

## Crohn's disease: Why the ileum?

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### Abstract

Crohn's disease (CD) is an inflammatory bowel disease characterized by immune-mediated flares affecting any region of the intestine alternating with remission periods. In CD, the ileum is frequently affected and about one third of patients presents with a pure ileal type. Moreover, the ileal type of CD presents epidemiological specificities like a younger age at onset and often a strong link with smoking and genetic susceptibility genes. Most of these genes are associated with Paneth cell dysfunction, a cell type found in the intestinal crypts of the ileum. Besides, a Western-type diet is associated in epidemiological studies with CD onset and increasing evidence shows that diet can modulate the composition of bile acids and gut microbiota, which in turn modulates the susceptibility of the ileum to inflammation. Thus, the interplay between environmental factors and the histological and anatomical features of the ileum is thought to explain the specific transcriptome profile observed in CD ileitis. Indeed, both immune response and cellular healing processes harbour differences between ileal and non-ileal CD. Taken together, these findings advocate for a dedicated therapeutic approach to managing ileal CD. Currently, interventional pharmacological studies have failed to clearly demonstrate distinct response profiles according to disease site. However, the high rate of stricturing disease in ileal CD requires the identification of new therapeutic targets to significantly change the natural history of this debilitating disease.

**Key Words:** Ileum; Crohn's disease; Bile acids; Paneth cells; Diet; Genetics; Strictures

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**Core Tip:** The ileum is most frequently affected by Crohn's disease (CD). Ileal CD differs from other CD types in its epidemiology and natural history. Anatomical and histological features of the ileum provide the keys to understanding this distinct phenotype. Moreover, we discuss herein the crosstalk that occurs in the ileum between an individual and her/his environment and the clinical significance.

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## INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by repetitive inflammatory flares, and often chronicity. Unlike ulcerative colitis (UC), the other main subtype of IBD, CD can affect any part of the digestive tract. The site of the disease is a critical biological aspect of CD whereas inflammatory, stricturing or penetrating behaviour is thought to be a reflection of disease progression[1].

Data on the epidemiology of IBD are provided by population-based studies showing an increasing incidence and prevalence of IBD in the West over the last 50 years[2,3]. In a systematic review pooling all epidemiological studies on IBD worldwide since 1990, the global prevalence of IBD is higher in Western countries (322 per 100000 in Germany) than in newly industrialized countries[4]. In newly industrialized countries like Asia and the Middle East, epidemiological studies report a rising incidence of CD[4,5]. The Montreal classification distinguishes CD involving the ileum, the colon and both the colon and the ileum[6]. About one third of patients with CD presents a disease involvement limited to the ileum and this proportion does not vary between 'Western' and newly industrialized countries[3,5,7]. Once the diagnosis of ileal CD is made, less than one fifth of patients will present colonic lesions over time[3]. In addition, ileal CD occurs in younger patients than colonic CD[1]. These epidemiological observations have led some experts to plead for personalized approaches to therapy based on the disease site.

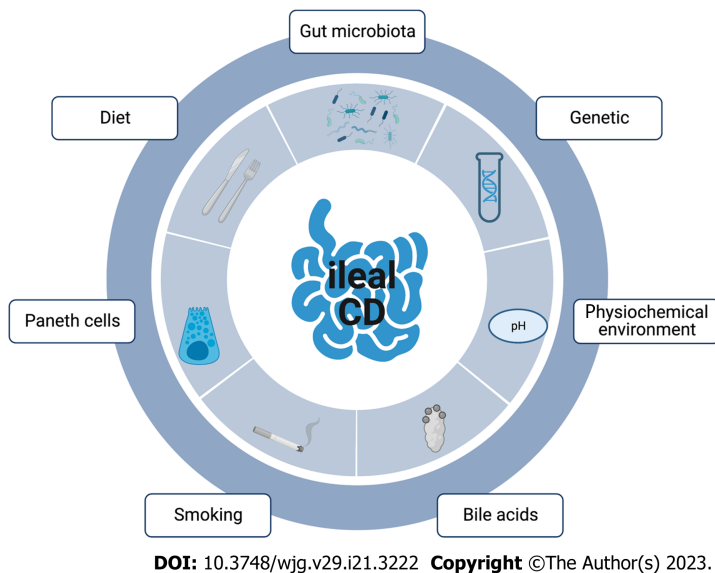
Even though CD pathogenesis remains elusive, current consensus considers CD a result of genetic, immunological and environmental factors[2]. Of relevance, the ileum is the site for the crosstalk of these multiple etiological factors in CD. In this review, we will depict the different physiopathological aspects of ileal CD and their clinical impact (Figure 1).

## GENETIC SUSCEPTIBILITY

Genetic factors are involved in IBD physiopathology and genome-wide association studies have linked several genes with the site of the disease. In a large epidemiological study performed in more than 34000 patients with IBD across Europe, North America and Australia, susceptibility genes were determinants of the site of the disease whereas inherited genes showed a loose link with the inflammatory, penetrating or stricturing behaviour of the disease[1]. The genetic variants presented herein sum up the current state-of-the-art but new techniques such as genomic DNA are likely to provide new insights in the next few years.

### NOD2

NOD2 is a sensor of the innate immune system, able to detect bacterial fragments, specifically muramyl dipeptide[8]. During *in vitro* differentiation of intestinal epithelial cells into Paneth cells, NOD2 signalling can modulate the expression of enteric antimicrobial peptides[9]. Even though intracellular pattern recognition receptor gene *NOD2* is widely associated with CD risk[2], mutations in the *NOD2* gene are strongly associated with ileal CD and are correlated with a younger age at diagnosis[1,10,11]. The specific association between *NOD2* mutations and ileal CD is partially explained by its distribution along the gastrointestinal tract. Histologically, *NOD2* is overexpressed in ileal crypts compared to colonic crypts[12].



