoing investigations on their antiviral potential [28, 29]. There is numerous evidence for a link between the Paneth cell and ileal Crohn's disease. It is reported that NOD 2 is heavily expressed in Paneth cells and ileal CD is associated with a diminished synthesis of Paneth cell defensins [30, 31]. The role of NOD2 as an intracellular receptor for bacterial dipeptide in regulating Paneth cell defensin formation was confirmed in NOD-2 knockout mice and in patients after small intestinal transplantation [32, 33].

Being a genetically complex system, pathogenesis of IBD can be closely linked to numerous other genomic regions. Autophagy 16-like 1 (ATG16L1) is responsible for encoding a protein component of the autophagy complex and it has been strongly related to CD [34]. ATG16L1 is extensively expressed, including in Paneth cells, where it has a role in exocytosis of secretory granules containing antimicrobial products [35].

Other genes that regulate autophagy and that have been closely related to CD in genome-wide association studies are immunity-related guanosine triphosphotase M (IRGM) and leucine-rich repeat kinase 2 (LRRK2) [36, 37]. A recent study by Brinar et al. [10] investigated a relationship between variants in autophagy genes and granuloma formation in CD. The authors hypothesized that genetic variants in autophagy genes in CD patients may lead to impaired processing of intracellular bacterial components, thus contributing to granuloma formation. [10]. This cohort study detected an association in four autophagy genes, ATG4A, ATG4D, FNBP1L and ATG2A. The study has also shown that granuloma positive patients were significantly younger at diagnosis, that they had surgery at significantly younger age after a shorter duration of the disease. These findings suggest that there is a significant relationship between earlier mentioned variants in autophagy genes and granuloma formation, which could be a marker of a more aggressive disease course. [10]

After variants in NOD2, most significantly associated with CD is the amino acid change Arg381Gln variant in the IL-23 receptor (IL23). In comparison to Arg381 carriers, Glutamine 381 reduces risk for IBD by nearly 3-fold and studies on the proinflammatory role of IL-23 prioritize its signaling pathway as a therapeutic target in inflammatory bowel disease [38]. Many genes that encode factors in the IL-23 pathway have been associated with both psoriasis and IBD and numerous loci have been associated with both IBD and celiac disease [39,

40]. Studies show that neither IL23 nor ATG16L1 genes are associated with CD in Japanese and Korean patients [41].

There are numerous other loci associated with both CD and UC and the number of potential IBD genes continues to increase and searching for other genotype-phenotype correlations in the matter of IBD continues to be an important step in future studies. Despite all the facts specified, indications for genetic tests in everyday clinical practice still do not exist.

2.3. Host immune response

In order to develop IBD, both innate (macrophage, neutrophil) and acquired (T and B cells) immune responses combined with loss of tolerance to enteric commensal bacteria need to be activated in a host.

2.3.1. Innate immune responses

Studies have shown that there is an increase in the absolute number of macrophages and dendritic cells in both forms of IBD, with an enhanced production of proinflammatory cytokines and chemokines and an increase in the expression of adhesion molecules and co-stimulatory molecules [41].

Adhesion molecules (such as intracellular cell adhesion molecule 1, *ICAM1*) are crucial when it comes to binding circulating cells to the activated endothelium [42]. These molecules also have an important role in later mediation of migration of the extravagated immune cells through the stroma to the source of optimum chemokine production as well as through the epithelium to the lumen [43]. Mucosal dendritic cells are activated, express higher levels of the toll like receptors (TLR) 2 and 4, (which have an important role in recognition of bacterial products) and CD40, all of which is followed by increased production of IL-12 and IL-6 [44]. TLRs are profusely expressed on the surface of monocytes, macrophages, dendritic and epithelial cells and are responsible in identification of the commensal microflora as well as maintenance of the intestinal homeostasis [45]. Like NOD2, they selectively bind to specific microbial adjuvants and initiate signaling through nuclear factor kappa-light-chain-enhancer of activated B cell, *NF-κB.* Activation of NF-κB triggers expression of various molecules involved in the inflammatory response (such as IL-1β, TNF, IL-6, IL-8, ICAM1, CD 40, CD 80 and other chemokines, adhesion molecules and co-stimulatory molecules), all of which have an increased expression in IBD [41]. NF-κB is activated in tissues of IBD patients and its inhibition can attenuate experimental colitis [46].

