Pathogenesis of Ulcerative Colitis and Crohn’s Disease: Similarities, Differences and a Lot of Things We Do Not Know Yet

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Abstract

The pathogenesis of inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn’s disease (CD) is complex, and our knowledge on the topic is constantly growing. The two disorders are distinct, yet overlap in their clinical manifestations and underlying causes. This review aims to provide a broad overview of the numerous pathogenetic factors that can lead to the development of IBD, focusing on novel findings and on the differences between UC and CD. Recent advances in genetics have identified new components in the pathogenesis, as an example, the importance of Th17 lymphocytes and the IL-17/IL-23 pathway have been highlighted in both diseases, apart from the previously known Th1-Th2 driven processes. Genetic background of increased permeability has been explored in UC, and the role of defective autophagy was recently described in CD. Genetic alterations can lead to an exaggerated immune response to the resident microbial flora. This microflora is altered in IBD patients, probably due to their reduced ability to stabilize its bacterial components and due to different environmental factors. An exhaustive exploration of environmental factors is particularly important, as they can be influential in many cases. The impact of smoking is the most established environmental factor, having deleterious effects in CD and protective in UC. Recent opinions on other factors, such as early appendectomy, diet, reduced vitamin D levels, the use of specific medications, breastfeeding, personal hygiene and psychological factors are also discussed. Epigenetics, a new field of research, links environmental factors to genetics. Understanding these factors is of great significance as changing lifestyles and improving life circumstances have started to increase the prevalence of IBD also in developing countries.

Keywords: Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Pathogenesis

Abbreviations

CD: Crohn’s disease; COX: Cyclooxygenase; DCs: Dendritic Cells; DR3: Death Domain-containing receptor 3; FUT: Fucosyltransferase; HLA: Human Leukocyte Antigen; HVEM: Herpes Virus Entry Mediator; IBD: Inflammatory Bowel Disease; IEC: Intestinal Epithelium Cell; IL: Interleukin; ILCs: Innate Lymphoid Cells; IF-γ: Interferon-gamma; IRF5: Interferon Regulatory Factor; Itga: α- integrin; JAK: Janus Kinase; NOD2: Nucleotide-binding Oligomerization Domain 2; NSAIDs: Non-steroid Antiinflammatory Drugs; NF: Nuclear Factor; OCTN: Organic Cation Transporters; PTPN: Protein Tyrosine Phosphatase Non-receptor type; PUFA: Polyunsaturated Fatty Acid; SLC9A: Solute Carrier family; STAT: Signal Transducer and Activator of Transcription; Th: T helper; TLR: Toll-like Receptor; TNF-α: Tumor Necrosis Factor-α; 25[OH]D: 25-hydroxi-D-vitamin; UC: Ulcerative Colitis; VDR: Vitamin D Receptor; XBP: X-box Binding Protein

Introduction

Inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn’s disease (CD) are chronic, remittent gastrointestinal disorders with a multifactorial pathogenesis (Figure 1). The most accepted explanation of their development is an inadequate immune response to the intestinal microbial flora, which appears in a genetically susceptible host [1]. This review aims to summarize recent updates in genetics and microbiota, complete with environmental factors and epigenetics. The role of environmental factors is supported by the fact that IBD is more prevalent in countries with a westernized lifestyle compared to developing countries. Western Europe is an outstandingly high-prevalence area, with twice as high annual incidence rates (CD: 6.3/100,000; UC: 9.8/100,000) than in Eastern Europe (CD: 3.3/100,000; UC: 4.6/100,000), although the availability of diagnostic tools is better in Eastern Europe in terms of the use of colonoscopies and diagnostic delay [2]. Methodological differences probably also exist, since incidence rates reported from Hungary, although situated in Eastern Europe, are similar to that of Western countries [3]. Interestingly, dietary risk factors of IBD were found higher among Eastern European patients, which may at least partly explain the rapid increase of the disease in this area in recent decades [4]. The increased occurrence of IBD among immigrants from developing countries to high incidence areas also provides evidence that this difference between industrialized and developing countries is not explained purely by genetics [5]. The growing incidence of IBD highlights the importance of understanding the role of environmental factors, and the use of this knowledge in the prevention and treatment of the disease.
Figure 1: Pathogenetic factors of UC and CD. Blue rectangles: common factors; red rectangles: factors in UC; green rectangles: factors in CD. +: proinflammatory effect; -: antiinflammatory/tolerogenic effect.

UC and CD are separate entities, although they sometimes overlap. For instance, UC is usually present with diffuse continual mucosal inflammation involving the rectum and possibly extending more proximal in the colon, while in CD any part of the gastrointestinal tract can be affected with focal, discontinuous inflammation [6]. Endoscopically, UC presents with continuous mucosal friability and small, superficial ulcers. Nevertheless, in CD, deep fissuring ulcers and aphthous lesions are seen. Histologically, the inflammation is limited to the mucosa in UC. To the contrary, in CD it is transmural, and typical histological features are the so-called granulomas. The occurrence of extraintestinal manifestations, mostly affecting the skin, the eye, the joints and the biliary system are more frequent among CD patients compared to UC patients [7]. Although the pathogenesis of UC and CD are similar in many aspects, important differences are also observed, which will be collected in this review.

The Intestinal Immune System

The immune system of the gastrointestinal tract differs from the systemic immune system in many ways. It has to create and maintain the equilibrium between the host and the large non-noxious microflora that inhabit the human intestines, and at the same time it must identify and overcome pathogens. The failure of the latter permits infections, while disturbances in the former may lead to the development of IBD [8].