**Figure 1 Potential factors involved in ileal Crohn's disease.** While Crohn's disease (CD) occurs in any part of the gastrointestinal tract, the ileum is frequently involved. Potential factors involved in ileal CD are genetic susceptibility genes and most of these genes are associated with Paneth cell dysfunction. Environmental factors may also be involved such as diet, gut microbiota and smoking. Diet can modulate the composition of bile acids and gut microbiota, which in turn affect the susceptibility of the ileum to inflammation. Created with BioRender.com. CD: Crohn's disease.

### **LRRK2**

Like *NOD2*, the *LRRK2* gene is expressed in Paneth cells. *LRRK2* gene is implicated in vesicular trafficking, cytoskeleton homeostasis and consequently in inflammation and immune response[13]. More specifically, *LRRK2* is overexpressed in Paneth cells and its deficiency causes deprivation of lysozyme in Paneth cells[14]. In a case-control study, mutations of *LRRK2* were associated with ileitis and an early onset of CD[15].

### **Major histocompatibility complex**

The expression of other genes involved in immune response is likewise implicated in ileal CD. The major histocompatibility complex is involved in the presentation of antigen in a large variety of cell types including T-cells. In a recent meta-analysis, several mutations of these genes were associated with CD especially in the Korean population but also in the European population[16]. Of note, single nucleotide polymorphisms of these genes were more common in patients with ileal CD compared to patients with colonic CD[1].

### **ATG16L1**

Among susceptibility genes identified in CD, the allele *ATG16L1*<sup>T300A</sup> was associated with impaired autophagy[17,18]. The expression of *ATG16L1* was decreased in CD patients[19]. In 9-10-month-old mice, the specific deletion of *Atg16L1* allele in intestinal epithelium cells (IEC) led to a transmural CD-like ileitis associated with endoplasmic reticulum stress[20]. Interestingly, *NOD2* mutations are also associated with autophagy defects.

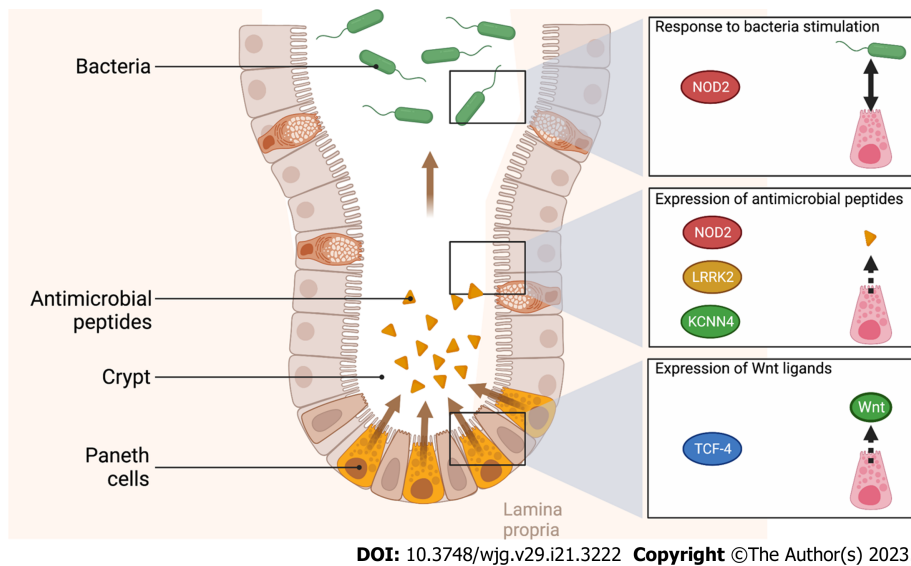
### **Tcf-4**

In IBD patients, the reduction of the Wnt-signalling pathway transcription factor Tcf-4 was associated with a predisposition for ileal CD[21,22]. A reduced expression of Tcf-4 resulted in a reduced expression of Paneth cell defensins[21]. In a murine Tcf-4 knockout model, a decreased expression of alpha-defensin levels and a reduced capacity of bacterial killing were observed[21].

### **KCNN4**

Finally, in the array of genes implicated in the immune response mediated by Paneth cells, the conductance calcium-activated potassium channel protein (*KCNN4*) is part of the potassium pump in the human intestine[23]. The blocking of this calcium-activated potassium channel protein reduced mouse Paneth cell secretion in response to bacterial stimulation[24]. In human, mutation of the *KCNN4* gene was associated with ileal CD in the Australian and New Zealand population[25].

In the susceptibility genes mentioned above, most genes are associated with Paneth cell dysfunction as illustrated in Figure 2. We will detail below the potential involvement of Paneth cells in ileal CD.



**Figure 2 Putative role of gene susceptibility in Paneth cell dysfunction.** Paneth cells are secretory epithelial cells located in the intestinal crypts. Paneth cells produce antimicrobial peptides in response to bacterial components and support stem cell function through Wnt signalling. Most of the susceptibility genes associated with ileal Crohn's disease (CD) involve Paneth cell dysfunction. NOD2 and *LRRK2* genes are expressed in Paneth cells and their deficiency in ileal CD modulates the expression of antimicrobial peptides such as alpha-defensins or lysozyme. Similarly, the reduction of the Wnt-signalling pathway transcription factor Tcf-4 is associated with a predisposition for ileal CD and leads to a reduced expression of Paneth cell defensins. The blocking of calcium-activated potassium channel protein (KCNN4) inhibits mouse Paneth cell secretion in response to bacterial stimulation. Created with BioRender.com.