In both forms of IBD, alterations of TLR 3 and 4 have been described, suggesting that abnormal bacterial sensing has a role in the disease pathogenesis [47]. As explained earlier, ileal Paneth cells also express the NOD-2 protein, and their production of mucosal α-defensins is decreased in CD patients with NOD-2 mutations.

2.3.2. Adaptive immune responses

Adaptive immune responses should be considered separately for CD and UC, due to their distinct profiles in those two entities.

2.3.2.1. Crohn's disease

Crohn's disease is predominantly T_H1 and T_H17 mediated process. Antigen presenting cells produce IL-12, which is responsible for stimulation of IFN-γ. IFN-γ then mediates traditional T_H1 responses. As the inflammatory response matures, in several models T_H1 responses can change into T_H2 responses [48]. On the other hand, IL-17 mediates T_H17 responses [49]. The production of IL-17 is impacted by innate immune cells and antigen presenting cells, which produce Il-6, IL-23 and TGFB [50].

When it comes to estimating the importance between T_H1 and T_H17 responses in CD development, studies have shown that even though Th17 responses play a role in the inflammation, the Th1 response is quantitatively greater [51]. This conclusion agrees with the intestinal pathologic effects of IFN-γ and the relation of Th1 responses to granulomatous disease [51]. In contribution, double blinded clinical trial of anti IL-17 in patients with CD has been carried out recently and the study showed that blockage of IL-17A is ineffective in tested subjects [51]. The role of IL-17 in patients suffering from CD is still under intense investigation.

2.3.2.2. Ulcerative colitis

Ulcerative colitis is considered to have an atypical T_H2 response, mediated by natural killer T cells that secrete IL-13 and IL-5 [52]. The T_H2 response is an atypical one due to the fact that concentrations of IL-4 and IL-5, which are normally elevated in T_H2 response, have been found to be variable in UC tissues [53]. Recent studies have shown an increase in IL-17 levels in UC (in compare to control groups), but that increase was found to be far less than the one found in CD patients. T-cell subsets are stimulated by antigen presenting cells, particularly dendritic cells, which have a unique capacity to activate naïve T cells. Dendritic cells are found in the lamina propria and Peyer's patches of normal intestine. Interaction between antigen presenting cells and T cells occurs by presenting an antigen on the surface of the major histocompatibility complex, which is then recognized by the appropriate T-cell receptor, followed by secretion of cytokines (such as IL-6, IL-10, IL-12, IL-23, TGF β).

The results of this pathway are increased levels of dendritic cells in patients with active IBD and in experimental colitis models [44, 54]. Peyer's patches, which can be considered as the immune senses of the intestine, seem to play a key organ in the relationship between innate and adaptive immunity in the human gut [55].

2.4. Intestinal microbiota

The understanding of the development of gastrointestinal (GI) tract microbiota has greatly developed, due to decreased costs of DNA sequencing and evolution of bioinformatics.

The human intestinal microbiota can be defined as a community of microbes that is either commensal or beneficial to human health. The adult human gut contains around 10^{14} bacterial cells and up to a 1000 different bacterial species [56]. The most abundant bacterial phyla in the healthy human large intestine are *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria,*

Fusobacteria and *Verrucomicrobia* [56]. The gut microbiota composition varies between individuals and remains highly stable over time. A recent study performed by Arumugam et al. combined 22 newly sequenced faecal metagenomes of individuals from Denmark, France, Italy and Spain, resulting in three distinctive enterotypes. Furthermore, these results were combined with existing gut data-sets, 13 Japanese and four American, returning the same three clusters. These isolated bacterial communities were dominated by one of the three main distinct bacterial genera – *Bacteroides, Prevotella* and *Ruminococcus* [56]. In terms of function, it is indicated that drivers of each of the three enterotypes use different routes to generate energy from substrates available in the colon. *Bacteroides* seem to derive energy primarily from carbohydrates and proteins through fermentation, *Prevotella* is a known mucin degrader and *Ruminococcus* is linked to both mucin and sugar [56].