The first line of defense is the intestinal epithelium cell (IEC) layer, a single, polarised columnar layer consisting of differentiated cell types such as enterocytes, Goblet cells, Paneth cells, enteroendocrine cells and M cells. Goblet cells secrete mucin glycoproteins (MUC2) that form the mucus layer, which limits colonization to the outer, loose part, while the ‘inner’ adherent mucus layer is almost free from microbes [9]. Paneth cells can be found in the base of small intestinal crypts, where they produce antimicrobial molecules, such as alpha-defensins, which are crucial mediators of host-microbe interactions. Paneth cells also contribute to epithelial cell renewal [10].

The next step of innate immunity is represented by intestinal macrophages, which are unique in many respects. For instance, unlike other macrophages in the body, they do not express the lipopolysaccharide co-receptor CD14 and do not produce proinflammatory cytokines in response to toll like receptor (TLR) ligands [11]. Furthermore, they secrete antiinflammatory molecules including IL-10 and contribute to the differentiation of regulatory T (Treg) cells, while they suppress the secretion of IL-17 from dendritic cells (DCs). Based on their distinct characteristics, resident intestinal macrophages are largely anergic to inflammation but still exert active
defense function against pathogens [12]. DCs are specialized antigen-presenting cells, which can coordinate innate and adaptive immune responses [13]. For example, they initiate an immunoglobulin isotype switching to IgA, and induce the differentiation of T lymphocytes to either Treg or Th helper (Th) 17 cells. A newly described lymphoid cell type is the innate lymphoid cells (ILCs). ILCs develop from the common lymphoid progenitor, but lack a specific antigen receptor [14]. ILCs are classified in three groups, and secrete similar cytokines to those of Th cells [15]. Indeed, group 1 ILCs produce Th1 type cytokines, and natural killer cells are thought to belong in this group. Group 2 ILCs secrete Th2 type cytokines, and play important roles in allergy and defense from parasites. Group 3 ILCs are mostly characterized by the secretion of Th17 cytokines, and are considered to play the most important role among ILCs in mucosal homeostasis and intestinal inflammation. A subset of group 3 ILCs, lymphoid tissue inducer cells, are essential in lymph node organogenesis and development of Peyer’s patches, a specific lymphoid tissue of the small bowel [16]. Another subset, NCR-ILC3 cells are a major source of IL-22, a cytokine responsible for host defense and tissue repair, but also enhancing colonization of pathogens [17].

Specific aspects of the adaptive immune system in the gastrointestinal tract are also known. Treg cells are essential for the maintenance of tolerance for the resident microflora. They produce IL-10 and transforming growth factor β in response to microbial stimuli to suppress both T-cell mediated and T-cell independent intestinal inflammation [18]. A small population of DCs constitutively secrete IL-23 in response to microbial signals, which activates Th17 cells. Th17 cells have important homeostatic functions in the intestine, apart from their role of orchestration of neutrophils during inflammation [8]. Therefore the role of Th17 cells is very complex, and they secrete both pro- and antiinflammatory cytokines, which will be detailed below.

Genetics and the Immune System

The role of genetics in the development of IBD began to be outlined in the 1980s, based on studies showing increased number of cases among patients’ family members [19]. However, only genome-wide association studies were capable of providing the basis for the identification of up to 163 loci in the human genome associated with either Treg or Th helper (Th) 17 cells. A newly described lymphoid cell type is the innate lymphoid cells (ILCs). ILCs develop from the common lymphoid progenitor, but lack a specific antigen receptor [14]. ILCs are classified in three groups, and secrete similar cytokines to those of Th cells [15]. Indeed, group 1 ILCs produce Th1 type cytokines, and natural killer cells are thought to belong in this group. Group 2 ILCs secrete Th2 type cytokines, and play important roles in allergy and defense from parasites. Group 3 ILCs are mostly characterized by the secretion of Th17 cytokines, and are considered to play the most important role among ILCs in mucosal homeostasis and intestinal inflammation. A subset of group 3 ILCs, lymphoid tissue inducer cells, are essential in lymph node organogenesis and development of Peyer’s patches, a specific lymphoid tissue of the small bowel [16]. Another subset, NCR-ILC3 cells are a major source of IL-22, a cytokine responsible for host defense and tissue repair, but also enhancing colonization of pathogens [17].

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function. Many alleles have been identified lately that increase the risk of developing IB, mostly variations of the HLA-DR gene. This belongs to the classical class II. HLA genes, which encode cell-surface glycoproteins expressed on antigen presenting cells [38]. Some alleles, notably DRB1*0103 and B*52, are associated with both UC and CD. While DRB1*0103 predicts overall susceptibility in UC, it is associated with extensive or severe disease forms in CD.

Another important susceptibility gene is MUC1, encoding the mucin 1 glycoprotein which is normally expressed at a low level on the luminal side of colonic epithelial cells, and is required for normal epithelial defense. MUC1 is also considered as a tumor associated antigen, and is overexpressed and hypoglycosylated in IB patients [39]. Hypoglycosylated MUC1 has chemotactic properties for the cells of the innate immune system, and IB patients have anti-MUC1 antibodies in their serum. Vaccination against MUC1 in MUC1+/ IL-10 deficient mice significantly attenuated the development of colitis and prevented colitis-associated colon cancer [40]. The prevention of cancer may be explained on one hand by a specific adaptive immunity that eliminates cells with abnormal mucin expression, but on the other hand, it may be linked to the changes in microenvironment. That is, in vaccinated mice, smaller mononuclear cells represented the major infiltrate in the inflamed colonic tissue, contrary to a neutrophil-dominant infiltrate seen in non-vaccinated animals. Although it is too early for strong conclusions, development of a similar vaccination therapy for humans could open new perspectives in IB treatment and the prevention of colon cancer.