## THE ILEUM, A SPECIFIC PART OF THE GASTROINTESTINAL TRACT

Beyond genetic factors, the histological and anatomical features of the ileum itself may partially explain the propensity of this specific part of the gastrointestinal tract to be affected by CD.

### Physicochemical environment

The ileum presents a unique chemical microenvironment. The intraluminal pH in the ileum is 7.4, the highest of the human digestive tract as a result of small bowel mucosal bicarbonate secretion[26]. Comparatively, the intraluminal pH in the caecum is lower, 6.5, due to the bacterial production of short fatty acids by colonic bacteria[26,27]. The functional characteristics of the digestive tract microbiota are modulated by pH level. In the environment of the ileum (pH = 7.4), short chain fatty acids increase the growth and the motility of pathobionts whereas, in the colonic environment (pH = 6.5), short chain fatty acids downregulate the virulence of gene expression of these strains[28].

### Histological changes in ileal CD

From a clinical point of view, most of histological features encountered in ileal CD were also found in other diseases as backwash ileitis in UC for instance[29]. Although epithelioid granuloma is considered as the histological hallmark for the diagnosis of ileal CD, it is not a mandatory prerequisite[30]. In about one quarter of patients with ileal CD, pyloric gland metaplasia resulting from the expression of mucin genes normally specific to the stomach (*MUC5AC* and *MUC6*) were noted[30,31]. Although numerous other histological features are described in ileal CD, focal crypt irregularities are considered by expert consensus as one of the most reliable signs of CD[30].

From a biological point of view, the most noteworthy change is found in Peyer's patches. Peyer's patches are ileal immune structures characterized by a B-cell germinal centre surrounded by a T-cell interfollicular region. These mucosal-associated lymphoid tissues can act as "gateways" of the intestine. The epithelium and the underlying lymphoid follicle differ from the surrounding villus epithelium of the ileum. Indeed, the function of this follicle-associated epithelium consists in sampling and transporting luminal antigens through M cells and dendritic cells to CD4<sup>+</sup> cells[32]. Early histological changes in Peyer's patches were reported in ileal CD such as an increase in mast cells or erosive epithelial lesions[33,34]. Further, the increased number of glial cells in the Peyer's patches of patients with ileal CD resulted in an enhanced intestinal permeability[34]. Together these phenomena may explain the increased vulnerability of the ileal mucosa to bacterial invasion in CD patients[35].

### Enteric nervous system

As mentioned in the previous section, the histological changes observed in ileal CD include glial cells and the enteric nervous system (ENS). In patients with ileal CD, both the submucous and the myenteric plexus present an overall increase in the number of neuronal cell bodies, enteroglia and interstitial cells

of Cajal associated with an upregulation of apoptosis in enteric neurons and enteric glial cells[36,37]. To that extent, although functional evidence is lacking in the literature to fully support this hypothesis, the increased transit time observed in CD patients could be seen as a consequence of ultrastructural injury to interstitial cells of Cajal in the myenteric plexus[38,39].

Beyond the role of the ENS in intestinal motility, the density of enteric glial cells conveys a higher risk of ileal CD recurrence after surgery. Thus, after ileocolonic resection for CD, inflammation in or around nerve bundles or enteric ganglia was reported in several clinical studies as a risk factor for CD recurrence[40-43]. In the uninfamed section from ileocolonic samples, the number of S100-positive enteric glial cells was enhanced in patients with relapsing disease unlike vasoactive intestinal polypeptide or substance P positive cells[44]. Furthermore, the ileum of CD patients harbours a different distribution of enteric glial cells with a higher density of these cells around Peyer's patches. In parallel, the mediators of enteric glial cell increased the permeability of the ileal mucosa in CD patients whereas they decreased the permeability of the mucosa in non-IBD patients[34]. The importance of these findings on the natural history of CD remains to be determined. In particular, the effect of the modulation of the ENS in neuro-immune interplay needs to be investigated.

### **Paneth cells**

Paneth cells are mostly located in the ileum and nearly absent from the colon[45]. This cellular type is found between intestinal stem cells in the small intestinal crypts. Paneth cells produce not only antimicrobial peptides that regulate host-microbe interplay but also factors such as Wnt ligands modulating the activity of intestinal stem cells. Many of the ileal CD-associated mutations discussed before involve cellular pathways of Paneth cells.

Paneth cells are rich in mitochondria to sustain their energy-expending secretory functions. In *SAMP1* mice, mice genetically predisposed to CD-like ileitis, the number of Paneth cells was decreased and abnormal Paneth cells were associated with disease progression[46,47]. Likewise, the number of Paneth cells is decreased in the small intestine of CD patients. This observation was made in several ethnic populations and particularly in paediatric cohorts[19,48,49]. Mucosal biopsies from adult CD showed ultrastructural abnormalities in mitochondria, especially in CD patients with inflammation (73.3%) but also in inactive CD patients (20.3%) which was not the case for goblet cells and enterocytes[50]. In patients with ileal CD, the count of abnormal Paneth cells correlated with disease activity and was predictive of recurrence after surgery[51]. Some authors hypothesised that this dysfunction in Paneth cells could result from mitochondrial impairment[50-52]. Besides, in mice, Paneth cell defects triggered by loss of prohibitin 1, a major component protein of the inner mitochondrial membrane implicated in cell respiration, caused ileitis[52]. This effect is mediated by oxidative stress. Furthermore, the use of a specific mitochondrial-targeted antioxidant (Mito-Tempo) ameliorates ileitis in mice. The use of the same mitochondrial-targeted antioxidant (Mito-Tempo) in human ileal biopsies of CD patients normalized the expression of 25% of altered CD genes, including genes implicated in antigen processing, lipid metabolism, apoptosis, and interleukin (IL)-17/IL-23 signalling[50].