Numerous studies have shown that colonization of the GI tract in infants depends upon delivery mode and that the vagina has evolved to serve the fundamental inoculum for all mammals [57]. If a baby is exposed to vaginal microbes during birth, its initial gut bacteria will consist dominantly of *Lactobacillus* and *Prevotella* spp [58]. The bacteria, acquired from their mother's vaginal canal, can be found in the skin and mouth and the meconium of the baby. Many babies are not exposed to their mother's vaginal flora, due to the cesarean section-birth method (C-section). In contrast to vaginally delivered babies, those delivered by C-section accommodate bacterial communities that resemble bacteria of the skin: *Staphylococcus, Corynebacterium* and *Propionibacterium* spp [59]. In early childhood, the initial strains of GI bacteria are outcompeted by other bacterial strains, of a less certain origin, which rapidly increase in diversity and shift in response to dietary changes and/or illness [60, 61]. During early childhood, when peas and other plant-derived foods are introduced, the bacterial phyla of the GI tract changes and *Firmicutes* and *Bacteroidetes* are now dominant [62]. Microbial community can change, but the changes are now of a much slower rate than in early childhood and with unknown effects on health. The mentioned data and the development of the GI tract colonization in infants and early childhood can be seen in Table 1.

	INFANTS		EARLY CHILDHOOD
PREDOMINANT BACTERIAL COMMUNITES	Vaginal birth	C-section	Firmicutes
	Lactobacilus	Staphylococcus	Bacteroidetes
	Prevotella spp.	Corynebacterium	
		Propionibacterium spp	

Table 1. Development of the GI tract colonization in infants and early childhood

Children from different parts of the world have different gut microbiota (for example Burkina Faso and Italy) [63], and when it comes to elderly, their GI tract microbiota is substantially different than in young adults [64]. According to Zoetendal et al., the gut microbiota composition of spouses showed the least degree of species similarity, while siblings showed increased degree of similarity in species make up [65].

The gut microbiota acts as a metabolic organ via production of short chain fatty acids and vitamins and it contributes to the barrier effect by preventing colonisation by pathogens. Recent studies have shown that a modulation of a gut microbiota using prebiotics increases epithelial barrier integrity by increasing expression of tight junction proteins [66]. The gut microbiota also helps to shape and maintain normal mucosal immunity.

The human gut microbiome consists of 150x more genes than the human genome [67]. In 2010, initiative called Meta-HIT (Metagenomics of the Human Intestinal Tract) published a catalogue of the microbial genomes strained from 124 faecal samples. The results found that the gene set was approximately 150 times larger than the human gene complement with 3,3 million different microbial genes [68]. Recent studies have shown that the intestine is home to specialized dendrytic cells, whose function is to induce a highly tolerogenic response from T and B cells, through induction of regulatory T cells and secretion of IgA [69]. Activated immune cells, such as mucosal dendrytic cells, constantly sample luminal microbial antigens and present them to adaptive immune cells [70]. There are three main ways by which flagellin from commensal microbes may play a role in IBD. Flagellin from commensal microbes may cross the altered epithelial barrier that occurs in IBD. Such flagellin can, via Toll-like receptor 5 (TLR5), induce the epithelium to secrete cytokines that recruit polymorphonuclear neutrophils (PMN) [71]. Such cytokines may promote adaptive immunity and/or, alternatively, flagellin may activate dendritic cells and directly promote adaptive immune immunity. Flagellin is also targeted by the CD-associated adaptive immune response [71].

In healthy hosts the pro-inflammatory pathways associated with TLR and NLR are suppressed by inhibitory molecules of both human and bacterial origin, such as COX-2 inhibitors, NF-κβ inhibitor, IL-10, TGF-β, IFN-α/β etc. [72, 73]. A disruption of this homeostasis threatens the state of immune tolerance and may result in gut inflammation. How the host tolerates resident bacteria whilst being able to mount an effective inflammatory response to invading pathogens is still not fully understood.

Gut microbiota and activity in IBD patients are proven to be abnormal. IBD patients are characterized by a reduced abundance of dominant members of the gut microbiota. According to *Frank et al*., mucosal biopsies taken from CD and UC patients showed reduced abundance of *Firmicutes* and *Bacteroidetes* and a concomitant increase of *Proteobacteria* and *Actinobacteria*, compared to non-IBD control [74]. As a consequence of this dysbiosis, the relative abundance of *Enterobacteriaceae* was increased in IBD patients compared to healthy control [75, 76]. Significantly lower counts of *Bifidobacterium* populations were found in rectal biopsies of patients with UC [77]. Study performed by *Macfarlane et al*. showed that *Clostridium leptum* (*Firmicutes*) is less abundant in fecal samples of CD patients (Table 2) [77].