Interestingly, 70% of IB associated loci are common with other complex diseases [20]. More than half of them are connected to other immune-mediated disorders, mostly to diabetes mellitus type I, ankylosing spondylitis, psoriasis, and primary immunodeficiencies [20]. The genes involved in both IB and immunodeficiencies are those causing decreased levels of circulating T-cells, (e.g. ADA and CD40), or reduction in specific T-cell lines like Th17 (STAT3), memory (SP110), or regulatory T-cells (STAT5B).

**Important gene loci in UC**

Increased intestinal permeability has been well described in UC. However, whether it was a preceding condition or only the consequence of inflammation was not clear. Recent studies have clarified that defects of the epithelial barrier can indeed be determined by genetic alterations [41]. Thus, HNF4A, accounting for the regulation of multiple components of the cell-cell junction, such as adherens junctions, tight junctions and the desmosomes; CDH1, a gene which encodes E-cadherin, the key component of adherens junctions; and LAMB1 encoding laminin β1 subunit, a crucial component of the intestinal basement membrane have all been implicated in UC [41]. Interestingly, CDH1 is also associated with colorectal cancer, a severe complication of UC. Additionally, two years later GNA12, encoding a membrane-bound GTPase, which plays an important role in the tight junction integrity in epithelial cells, has been added to this palette [22]. Enhanced permeability may lead to colonic inflammation by increasing the contact of luminal antigens with the mucosal immune system, thereby creating the basis of an exaggerated immune response.

The solute carrier family 9 member (SLC9A) 3 gene, encoding an epithelial Na⁺/H⁺ exchanger, has also been implicated in UC, but not in CD [20]. SLC9A3 deficient mice spontaneously develop chronic distal colitis, which can be reduced by broad spectrum antibiotic treatment. Similarly, when these mice are kept in an ultraclean barrier facility, the symptoms of colitis are significantly reduced [42]. Recolonisation of SLC9A3 deficient mice with the conventional microflora reinduced colitis, while reduced number of Clostridia clusters IV and XIVa were detected in the colonic content. This observation is an elegant example of the connection between genetic alterations, disturbances in the microflora and consequent colitis.

Some UC-associated genes are involved in immune functions. The genetic deficiency of α-integron (Itga) l, encoded by the gene ITGAL, blunts the adhesion of T cells to the stimulated colonic epithelium, and decrease T cell rolling behaviour [43]. In a recent study, the ITGAL gene locus has been found to be associated with erythema nodosum, an extraintestinal skin manifestation in IB patients [44]. The UC-specific TNFRSF14 gene encodes herpes virus entry mediator (HVEM), a member of the tumour-necrosis factor receptor family, which is a key orchestrator of mucosal immunity [45]. The role of HVEM includes the augmentation of immune responses by inducing an optimal level of STAT3 activation, which then leads to the epithelial expression of genes required for host defense. HVEM deficient animals have shown an impaired response to bacterial infection of the colon, with increased bacterial burden and mortality. Likewise, polymorphisms of the TNFRSF14 gene predispose UC patients to Clostridium difficile infections [46]. The next gene implicated in immune responses is IRFS, encoding interferon regulatory factor 5, a transcription factor which regulates activity of type I interferons and induces proinflammatory cytokines such as IL-6, IL-12 and TNF-α [22]. Primary lymphocytes from control individuals with two copies of a specific polymorphism of the IRFS gene showed increased proinflammatory IL-12p70 production [47]. This is in agreement with data showing the association of this haplotype with IBD in Jewish patients.

Autophagy is a pathomechanism in IB that previously has been only implicated in CD, but the association of death associate protein (DAP), also with UC suggests a possible role of autophagy in both disorders [22]. It is known that DAP is a negative regulator of autophagy, and acts as a positive mediator of programmed cell death, but its role in UC has not yet been clarified. Among HLA genes, a specific haplotype in the Japanese population was significantly associated with an increased risk of UC, and a reduced risk of non-colonic CD, demonstrating a genetic difference between the two disorders [48]. Furthermore, an excess of a specific HLA-DRB1 allele (DR13) was associated with pancolitis, surgical resection, and extraintestinal manifestations in UC patients [49].

**Important gene loci in CD**

It is already known from twin studies that genetic heritability is more expressive in CD than in UC [50]. In the update of the first Swedish monozygotic twin study, disease concordance rates of 15% for UC and 27% for CD were found [51]. Location and behaviour of the disease in monozygotic CD patients was highly concordant both at diagnosis and 10 years later [50,51]. A recent study investigating all known 163 IB risk gene loci in CD and UC patients has found that increased genetic burden was associated with early diagnosis of CD, but not of UC [52]. Ileal disease was also predicted by higher genetic burden in CD, however, in UC there was no association with disease phenotype. Accordingly, ileal CD is probably determined by genetic factors, while CD with colonic localisation can be explained more by environmental factors [51].