### **Immune response**

As highlighted by research in immunological processes, Paneth cells are part of the crosstalk with the immune system to maintain intestinal microbial homeostasis and intestinal barrier[53,54]. When biopsies from CD patients were compared according to the site of inflammation in the gastrointestinal tract, differences in neutrophil activities were observed. For instance, matrix metalloproteinase-9 and myeloperoxidase were relatively less increased in ulcer edges of ileal CD compared to colonic CD, suggesting less neutrophilic degranulation in ileal CD[55].

Likewise, innate lymphoid cells (ILCs) are gaining interest as components of the immune system. Three groups have been individualized according to their properties: ILC1, ILC2 and ILC3. A switch was noted in the inflamed ileal mucosa of CD patients, from an ILC3 phenotype limiting commensal bacteria specific CD4<sup>+</sup> T cell response to an ILC1 phenotype associated with interferon (IFN)- $\gamma$  production[56]. The aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor, was involved in this process and downregulated in inflamed mucosa of IBD patients[57,58]. Pharmacological or genetic activation of the AhR enhanced ILC3 maintenance conferring a protection against pathogenic bacteria in mice and downregulated ILC2 maintenance implicated in immune response in worm[59]. AhR agonists arise from the environment, commensal flora and tryptophan metabolism[60]. In patients with ileal CD, impaired tryptophan metabolism was observed with decreased levels of kynurenine and expression of kynureninase[61].

Concordantly with a typical cellular immune response, ileal CD instigates a specific cytokine profile. Interferon lambda (IFNL) is secreted in response to microbial stimulation or to T-cell-mediated mucosal inflammation. IFNL was upregulated in the ileal mucosa of patients with CD and triggered ileitis in a murine model and induced Paneth cell depletion independently of tumour necrosis factor (TNF)[62]. The effect of IFNL in the ileum is mediated by the JAK-STAT pathway which represents a promising therapeutic target already being used in the clinic[62].

Besides the role played by IFNL, IL-22 contributes to the pathogenesis of ileal CD. IL-22 is produced by T-cells and ILC3 during IBD flares[63,64]. IL-22 is thought to assume an immunoregulative role as its inhibition by the IL-22 binding protein induced a severe inflammation in a rodent colitis model[64]. In

the ileum, interestingly, the levels of IL-22 binding protein were specifically high in comparison with the colon[65]. This heterogeneous distribution along the gastrointestinal tract may result from the infiltration of eosinophils in the ileum and the production of IL-22 binding protein[64,65].

### **The ileum as an endocrine organ**

If a high proportion of eosinophil cells was present in the ileum, an enhanced enteroendocrine cell activity was also found[66]. Additionally, terminal ileal chromogranin A cells and glucagon-like peptide 1 (GLP-1) positive L-cells were increased in ileal CD specifically[66]. However, studies on the serum levels of GLP-1 are rare and include small cohorts (< 20 patients). Data were inconclusive and showed similar serum levels of GLP-1 between patients with ileocolic CD and colonic CD but a higher serum level of GLP-1 in IBD compared to healthy controls[67,68]. Thus, no firm conclusion can be drawn regarding the nutritional and immune impact of this discovery.

Besides harbouring enteroendocrine cells, the ileum harbours oestrogen receptor subtype  $\beta$ , whether the ileum is affected by CD or not. The expression of subtype  $\beta$  was associated with a milder disease course in a cohort of 37 patients with ileal CD. Accordingly, the inflammation score was inversely correlated with the expression of oestrogen receptor  $\beta$ . Similarly, a higher expression of oestrogen receptor  $\beta$  was found in patients with non-stricturing non-penetrating disease[69]. In a chemical colitis model in rats, the activation of oestrogen receptor  $\beta$  reduced inflammation score as well as inflammatory pain and inhibited the ionotropic P2X3 receptor[70]. Notwithstanding this observation, female sex was not independently associated with ileal CD[1,71].

### **Myofibroblasts**

While ileitis is often studied from an inflammation perspective, little is published about cell repair. The gene encoding tumour progression locus-2 kinase, a proinflammatory enzyme, was associated in a genetically invalidated murine model with a surprising homeostatic role, modulating the effect of chemically induced colitis. Mechanistically, this gene does not directly impact the immune response but plays a critical role in intestinal myofibroblasts which contribute to the healing of intestinal epithelium. In response to inflammatory signals from the microenvironment, intestinal myofibroblasts trigger compensatory epithelial proliferation in the intestinal crypts[72].

### **Transcriptome studies**

The integration of the different pathways mentioned above in the pathogenesis of ileal CD is facilitated by multi-omic studies. Thus, differences in pathogenesis between the ileum and the colon are highlighted by these techniques. For instance, in CD patients, the metabolomic study of non-inflamed ileum and non-inflamed colon biopsies distinguish clearly different profiles. It is noteworthy that these differences were blurred in inflamed ileum and colon samples[73].

Although the physiopathology of ileal CD has been studied as a unique phenomenon, emerging evidence advocates for a more heterogeneous process in which physiopathological pathways differ from one patient to the other. Thus, transcriptomic data analysis from CD ileal tissue sample was able to identify subgroups of patients with distinct recurrence rates after surgery[74].