Clostridium and *Bacteroides* species are the cardinal producers of short chain fatty acids (SCFA) in the human colon [66]. There were decreased SCFA concentrations found in fecal samples of IBD patients, which could be explained by decreased clostridia of groups IV and XIVa (a broad phylogenetic classification comprised of several genera and species of gram positive bacteria). Among the SCFA produced upon carbohydrate fermentation, butyrate has an important role as a major source of energy for colonic epithelial cells, an inhibitor of pro-inflammatory cytokine expression in the intestinal mucosa and an inductor of production of mucin and antimi-

crobial peptides, thus strengthening epithelial barrier [66, 78]. A decrease of butyrate levels could be involved in the increased inflammatory state characteristic of IBD. Stimulation of butyric acid production could be achieved through repopulation of clostridial clusters IV and XIVa, or even through probiotic therapy with lactic acid bacteria [79]. Some evidence has indicated a promising therapeutic effect of pro, pre and synbiotics in IBD.

	BACTERIAL COMMUNITIES
MOST ABUNDANT BACTERIAL PHYLA IN HEALTHY HUMAN LARGE INTESTINE	Firmicutes Bacteroidetes Actinobacteria Proteobacteria Fusobacteria Verrucomicrobia
ALTERED INTESTINAL MICROBIOTA IN IBD	↓Firmicutes, Bacteroidetes ↑Proteobacteria, Actinobacteria ↓Clostridium leptem (Firmicutes) in CD ↓Bifidobacterium in UC

Table 2. Most abundant bacterial communities in healthy human large intestine and its alterations in IBD

Paneth cells of the small intestine also have an important role in the human gut microbiota, as they are a source of α defensins 5 and 6, which may regulate and maintain microbial balance in the intestinal lumen. The α defensins 5 and 6 are efficacious against *Enterobacteriaceae* and *Bacteroides* vulgatus and studies have shown their levels are increased in chronic inflammatory conditions [80, 81]. In association with ileal CD, they are significantly reduced, particularly in patients with NOD-2 mutations. Colonic CD (but not UC) is associated with β defensins 2 and 3, which are secreted by leukocytes and epithelial cells of many kinds [82].

As explained above, it is a widely accepted hypothesis that the bacteria play an important role in the pathogenesis of IBD. There are several ways in which the microbiota might be linked to IBD. The microbiota as a whole could act as a surrogate pathogen, or specific members of the microbiota could be overt pathogens.

It remains unclear whether the altered gut microbiota composition is a cause of the disease or a consequence of the inflammatory state, but it is most likely that microbial dysbiosis and lack of beneficial bacteria, together with genetically predisposed increased epithelial permeability, bacterial translocation into the lamina propria, defective innate immunity and loss of tolerance to the resident microbiota eventually lead to IBD.

3. Conclusion

Chronic intestinal inflammation in inflammatory bowel disease develops under the influence of environmental triggers in genetically susceptible individuals with an altered im-

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mune response. The role of the intestinal microbiota in the pathogenesis of IBD still remains unclear, but even though some enteric bacteria are detrimental and some are protective, their involvement in the pathogenesis of IBD is unquestionable. Table 3 lists main factors associated with IBD development, including known differences between UC and CD ethiopathogenesis.

Since we currently lack complete understanding of the mechanisms leading to the disease, this topic remains to be exceedingly interesting and enigmatic and most certainly a challenging clinical entity that yet remains to be further investigated and unraveled.

	ULCERATIVE COLITIS	CROHN'S DISEASE
ENVIRONMENTAL FACTORS	'westernization of lifestyle'	
	Smoking (protective in UC , detrimental in CD) Use of antibiotics Use of NSAIDs Stress Infection Diet Appendectomy	
GENETIC PREDISPOSITION	Major histocompatibility complex region (6p21)	mutations in genes encoding interleukin (IL)-10 receptor and the IL-10 cytokine
	genes mediating epithelial defense function	NOD2 mutations
		ATG16L1 expression
HOST IMMUNE RESPONSE	Higher level of TLR2, 4 and CD 40, followed by increased production of IL-12 and IL-6	
Innate immune responses	↓ Activation of NF-κB ↓ Expression of IL-1β, TNF, IL-6, IL-8, ICAM1, CD 40, CD 80 and other chemokines, adhesion molecules and co-stimulatory molecules	
Adaptive immune responses	atypical T_H2 response, mediated by NK-T cells that secrete IL-13 and IL-5	predominantly TH1 and TH17 (mediated by IL 12 and IL17)
INTESTINAL MICROBIOTA **see table 1 and 2 for further information*	microbiota as a whole acts as a surrogate pathogen, or specific members of the microbiota could be overt pathogens*	

Table 3. Interaction of environmental factors, genetic predisposition, host immune response and intestinal microbiota, main factors associated with CD and UC ethiopathogenesis

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