The most well-known gene associated with CD is CARD15, encoding nucleotide-binding oligomerization domain 2 (NOD2)
[53,54]. NOD2 plays a role in pattern recognition of pathogen microbiota, activates nuclear factor (NF)-κB in monocytes following lipopolysaccharide stimulation, and leads to the induction of proinflammatory cytokines. Three common and several rare NOD2 mutations have been identified so far, affecting almost exclusively the leucine-rich repeat region of NOD2, which is in the ligand-binding domain of the receptor [55]. NOD2 is expressed in Paneth cells, DCs, macrophages and IECs, but the mediating cell type and the mechanism by which NOD2 gene polymorphism leads to CD is still not clear. Animal studies have shown that NOD2 deficiency caused impaired intestinal barrier function and predisposed to intestinal bacterial infections [56]. Ileal CD patients have been demonstrated to present reduced levels of the antimicrobial peptide alpha-defensin originating from Paneth-cells [57]. This decrease was more pronounced in patients with a NOD2_1007fs variant, and was suggested to alter the intestinal microbial flora and compromise innate immunity. However, this observation has been questioned by others, claiming that the reduced alpha-defensin expression is simply the consequence of inflammation and independent of NOD2 status [58]. Furthermore, in a recent study on C57BL/6 mice, NOD2 deficient animals presented with equivalent defensin levels and identical antimicrobial activity against commensal and pathogenic bacterial strains as their wild type littermates, and their gut microbiota composition was also similar [59]. Nevertheless, other animal experiments have suggested distinct mechanisms connecting NOD2 deficiency to CD. In a murine model, NOD2 deficiency increased Toll-like receptor (TLR) 2-mediated activation of NF-κB, and resulted in enhanced Th1 responses, a characteristic of CD [60]. Additionally, chronic stimulation of NOD2 caused tolerance to a repeated induction by NOD2, TLR 2 or TLR 4 ligands, and decreased the production of the proinflammatory cytokines in macrophages from a large cohort of individuals, but not in macrophages with a mutant NOD2 variant [61]. This suggests that NOD2 polymorphism may predispose to CD by decreasing tolerance to the resident microbial flora. CD in patients carrying at least one major variant of CARD15 tends to show a more aggressive clinical course [62]. Interestingly, CD risk alleles of NOD2 were found significantly protective against UC [20].

A relatively new discovery in the pathogenesis of CD is the association of the disease with autophagy genes (ATG16L1 and IRGM). Autophagy is a catabolic process that ensures the breakdown and recycling of damaged or unnecessary cellular components or intracellular bacteria via the lysosomes. Deficiency in autophagy related to a homozygous ATG16L1 allele causes impaired engulfment and degradation of the cytoplasmic content and microorganisms, defective presentation of bacterial antigens to CD4+ T-cells, and increased inflammatory cytokine production by Paneth-cells [55]. NOD2 and ATG16L1 are involved in common processes, as bacterial cell wall components can stimulate autophagy and increase killing of Salmonella in human colonic epithelial cells via a NOD2 dependent pathway [63]. However, in cells transfected with CD-associated NOD2 variants, both autophagy and antimicrobial activity were defective. Furthermore, another CD associated gene, protein tyrosine phosphatase non-receptor type (PTPN) 22 controls NOD2 induced cytokine release and autophagy, and its deficiency causes an enhanced monocyteic response towards bacteria [64]. Perturbation of bacterial killing and defective antimicrobial pathways may cause an uncontrolled inflammation and ultimately lead to CD [55].

The mucus layer, an important component of the innate protective barriers is also affected in CD [65]. Gene loci associated with mucus production (MUC1, MUC19) [30,66], and more specifically to CD, fucosyltransferase (FUT) 2, a gene encoding alpha 1,2 fucosyltransferase, are all implicated [65]. FUT2 regulates gastrointestinal mucosal expression of blood group A and B antigens, and 20% of Caucasians are non-secretors. It has been shown that the non-secretor state is associated with altered mucosal microbial flora, and susceptibility to different infections beside CD [67]. In non-secretors, the metabolism of luminal microbiota was also disturbed, accompanied by a subclinical inflammation of the intestinal mucosa [68]. The metabolism of the epithelium in CD may also be impaired, as the functional variants of genes encoding the organic cation transporters (OCTN) -1 and -2 are linked to the disease [69]. In the last decade, polymorphism of OCTN has been associated with increased risk [70] or perianal and penetrating forms of CD [71], and even with UC [72]. The impaired function of OCTN can reduce carnitine transport to cells, which may lead to defects in oxygen burst-mediated pathogen killing or altered fatty acid β-oxidation in the intestinal epithelium. Regarding HLA genes, a CD-specific haplotype has also been described. Indeed, HLA-DRB1*0401 is a susceptibility allele in CD and a protective allele in UC, although the effect seems weak and population-specific [38].

**Intestinal Microbiota**

The intestinal microbial flora, consisting of up to 15,000-36,000 different species of bacteria, numerous fungi, viruses and bacteriophages, is a crucial component in the pathogenesis of IBD. Animal models have demonstrated that the presence of a bacterial flora is essential for the development of colitis [73,74]. The main theory suggests that a dysregulated immune activation in a genetically susceptible individual leads to an excessive response to the normal microbial flora. However, others suggest that it is an altered microbial flora which provokes an abnormal response from the normal immune system in these patients. Our current understanding assumes that the reality is probably a combination of both hypotheses [15]. The dominant members of intestinal bacterial flora in healthy individuals are Bacteroidetes and Firmicutes, but Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia are also present [75]. Several data exist showing an altered microbial composition both in UC and CD, however, examinations have failed to identify a single bacterial strain specific to these diseases [76].

**Dysbiosis in UC**

The biodiversity of active bacteria is reduced in UC patients compared to controls [77]. A decreased number of gastrointestinal health-promoting bacteria, Bacteroidetes and Lachnospiraceae, were found in surgical specimens from UC patients by rRNA sequence analysis compared to controls [76]. Another study has shown a decrease of the beneficial Bifidobacteria in rectal biopsy specimens of UC patients, parallel to an increase of Clostridia and E. coli [78]. E. coli is also overrepresented among active fecal bacteria of UC patients, and is suggested to have a role in the development of colitis [77]. The number of *Faecalibacterium prausnitzii*, associated with mucosal protection, was also reduced in fecal samples of UC patients recovering from a relapse [79]. Similarly, in an *in vitro* dynamic gut model called M-SHIME, butyrate producing bacteria were less abundant and butyrate production was reduced among luminal microbiota from UC patients, which may cause energy deficiency in colonocytes [80].
Dysbiosis in CD

The intestinal bacterial profile in CD also differs from healthy controls [81]. The abundance of mucosa-protective Faecalibacterium prausnitzii is reduced, while the number of potentially harmful Clostridia and Escherichia are increased in CD patients. Patient-to-patient variations are greater than differences between healthy controls, suggesting that individuals predisposed to CD are less able to regulate the microbial composition of their intestines. Occasionally, opportunistic pathogens, such as Enterobacter, Proteus, Haemophylus and Klebsiella, were also found in the mucosal samples of these patients, but had never detected in the samples from healthy controls. The importance of Faecalibacterium prausnitzii has been underlined by the fact that a decreased number of these bacteria in the ileal mucosa at the point of surgery are associated with increased endoscopic recurrence rates 6 months after surgery in CD [82]. This observation is in accordance with animal studies showing that Faecalibacterium prausnitzii and its supernatant also displays anti-inflammatory properties in rodent colitis models [83].