In a recent transcriptomic study of ileal mucosa samples, inflammatory genes (IL-6, IL-8, IL-1 $\beta$ ) were upregulated whereas metabolic process genes were downregulated in ileal samples from CD patients compared to controls. Early post-operative recurrence of CD was associated with an overexpression of TNF- $\alpha$ , IFN- $\gamma$ , IL-23A and IL-17A upregulation. In addition, using a regression model to predict post-operative recurrence of CD, mitochondrial dysfunction and JAK/STAT upregulation in the ileum were independently associated with post-operative recurrence[75]. Transcriptomic studies also provide new insights into cell population specificities in ileal CD. When mapping the cell type of the ileal mucosa of CD patients, tuft and BEST<sup>+</sup> cells were the cell types associated with CD, irrespectively of the treatment status[76]. Intestinal tuft cells are a rare cell type implicated in the defence against helminthic and protozoan infections[77]. BEST<sup>+</sup> cells represent about 1% of ileal epithelial cells and plausibly contribute to the mucus secretion of goblet cells[78]. Surprisingly in this ileal cell type study, immune compartment was slightly affected by CD despite the fact that treatment status in CD patients modified the epithelial and immune compartment[76].

Among the differentially expressed genes in ileal inflammatory response, activating transcription factor 4 (ATF4) is a transcription factor widely expressed in the human body, including the ileum. ATF4 downregulation in intestinal epithelial cells has been observed in active CD in patients and causes spontaneous enterocolitis in mice while altering ileal Paneth cell function. Furthermore, murine ATF4 deletion impaired the glutamine uptake of the intestinal epithelium and concordantly glutamine supplementation restored Paneth cell function and decreased intestinal inflammation[79]. A few years earlier, the inhibition of the ATF4 pathway demonstrated an altered autophagy in human intestinal epithelium in the presence of adherent-invasive *Escherichia coli* (AIEC). This pathological response resulted in the intracellular bacterial replication of AIEC and consequently in pro-inflammatory patterns[80].

## BILE ACIDS

The role of bile acids is largely reported in liver disease in which bile acids are inflammatory cues and treatment targets[81]. The involvement of the gut in the pathogenesis of inflammatory liver diseases and similarities in etiological factors has led to consideration of the role of bile acids in IBD[82].

Primary bile acids are produced in the liver and secreted through the biliary tree into the gastrointestinal tract. Most primary bile acids are reabsorbed by the ileum and hence recycled several times. A minority of primary bile acids are transformed into secondary bile acids by a narrow range of gut bacteria. The pool of bile acids influenced the composition of gut microbiota which in turn modulated the composition of the bile acid pool[83]. Thus, impaired bile acid pools in relation to impaired microbiota enzymatic activities have been described as contributing to the inflammatory loop of IBD[84]. Bile acid composition in the lumen of the ileum differs between CD and non-CD patients with a relative decrease of primary bile acids in the ileum of CD patients[85]. Nevertheless, this finding should be interpreted with caution as malabsorption of bile acids was documented as a consequence of ileal CD especially in patients with a history of ileal resection[86,87]. Moreover, in a cohort of 166 patients, enhanced primary biliary level in the stool was independently associated with ileitis[88]. In a multi-omics approach based on a stool collection of 200 IBD patients, ileal CD profile was characterized by increased primary and secondary bile acid levels and shifts in taxa in favour of bacteria associated with bile acid-rich environments (*Gammaproteobacteria* and *Blautia* sp.)[89]. Further, the level of secondary bile acids in patients with inflammation limited to the ileum tended to increase after biological treatment reaching a similar level with control subjects[90].

In addition, bile acids exert inflammatory modulating properties through the stimulation of farnesoid X receptor (FXR). In a murine model of chemically induced inflammation, the activation of FXR demonstrated anti-inflammatory effects through a reduction of epithelial hyperpermeability and of proinflammatory cytokine production[91]. Furthermore, the obstruction of bile flow in mice induced mucosal ileal injuries reversed by administration of bile acids. In detail, this result may be explained by the activation of FXR by bile acids which promoted enteroprotective genes and limited ileal bacterial overgrowth[92]. Furthermore, bile acid pool modulation directly affects the ileum and Paneth cells. According to a recent article, Paneth cell number was linked to diet and to microbiota by bile acid in obese CD and non-CD patients irrespectively of other risk alleles (ATG16L1 and NOD2)[93]. In fact, in mice fed with a high fat diet, a similar phenomenon was observed and notably, high fat diet alone in germ-free mice as well as microbiome transfer alone in mice fed with standard diet were unable to induce an alteration in Paneth cells. The reason for this phenomenon was also dependent on FXR activation by the bile acid pool. Thus, the conjunction of a high fat diet and *Clostridium*-mediated production of secondary bile acids may explain the role of both diet and microbiome in this mechanism [93].

Lastly, bile acids promoted the expression of long polar fimbriae favouring the interplay of these strains with Peyer's patches and bacterial translocations[94]. For example, primary bile acid level was inversely correlated with the abundance of *Faecalibacterium prausnitzii* (*F. prausnitzii*) and its acetate and L-methionine producing enzyme[88]. In patients treated by surgery for ileal CD, bile acid metabolism specificities were associated with an ileal recurrence of CD[89].

Nevertheless, there is only limited evidence on the therapeutic role of bile acids in ileal CD. While several authors reported the protective role of ursodeoxycholic acid and of its precursor, the lithocholic acid, against chemically induced colitis in mice[95-97], there is a lack of data about the effect of oral supplementation with ursodeoxycholic acid in patients with IBD. Thus, only one small single-centre trial examined the effect of ursodeoxycholic acid in UC and none was performed in patients with CD [98].