Environmental Factors

Smoking

Smoking is the most studied environmental factor in IBD, and is also a particular factor where CD and UC clearly split up.

UC

The first report on non-smoking as a risk factor in UC was published in 1982, and several more have confirmed this observation [84]. Smoking is associated with lower onset risk, fewer hospitalizations, lower relapse rate and decreased need for colectomy in UC [85-87]. Quitting smoking increases the risk to develop UC in the following years, and this risk remains elevated over 20 years [88,89]. Passive smoking is not protective against UC, and it predisposes to ileal disease (pouchitis and backwash ileitis) compared to non-passive smokers [90]. The pathomechanism of the effect of smoking in IBD is not yet established. However, it is generally believed that the beneficial effect of smoking in UC is mostly related to nicotine [91]. Nicotine increases mucine secretion in the colon, provokes the release of NO, and has several anti-inflammatory properties [92-94]. IgA concentration is markedly decreased in the intestinal fluid of smoking UC patients compared to healthy non-smokers [95]. Smoking also increases the level of suppressor CD8+ T cells, decreases the synthesis of proinflammatory molecules, such as IL-1β, IL-2, IL-8, TNF-α, and impairs phagocytosis, which may explain its positive effects in UC [91].

CD

Contrary to UC, passive and active smoking is both risk factors of developing CD, and this risk can be attenuated by cessation of smoking [89,90,96,97]. Several studies have found that steroid and immunosuppressive therapy are more frequently needed, recurrence rates are significantly higher and surgery is more often required in CD patients who are currently smoking [98-100], although these observations are questioned by others [101]. Deleterious effects of smoking in CD may be related to different mechanisms than described above, such as the increase of oxygen free radial production by polymorphonuclear leukocytes in smokers, smoke-related functional impairment of monocytes in CD patients, and reduced expression of NOD2 in intestinal epithelial cells by cigarette smoke [102-104].

Appendectomy

The appendix is an important lymphoid organ along the gastrointestinal tract, which helps to maintain the healthy gut microbial flora by modulating the epithelial regeneration and protecting from pathogen microbes via the production of biofilms and compounds such as mucin and IgA [105]. It may also regulate the immune response to host microflora by acting as a reservoir of enteric bacteria [106]. The possible role of the appendix in the development of UC and CD has been raised following recent epidemiological studies.

UC

Large number of studies have found a highly significant negative association between appendectomy and UC [106]. Indeed, previous appendectomy, especially before the age of 20, protects from UC, delays the onset of the disease, and is associated with a milder disease course [107]. Previous observations have highlighted a crucial role of the humoral immune system and B-lymphocytes in UC, therefore the removal of the appendix rich in B-lymphocytes in a genetically susceptible individual may be sufficient to prevent or ameliorate the disease [107]. Another hypothesis claims no causal relationship between appendectomy and UC, but assumes that appendectomized individuals probably represent a distinct group in the population in terms of genetic or environmental risk factors. This is supported by observations that appendectomy prevents UC only if performed on an inflamed appendix or in the case of mesenterial lymphadenitis, and before the age of 20, but not in cases of non-specific abdominal pain [108].

CD

The link between appendectomy and CD are controversial. Although most studies report an increased risk, protective or no effect was also found in some cases [107,109]. The fact that the increased risk of CD returns to normal levels 5 years after appendectomy suggests that it is probably related to diagnostic problems in incipient CD, and is not a real causative factor [75]. That is, the misleading right lower quadrant pain incite clinicians to perform appendectomy in a notable amount of cases, before the diagnosis of CD is established.

Diet

Dietary intake has dramatically shifted to a high-fat, high-carbohydrate diet in Western countries in the last decades, which is thought to increase the risk of several chronic illnesses. However, obesity as measured by the body mass index by itself is not associated with the development of UC or CD [110]. A systematic review of the literature has revealed that high intake of saturated fats, total polyunsaturated fatty acids (PUFAs), omega-6 fatty acids and meat predisposes to the development of both CD and UC, whereas dietary fiber and fruit consumption decreases the risk of CD, and high vegetable intake reduces the risk of UC [111]. Another study has confirmed that low intake of fruits and/or vegetables were associated with an increased onset risk of IBD, and grain consumption may have a protective role in CD [112]. High intake of sugar was also identified as a risk factor of the development of IBD. Furthermore, regular consumption of fast food was associated with an increased risk [113] and a younger age at diagnosis [4] of both UC and CD. IBD patients,
especially those suffering from CD, are clearly convinced of the importance of diet; 70% of them rating it to be as important as medical therapy [114]. Further, 86% of patients could identify drinks and specific food as provocative factors for a relapse, mostly alcoholic beverages, soda, coffee and strong spices.