## MICROBIOTA

An increasing number of authors have investigated the link between gut microbiota and CD. However, many of these studies focused on the analysis of DNA extracted from stool. This methodology shed light on the colonic microbiota of the colonic lumen but was unable to draw any conclusions on the microbiota associated specifically with the ileum. Moreover, in a systematic review, the study mucosa-associated microbiota was regarded as more relevant in the understanding of CD pathogenesis[99]. In addition, dysbiosis was described in some mice models as a by-stander of ileitis. For example, in genetically predisposed mice Atg16L1<sup>ΔIEC</sup>, dysbiosis was observed but litter cross-fostering predisposed to colitis but not ileitis[20].

### Host/microbiota interplay

Microbiota homeostasis plays a critical role in CD physiopathology[2]. Thus, mucosal immunity regulator molecules such as vitamin D receptors (VDR) have been associated with a susceptibility to bacterial and chemical colitis. The genetic inhibition of VDR in the Paneth cells of VDR<sup>ΔPC</sup> mice resulted in a lower expression of lysozymes in Paneth cells[19]. Inhibition of VDR influences the response to

pathogenic bacteria. VDR<sup>APC</sup> mice are not only more sensitive to bacterial infection but also to chemical damage. Conversely, this susceptibility in VDR<sup>APC</sup> mice was reduced in case of co-housing with non-VDR<sup>APC</sup> mice, indirectly suggesting a protective role of the microbiome[19]. In SAMP1/YitFcJ (SAMP1) mice which develop spontaneous terminal ileitis, dysbiosis occurred during disease progression with a decrease in *Lachnospiraceae* and in *Bacteroides*. In the same animal model,  $\alpha$ -defensins misfolding was associated with dysbiosis and even induced dysbiosis in wild-type mice[47].

In this regard, the barrier function of the ileum is also a major feature in the understanding of host-microbiota interplay. Accordingly, human  $\beta$ -defensin 3 peptide was decreased and redistributed to the basolateral surface of the ileal epithelium[100]. In parallel, increased enzyme indoleamine 2,3-dioxygenase 1 (IDO1) was found in patients with active CD. This enzyme is the first enzyme in tryptophan metabolism on the kynurenine pathway and is responsible for mucus layer thickening and mucus-associated modulation of microbiota. In a murine enterocolitis model, IDO1 upregulation reduced the abundance of enteropathogenic *E. coli* in the ileum. Likewise, IDO1 downregulated inflammation in response to chemical colitis in mice and augmented *A. muciniphila* and *M. schaedleri* abundance[101].

### AIEC

In the nineties, a French team identified a strain of *Escherichia coli*, AIEC, which was adherent to the ileum without harbouring virulence factor-encoding genes[102]. AIEC was shown to be associated with ileal CD in further studies and to be able to invade epithelial cells[102,103]. Interestingly, AIEC was able to induce granulomas *in vitro*, which is one of the main histologic features of CD[2,104]. AIEC is classically identified on ileal biopsy but a dedicated serology could also be informative and less invasive [105]. The invasive property of AIEC is favoured by the overexpression of the glycoprotein CEACAM6 in the ileal epithelium. The interaction of this glycoprotein with the bacterial adhesive factor FimH promoted AIEC-enterocyte interplay in the ileum[106]. Using this receptor, AIEC modulated the metabolism of the ileal epithelium and induced strong gut inflammation[107]. AIEC induced the expression of hypoxia inducible factor, overexpressed in the ileum of CD patients and promoted barrier defects in the intestinal epithelium paving the way for the onset of inflammation[108].

The relapse of CD in patients after surgical treatment may be used to understand the early steps in CD onset. In a recent prospective, multicentric cohort of patients with ileal resection, AIEC in the remaining ileum was associated with an early ileal lesion of CD recurrence. The presence of AIEC within the surgical ileal specimen was predictive of the endoscopic recurrence of CD[109].

As highlighted in a recently published article, factors influencing ileal susceptibility to AIEC were numerous and among them epigenetic regulators had a modulating effect on a large range of proteins [110]. For this reason, before considering a clinical application in ileal CD, further studies are needed to prevent possible adverse effects induced by the modulation of these epigenetic targets or to identify more specific genes associated with AIEC colonisation. Another promising approach would be the use of bacteriophages to target specifically AIEC in ileal disease[111]. To date, no bacteriophage has been approved for intestinal therapeutic use in human, either in the European Union or in the United States, despite numerous studies that have reported encouraging results *in vivo*. Therefore, data about the effect of bacteriophages on human microbiota are needed in the future[111].

### *F. prausnitzii*

In a stool based multi-omics analysis of 200 IBD patients, the abundance of a member of Firmicutes, *F. prausnitzii*, was highly discriminant of ileal CD compared to colonic CD[89]. Even in non-inflamed ileal samples of CD patients, the commensal bacterium *F. prausnitzii* was decreased in comparison with healthy controls which suggests a relevant causal link between this bacteria and CD onset[112]. Accordingly, a low level of *F. prausnitzii* in the ileal mucosa-associated microbiota was associated with a higher recurrence rate of CD after ileal resection, corroborating the putative role of *F. prausnitzii* in the pathogenesis of ileal CD[113]. In addition, a recent study confirmed the role of *F. prausnitzii* in ileitis after ileocollectomy, pointing to a possible association with a bile salt profile. Thus, elevated levels of primary bile acids were associated with a decreased abundance of *F. prausnitzii*. These two parameters were the only factors associated with ileitis in this cohort of 166 patients[88]. The administration of *F. prausnitzii* or of its supernatant *in vitro* and *in vivo* counterbalanced gut inflammation by blocking nuclear factor  $\kappa$ B activation and IL-8 production[113]. Interestingly, in CD patients, *F. prausnitzii* was associated specifically with ileitis, irrespectively of their genetic background[89,114]. In an original work conducted in twins in whom biopsies were performed in the lower gastrointestinal tract, the abundance of *F. prausnitzii* was specifically decreased in ileal CD, compared to colonic CD or in healthy twins[114].