Recent evidence has made it clear that changes in diet can induce significant modifications in the components of the colonic microbial flora. In germ-free mice colonized with human fecal microbiota, switching from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar “Western” diet altered microbiota composition after only one day, together with changes in mithabloc pathways and microbiome gene expression [115]. The mechanism of such microbial alteration was explored in a recent study, where a diet rich in high-saturated fat (derived from milk) and low in PUFA promoted tumour-conjugation of hepatic bile acids, which then increased the availability of organic sulfur, inducing the proliferation of the sulftie-reducing Bilophila wadsworthia [116]. These changes were followed by a Th1 immune activation and increased incidence of colitis in genetically susceptible IL-10−/−, but not in wild type mice. In humans, probably one single dietary factor can not be responsible for the development of IBD. Nevertheless, modification of the microbial flora by a favorable diet or by dietary supplements could help to induce and maintain remission [117].

**Vitamin-D**

Vitamin-D deficiency in IBD could be the consequence of the disease itself, due to insufficient intake, malabsorption, reduced sunlight exposure and low physical activity. Nevertheless, lower levels of vitamin-D are observed already in newly diagnosed patients, suggesting a possible role in the pathogenesis [118]. In a prospective study on female nurses, higher predicted 25-hydroxi-D-vitamin (25(OH)D) plasma levels significantly reduced the risk for the onset of CD and nonsignificantly reduced the risk for UC [119]. Serum 25-(OH)D was also inversely associated with disease activity in CD [120]. Further, human genome mapping has revealed recently that vitamin D receptor (VDR) binding sites are significantly enriched near PTPN2, a receptor (VDR) binding sites are significantly enriched near PTPN2, a

Medications

Some medications are suspected to participate in the development and in relapses of IBD [127]. First of all, previous antibiotic use has been suggested to increase the risk of IBD, particularly CD, by altering the intestinal flora. Antibiotic use in the first year of life was associated with increased risk of IBD—mostly CD—in childhood [128,129]. Furthermore, in several studies on adult patients, antibiotic treatment 2-5 years preceding the diagnosis was associated with CD [130,131] or with both CD and UC [132]. Out of the different types of antibiotics, the strongest correlation was found with metronidazol and the weekest with penicillin, while clindamycin showed no correlation [132]. Another study has noted a high association of doxycycline with CD 84, confirmed by recent observations in Australians, when deployment to a developed country and doxycyclin use was found as a risk factor of IBD onset [133]. Although this data shows an increased antibiotic use preceding the diagnosis of IBD, the causative link may be questioned. That is, it can be speculated that antibiotic treatment in childhood may be necessary for bacterial infections more easily acquired in future IBD patients based on their genetic background, while in adults high rate of antibiotic use preceding the diagnosis may be the consequence of a misinterpretation of the initial abdominal symptoms.

The next group of medications implicated in the pathogenesis of IBD are the non-steroid anti-inflammatory drugs (NSAIDs). Many of them are widely prescribed in the general practice, therefore it is crucial for clinicians to be aware of the risk of these medications, particularly in case of known IBD patients. Numerous studies have found a positive correlation between the use of NSAIDs and the onset of UC [134], CD [135] or both [136,137]. This can be mediated via several mechanisms, most notably, NSAIDs inhibit the cyclooxygenase (COX) enzyme, thereby decreasing the synthesis of prostaglandins, which are important to mucosal integrity and function [127]. They also alter mucosal microcirculation and cause direct damage to the epithelium, resulting in a permeability increase. The use of selective COX-2 inhibitors are considered somewhat safer than classical NSAIDs. Nevertheless, experimental and clinical data are not sufficient, and their prescription in IBD patients is suggested with caution [138].

Oral contraceptives can be capable of provoking IBD by the proinflammatory properties of estrogen and its effects on the mucosal microcirculation [127]. Several publications have reported an increased risk of CD [97,139] or both CD and UC [140] among women using oral contraceptives. Similarly, a recent prospective cohort study has found that oral contraceptive use increased the risk of CD, but elevated risk of UC was only observed in women with a history of smoking [141]. Postmenopausal hormone therapy has also been associated with the onset of UC [142] or CD [140]. Other studies have found no link between oral contraceptives and disease relapse [143]. Altogether the results are insufficient and controversial, therefore the use of oral contraceptives is still accepted in IBD, as accurate family planning is particularly important in these patients.

Anti-TNF-α monoclonal antibodies, namely infliximab and adalimumab are effectively used in IBD, unlike etanercept, a soluble TNF-α receptor, which was ineffective in moderate to severe CD patients [144]. Anti-TNF-α therapy is also applied in inflammatory rheumatic diseases, where it was associated with the paradoxical development of IBD in some cases. A retrospective study conducted in France has identified four new-onset cases of IBD during anti-TNF-α treatment in 296 patients with spondyloarthropathy, three receiving etanercept and one infliximab [145]. Another report from France
collected data from 16 patients with de novo IBD treated with etanercept (14 cases) or infliximab (2 cases) for inflammatory rheumatic diseases [146]. Among these patients, eight were identified as CD, six as CD-like, one as UC and one unclassified. On one hand, the explanation of these paradoxical adverse events may be that spondyloarthropathies are associated with IBD, and the doses applied in rheumatic diseases are simply not sufficient to prevent the development of an incidental extraskeletal manifestation [145]. On the other hand, etanercept is associated with increased production of TNF-α and INF-γ in CD4+ T-cells, contrary to the downregulation seen in infliximab treatment, which may explain its property to induce a new-onset IBD [147].