### Mycobiota

The study of microbiota in IBD is not limited to bacteria but also includes fungi. Fungal microbiota was suspected to be strongly involved in CD pathogenesis in particular because of the diagnosis value of anti-Saccharomyces cerevisiae antibodies in CD[2]. In a study of 168 ileal biopsies, mycobiota was modified in CD patients with an increased abundance of *Malassezia* and a decreased abundance of Saccharomyces. The increase of *Malassezia* was notably associated with a severe evolution of the disease



during follow-up[115].

The fungus *Debaryomyces hansenii* was increased in CD patients with inflamed ileum compared to non-inflamed ileum. Moreover, oral gavage with *Debaryomyces hansenii* impaired crypt regeneration and wound healing after biopsy injury[116].

## ENVIRONMENTAL FACTORS

The microbiota bridges the gap between host susceptibility factors and its environment. Most environmental factors are identified by epidemiological studies and associated with the onset of CD or its recurrence after surgery. Few of them though can impede the natural history of CD once the disease is established.

### Smoking

Cigarette smoking is a well-established risk factor for developing CD[1-3]. In patients with CD, the relative statistical weight of smoking was larger than the relative weight of the genetic variants presented in the previous section[1]. Besides, cannabis is frequently used as a symptomatic treatment by patients with CD involving the ileum and is associated with tobacco[117]. Regarding cannabis use, in a double-blind, randomized, placebo-controlled trial, cannabis oil induced clinical improvement without any endoscopic change[118].

Regarding tobacco, in mice, cigarette smoke extract induced intestinal inflammation and morphometric changes in the ileal epithelium regardless of the route of administration (intragastric or intraperitoneal), advocating for a systemic effect[119]. Moreover, mice exposed to cigarette smoking were more likely to develop pathological inflammation in response to bacterial inflammation which could be the hallmark of an impaired expression of antimicrobial peptides[119]. Besides, smoking was associated with a reduced number of normal Paneth cells in the ileum, both in patients presenting a CD susceptibility allele (ATG16L1<sup>T300A</sup>) as well as in mice presenting this genetic susceptibility. This defect in the ileum was mediated by the Paneth cell apoptosis driven by the activation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and prevented in mice by the use of anti-TNF- $\alpha$  drugs[120].

Moreover, smoking is associated with an upregulation of angiogenesis in smokers with CD compared to their non-smoking counterparts. Importantly, mice exposed to cigarette smoke for 8 wk presented mucosal tissue hypoxia associated with an increased expression of pro-inflammatory cytokines and of angiogenic factors whereas smoking cessation reversed this process in the ileal mucosa. In addition, cigarette smoke exposure was associated with an increased sensitivity to chemically induced colitis [121]. Although genes of hypoxia-inducible factor were overexpressed in the inflamed ileum and in the adjacent mesenteric tissue of CD patients, hypoxia in mice did not impact experimental ileitis[122-124]. All together, these results advocate for a specific impact of tobacco smoking in the pathogenesis of ileitis.

Evidence for other environmental factor is rare in the literature. Recently, serum levels of bisphenol A, a component used in the manufacture of various plastics, have been linked to inflammatory status in CD patients. Furthermore, patients with bacterial DNA translocation presented a higher serum level of bisphenol A associated with a reduced expression of tight junction genes[125].

### Diet

Western diet is characterized by a low intake of fibres contrasting with a high intake of refined sugar, animal protein and total fat. Numerous links between diet and IBD have been established[126]. To that extent, diet modulates the microbiota associated with the ileal epithelium. Thus, AIEC was associated with hyperacetylated histone H3 in the ileal epithelium and consequently histone deacetylase enzymes controlled the entry of AIEC in IECs in a murine model. Interestingly, a high fat diet enhanced histone acetylation in mice compared to a standard diet[110]. Overweight (body mass index > 25 kg/m<sup>2</sup>) in IBD and in non-IBD patients was associated with Paneth cell defects in the ileal epithelium. This defect can be induced by Western diet in mice[93].

Regarding fat intake, the ratio between n-3 and n-6 polyunsaturated fatty acids (PUFAs) is unbalanced in favour of an excessive intake of n-6 PUFAs in Western diet. Oral feeding with n-3 PUFAs in SAMP1/Yit mice ameliorated the histological features of ileitis, and decreased addressin molecule expression (MAdCAM-1) as well as lymphocyte infiltration in the ileum[127]. To that extent, oral supplementation with linseed oil rich in  $\alpha$ -linolenic acid (n-3 PUFAs), in a physically active murine model, reduced inflammation after oral challenge with AIEC[128]. However, oral n-3 PUFAs supplementation has not shown definitive results in patients with CD[129]. In all likelihood, n-3 PUFAs alone are unable to stop the inflammatory loop once started but remain putative candidates to prevent the onset of ileal CD.

Fibre intake was identified as a protective factor against CD onset but not UC[130]. Although epidemiological data were based on a 40-year-old population, fibre intake and more accurately inulin supplementation modulated PPAR $\gamma$  signalling pathway in pigs[131].