Breastfeeding

The role of breastfeeding at childhood is still a question of debate in the pathogenesis of IBD [148]. Some studies have found that breastfeeding is a risk factor for CD [149] or has no effect on the development of either CD or UC [150]. However, a large meta-analysis has concluded that breastfeeding is protective against UC and even more protective against CD [151]. Based on this data, the recent revisions of the Nordic Nutrition Recommendations have stated that breastfeeding has probable evidence against IBD [152]. Nevertheless, they also admit that most studies were retrospective, and sufficient data based on prospective studies are missing. Breastfeeding with normal milk (from wild-type mothers) has significantly reduced TNF-α and IFN-γ secretion and prevented development of colitis in IL-10 deficient mice, with normal levels of colonic adherent bacteria [153]. The reason for this beneficial effect is probably based on the development of a more advantageous intestinal flora rich in Bifidobacterium and Lactobacillus in the pups, stimulated by oligosaccharides found in the milk. Similarly, in human infants, the nature of early nutrition determines the constitution of the microbial flora, and influences the development of the immune system, which, if defective, may lead to the onset of IBD by an excessive immune response to the normal flora [154].

The “hygiene hypothesis”

Early postnatal and childhood infections can shape the immune system. It is well established that high sanitary standards and low exposure to infectious agents in childhood increases the risk of atopic diseases [155]. The lower incidence of IBD in developing countries suggests that these factors also predispose to the development of CD and UC. Nevertheless, studies aiming to clarify the association between childhood exposure to infectious agents and the risk of IBD have been inconclusive so far. For example, having a pet in childhood was shown to increase the risk of CD [156], while regular contact with farm animals or a cat in infancy was indeed protective against both CD and UC [157]. However, clear evidence was found on the beneficial effect of Helicobacter pylori infection and helminthiasis in IBD [158,159]. Less clear is the validity of the "cold chain hypothesis", suggesting that the development of CD is in association with the use of food refrigeration, which increases the possibility of particular infections such as Listeria monocytogenes, Yersinia enterocolitica, Clostridium botulinum and Bacillus cereus. The evidence supporting a causative role in utero or perinatal measles in the development of CD is also insufficient. Furthermore, results of well-designed studies did not support a link between vaccination against measles and the risk of of IBD. Similarly, the role of infectious gastroenteritis in childhood is also controversial. Some studies have shown an increased risk of CD, while others have claimed a decreased risk of both CD and UC [160]. Several studies have reported that higher domestic hygiene, such as hot water tap and higher socioeconomic status, are associated with the development of CD, but not with UC, by preserving the individual from contact with infectious agents, and predisposing to an inappropriate immune response, when the exposure occurs later [157]. Although hygiene practices and bathroom facilities have markedly improved in the last decades, and they therefore tend to lose their influence, a recent study has still identified higher social status, higher educational level of parents and living in urban areas as important risk factors for both UC and CD [160]. Novel experimental data have suggested that the background of these observations may lie at least partly on the ability of early gut microbial exposure to regulate the expression of chemokine receptor CXCR6 on mucosal invariant natural killer cells, modulating the accumulation and function of these cells in the colon and lungs, and consequently altering inflammation [161].

Personality traits

IBD was long considered to be psychosomatic disorder, and over 70% of patients still believe that the development of the disease is related to stress or their own personality [162]. Significant personality differences have been found in IBD patients compared to their healthy siblings, summarized as a fixation of dependency and lack of autonomy [163]. These characteristic personality traits in IBD could result from the longstanding chronic illness. However, a study examining a group of patients previous to an established diagnosis has shown that increased levels of neurotictism and introversion were highly prevalent, even before the diagnosis was established [164]. Further characteristics are perfectionism, and alexithymia (difficulty in recognizing, regulating and expressing emotions), which can lead patients to show distress by developing somatic symptoms instead of verbal communication [165,166].

Stress and mood disorders

Several studies have concluded that anxiety and depression are common in IBD patients, and their severity parallels the disease activity [167-170]. These psychological conditions may not simply be the consequences of the chronic illness. In a retrospective study both depression and anxiety preceded UC, but not CD, significantly more often than expected by chance [171]. Mood disorders may initiate and deteriorate inflammation by enhancing the release of proinflammatory mediators and by disturbing the immunoregulatory circuits [172,173]. The central nervous system is strongly connected with the enteric nervous system by several pathways, creating the so-called brain-gut axis. It is well known that stress induces central and peripheric secretion of corticotropin-releasing factor, which has been shown to inhibit upper GI motility and stimulate colonic motility, induce colonic mast cell degranulation, and increase colonic permeability in animal studies [174,175]. Increased permeability may lead to inflammation by altering host-microbial interactions, and consequently result in visceral hypersensitivity [176]. Stress also provokes the release of pro-inflammatory Th1 cytokines, such as TNF-α and neuropeptides, such as tachykinins [177]. In animal experiments, colitis can be exacerbated by early life stress (neonatal maternal deprivation) in genetically susceptible IL-10 KO mice, but not in wild type mice, probably through impaired intestinal barrier function [178]. Although most patients consider stressful life events important in the development of their disease, one study focusing on
life events occurring no more than six months prior to the onset of diagnosis failed to find any correlation in UC patients compared to controls [179]. In CD patients, life events occurred more frequently in the past 6 month preceding diagnosis, however, the association was no more significant when other factors were also taken into account. A metaanalysis pointed out that stress in UC and depressive symptoms in CD play roles in the disease course, but it also could not find evidence that they contribute to disease onset [180]. Recently it was also shown that job strain, indicating work-related stress, did not correlate with the onset of either CD or UC [181]. Taken together, stress and psychological issues are clearly important in the disease course and in the management of IBD patients, but their role in the pathogenesis could not be convincingly established so far.

Epigenetics

Environmental factors may lead to the development of IBD by various mechanisms, which are detailed above. However, a new field of research, namely epigenetics, which links environmental factors to genetics in IBD has been evolving. Epigenetics describes mitotically heritable modifications in gene expression not explained by changes in the DNA sequence [21]. Important epigenetic mechanisms are DNA methylation, histone modification, RNA interference, and the positioning of nucleosomes. Epigenetic changes are likely to occur in the prenatal and early postnatal periods, and animal studies have shown that DNA methylation links transient nutritional influences to a permanent phenotype modification [182]. A clearly visible example of this phenomenon is observed, when Avy (viable yellow Agouti) mice during pregnancy receive oral methyl-donor supplementation, which induces DNA methylation of the Agouti gene in the offspring, resulting in a decreased gene expression and brown-coloured offspring instead of yellow [183]. Recent data suggest that similar processes may work in humans, linking under nutrition during gestation and infancy to a higher risk of childhood infections and death by differential methylation at genes associated with defense against infection and immune response [184]. Methyl-donors are abundant in human maternal dietary supplements. In mice, maternal methyl-donor supplementation augmented susceptibility to colitis in offspring, parallel to colonic mucosal DNA methylation and expression changes, followed by a sustained effect of the diet on colonic mucosal microbiota [185]. Although similar data in humans is missing, a study on ileal CD patients has found that several of the known CD risk gene loci were enriched in methylation compared to healthy controls, including the Th17 pathway and NOD2 [186]. More studies are needed to elucidate the effects of periconceptional and prenatal nutrition on DNA methylation in humans, and to assess its possible role in the pathogenesis of IBD.

Conclusions

Knowledge of the pathogenesis of IBD has been rapidly growing in the past decades. Previously considered as a “psychosomatic disorder”, IBD has now evolved to an excessive immune response to the intestinal microflora in genetically susceptible individuals, influenced by several environmental factors. In our review we have summarized current knowledge of genetic and environmental factors participating in the development of IBD, with special focus on differences between UC and CD. Recent progress in the field of genetics has allowed us to understand new mechanisms participating in the pathogenesis, such as the involvement of Th17 cells in both UC and CD, or the role of autophagy in CD. These genetic discoveries create the basis for developing novel biological therapies or the expansion of existing therapies, which were originally developed for other diseases, to IBD [187]. For example based on the recently described pathway of IL-23/Th17 in IBD, ustekinumab (Janssen-Cilag), a human anti-interleukin-12/23 monoclonal antibody, which was previously applied in psoriasis, has been successfully tested in moderate to severe CD [188]. Nevertheless, a randomized clinical trial in active CD patients with everolimus (Novartis), an inducer of autophagy, was terminated in the enrollment phase due to the lack of efficacy [189]. This underlines the role of carefully designed studies in the future, where patients are genetically selected and only patients with defective autophagy are enrolled [187]. Such studies would be milestones on the road leading to personalized therapy, based on each patient’s genetic profile. Another possible use of genetic profiling would be to predict the disease course, and thus individualize therapy intensity. As mentioned above, some genetic variations, such as CARD15 mutations or specific HLA alleles are associated with more extensive disease or aggressive disease course, but they are not frequent or not significant enough to be used in the routine practice. Genetic studies have highlighted several common pathways among UC and CD, but differences are also present, which may explain the overlapping, yet usually distinguishable clinical entities. As these genetic variations are rare, developing a combined test based on different genetic markers specific to either UC or CD, such as NOD2 or some HLA alleles could be useful in the differential diagnosis in problematic cases, e.g. in children. Nonetheless, genetic screening of the general population to predict the onset of IBD would probably not be successful, as in most patients, genetic background in association with environmental factors leads to the onset of the disease. Thorough understanding of the role of environmental factors is extremely important, as they are easier to modify in order to prevent the onset or the relapse of IBD (Table 1). Nevertheless, in the case of many environmental factors, large-scale studies are missing, and results are controversial probably due to methodological differences, making interpretation difficult. It seems clear that dietary factors, reduced vitamin-D levels, and specific medications can participate in the development of IBD. These factors can be surveyed and adjusted in IBD patients to minimize the number of relapses. Furthermore, they also can be controlled in predisposed individuals, e.g. in a patient’s family members to reduce the risk of developing IBD. Patients tend to avoid specific foods that they believe provoke their symptoms, and a diet rich in fruits and vegetables and low in fat and sugar is advisable for many reasons beside IBD. Optimal vitamin-D level can be achieved in IBD patients. Among specific medications, it is generally believed that excessive prescriptions of antibiotics should be avoided to prevent the development of bacterial resistance and to preserve the normal colonic flora. Relapses in IBD, however, often require the use of antibiotics. NSAID consumption should be minimized in IBD patients to avoid relapses. Smoking is a strong risk factor of CD and a protective factor of UC. Nevertheless, it is advisable that UC patients stop smoking, considering the several well-known harmful and carcinogenic effects of smoking on other organs of the body. Appendectomy is protective in UC, while breastfeeding seems beneficial against both UC and CD, but inverse results also exist. The role of childhood infections is controversial. However, high hygienic standards in the early ages may predispose to IBD by reducing contact with infectious agents during development of the immune system. Specific personality traits may facilitate the development of IBD. Stress and psychosomatic disorders affect the disease course. Therefore patients with psychological issues should be encouraged to see a specialist for treatment, which can result in longer remissions.
Environmental factors may contribute to IBD in the prenatal and early postnatal period by mitotically heritable modifications in gene expression, such as DNA-methylation. Further research can shed light on the nature and importance of such factors, for example the possible role of maternal dietary supplements in epigenetic changes. Improving life standards and propagation of Western lifestyle promotes the increasing prevalence of IBD all over the world, including in developing countries. Therefore more large-scale, prospective studies are needed to firmly establish knowledge on the contributing factors to help us in the prevention and to open new perspectives in IBD therapy.

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<td>stress</td>
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*"-": decreased risk; "+": increased risk; "0": no effect; "?: question of debate

Table 1: Environmental risk factors of UC and CD.


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