Vitamin D deficiency in IBD patients has been reported in numerous studies reviewed elsewhere as an explanation of the North-South gradient of IBD prevalence[132]. In mice fed with a vitamin D deficient diet, miR-142-3p expression was upregulated, culminating in a reduction of ATG16L1 and autophagy specifically in ileal Paneth cells. In a paediatric cohort of IBD patients, colonic samples displayed likewise an enhanced expression of miR-142-3p statistically associated with low serum vitamin D levels[133]. As discussed previously, VDR were overexpressed in the ileum and were involved in the adequate response to enteropathogens[19]. When associated with a high fat diet, vitamin D deficiency and genetic VDR inhibition led to defective Paneth cell defensins secretion and gut permeability driving endotoxemia and systemic inflammation[134].

Last, Western diet is also characterized by a high intake of dietary additives related to the consumption of ultra-processed food. To that extent, dietary emulsifiers carboxymethylcellulose and polysorbate-80 were associated with an increased virulence and enrichment of ileal pathobionts[135].

More generally speaking, diet in patients with ileal CD should be based on the guidelines of the European Society of Nutrition. The findings discussed above and others have led to recommendations for a balanced diet rich in fruit, vegetables and n-3 fatty acids, avoiding a restrictive diet[136]. As highlighted in this European consensus, good quality data regarding the effects of experimental diets are rare in the literature. In particular, there is a lack of randomized control trials to recommend a more specific diet in patients with active ileal CD[136].

## CLINICAL IMPLICATIONS

The factors summarised in the previous paragraphs give rise to a distinctive natural history of ileal CD with specific clinical consequences and interventions necessary.

### **Natural history of ileal CD**

In CD, the shortest time from diagnosis to first surgery is in ileal CD compared to other disease sites. Thus, the median time to surgery in ileal CD is about 6 years. Thirty years after being diagnosed with ileal CD, almost all patients had undergone at least one surgery according to a broad international study [1]. At 12 mo after surgery, a recurrence was observed on colonoscopy, at and above this anastomosis in 73% of patients in absence of any treatment[137]. These data regarding recurrence rates published 30 years ago led to the development of preventive strategies after surgery.

In terms of behaviour, ileal CD was more likely than colonic CD to be complicated by penetrating or stricturing lesions[3]. These severe manifestations contribute to the high rate of surgery. Accordingly, strictures are challenging complications that are usually unresponsive to medical therapy in the absence of surgery[3]. Strictures result from the accumulation of fibrotic protein in the extracellular matrix produced by fibroblasts which are partially derived from epithelial cells *via* epithelial-mesenchymal transition (EMT)[138]. Accordingly, based on a comparative study of ileal *versus* colonic ulcers, EMT appeared to be a highly noticeable feature in ileal ulcers of CD unlike colonic ulcers of CD[55]. Ileal strictures were likely to present mesenteric fat wrapped around the stricture, known as creeping fat [139], which harbours viable bacterial translocation and leads to a pro-fibrosis M2-type microenvironment[140-143]. Remarkably, creeping fat associated with the ileum presented a 10-fold higher concentration of T-cells than colonic fat[144]. In addition, adipocyte hyperplasia was observed in ileal fat unlike colonic fat[144].

### **Beyond the ileum**

Ileal crypts have been reported in the colon of CD patients[12,45]. Recently, the presence of ectopic ileal crypts discriminated IBD subtype in patients with undetermined (unclassified) colitis. The presence of ileal metaplasia in the colon was strongly associated with a final diagnosis of colonic CD[145]. This interesting discovery could enhance understanding of ileal physiopathology, pivotal to understand CD.

In a specific statistical model based on HLA types and single nucleotide polymorphism, colonic CD appeared to be an intermediate between UC and ileal CD[1]. Consecutively, knowledge of ileal CD may pave the way to understanding other phenotypes of CD.

### **A dedicated treatment for ileal CD?**

Logically, the specificities of ileal CD discussed in this review should lead to a dedicated treatment strategy. Nevertheless, current ECCO guidelines on the medical management of CD do not advocate for a specific treatment in ileal CD[146]. Indeed, studies are controversial. Some studies reported a lower rate of response to infliximab, an anti-TNF treatment[147,148]. Conversely, numerous other studies did not describe such a difference in response rates with anti-TNF[149]. This discrepancy may result from a bias such as the extent of the disease irrespectively of the site of the disease. Interventional trials specifically dedicated to the study of ileal CD treatment are henceforth required. In the literature, colonic CD is more likely to respond to treatment compared to ileocolonic CD and mucosal healing may be more difficult to achieve in ileal disease. Likewise, ileal stricturing CD may have lower response rates [149].

As ileal stricture may develop in spite of CD treatment, an American team sought to determine the gene pattern associated with ileal stricturing in a paediatric CD cohort. This analysis identified a long-chain fatty acid, the eicosatetraenoic acid as a possible antifibrotic tool[150]. In a follow-up study, the same team showed a decrease in fibrosis and an improvement in stiffness in human intestinal organoids exposed to eicosatetraenoic acid[151]. In parallel, butyrate, a short-chain fatty acid, also downregulated fibrosis according to the same protocol[151].

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## CONCLUSION

The histological and anatomical features of the ileum are direct answers to the question “why the ileum?”. Furthermore, the recent works presented in this review highlight the specific interplay between environmental factors, like smoking or diet, and the ileum. Currently, the prevailing requirement for surgery in a significant proportion of patients with ileal CD testifies to the urgent need for a dedicated pharmacological approach according to disease site. As the ileum is the site of interplay between host characteristics and environmental influences, a full understanding of the molecular crosstalk that occurs in the ileum is crucial to identify new therapeutic targets to significantly change the natural history of this debilitating disease.

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