Defensin-immunology in inflammatory bowel disease
Rôle des défensines dans la physiopathologie des maladies inflammatoires chroniques intestinales

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Summary
Defensins are endogenous antibiotics with microbicidal activity against Gram-negative and Gram-positive bacteria, fungi, enveloped viruses and protozoa. A disturbed antimicrobial defense, as provided by Paneth- and other epithelial cell defensins, seems to be a critical factor in the pathogenesis of inflammatory bowel diseases. Conspicuously, there is a relative lack of Paneth cell β-defensins HD-5 and HD-6 in ileal Crohn’s disease, both in the absence of a pattern recognition receptor NOD2 mutation and, even more pronounced, in its presence. This deficit is independent of concurrent active inflammation and results in a diminished antibacterial killing by the mucosa. The Crohn’s disease mucosa has not only a significant lack in killing different \textit{Escherichia coli} but also an impaired ability in clearing \textit{Staphylococcus aureus} as well as anaerobic micro-organisms. Thus, this dysfunction in antibacterial barrier seems to be broad and is not restricted to a single bacterial strain. In addition to directly controlling barrier function, Paneth cell defensins also regulate the composition of the bacterial stool flora. In the majority of patients, the Paneth cell deficiency is mediated by WNT signalling which suggests a disturbed Paneth cell differentiation in ileal Crohn’s disease. In contrast, colonic Crohn’s disease is characterised by an impaired induction of mucosal β-defensins, partly due to a low copy number of the β-defensin gene cluster. Therefore it seems plausible that bacteria take advantage of a niche formed by defensin deficiency. This would represent a paradigm shift in understanding Crohn’s disease and provides a target for future therapeutic strategies.

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Résumé
Les défensines sont des « antibiotiques » endogènes exerçant une activité microbicide vis-à-vis de bactéries Gram-négatives et Gram-positives, de levures, de virus encapsulés

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et de certains protozoaires. Dans les maladies inflammatoires chroniques intestinales, la défense antimicrobienne, en particulier par les défensines produites au niveau des cellules de Paneth et des cellules épithéliales intestinales, est anormale. Ainsi, une diminution de production des α-défensines HD-5 et HD-6 par les cellules de Paneth a été décrite dans les formes iléales de la maladie de Crohn, et ceci d’autant plus qu’il existait une mutation dans le gène NOD2. Ce déficit est indépendant de la présence concomitante d’une inflammation muqueuse et se traduit par une diminution de la capacité de la muqueuse intestinale à exercer ses propriétés bactéricides, se traduisant au cours de la maladie de Crohn, par une réduction significative de la capacité de la muqueuse à détruire différentes souches bactériennes d’Escherichia coli, mais aussi de Staphylococcus aureus, ou de bactéries anaérobies. Cette anomalie dans la fonction de barrière antimicrobienne de la muqueuse intestinale n’est donc pas spécifique d’une seule souche bactérienne, mais semble concerner un plus vaste éventail de micro-organismes. Les cellules de Paneth n’interviennent pas uniquement vis-à-vis des bactéries potentiellement pathogènes ; leur activité anti-microbienne contribue également à réguler la composition de la flore digestive commensale. Chez la plupart des malades, les anomalies fonctionnelles des cellules de Paneth sont médiées par la voie WNT, suggérant une anomalie de différenciation de ces cellules dans la maladie de Crohn iléale. En revanche, dans les formes coliques de la maladie de Crohn, les anomalies de la défense anti-microbienne concernent les β-défensines. Au cours de la maladie de Crohn, ce déficit en défensine est donc susceptible de permettre le développement anormal de certaines espèces microbien

Based on current and future studies in animal models and patients, we currently see a paradigm shift in the field of inflammatory bowel diseases. In the past, most of the research focussed on a possibly dys-regulated adaptive immune function. Now, multiple lines of evidence support a primary disturbed barrier function which allows the entry of microorganisms and triggers a mostly secondary inflammatory response. Many scientist and especially physicians are becoming more and more critical about studying inflammatory cascades in artificial mouse models, especially about uncritically extrapolating these studies to human patients. On the other hand, our knowledge of antimicrobial peptides and their role in innate and acquired immunity has increased exponentially over the past decade [1]. A major group of cationic antimicrobial peptides in humans and other mammals are the defensins but there are others including lysozyme, cathelicidine LL37 and antimicrobial antiproteases. It is evident that defects in such a highly conserved defense system could lead to disease. In this review we will focus on inflammatory bowel diseases, one key example of the clinical relevance of innate immunity. Recent reviews have covered various aspects of the defensins, including general overviews [2], defensins in the gastrointestinal tract [3], and more specifically defensins in Crohn’s disease [4], an inflammatory disease of the intestinal tract. Inspired by recent studies this review focuses on the various known mechanisms of gastrointestinal defensin deficiency. In this review we aimed to express our opinion about recent data and the role of distinct defensin deficiencies in patients with inflammatory bowel disease. We are convinced that the discovery of some of these innate immune defects in gastrointestinal diseases will not only change the appreciation of the importance of host defense but also lead to new strategies of therapy.

**Antimicrobial peptides as guardians against gastrointestinal bacteria**

Although the gastrointestinal tract is colonized by and exposed to a multitude of different bacteria, intestinal infection or translocation of bacterial agents is the exception, not the rule, and mostly limited to highly pathogenic bacteria or predisposing disease states. The constitutive production of antimicrobial peptides including defensins, defensin like molecules (elafin and secretory leukocyte protease inhibitor (SLPI)), cathelicidine LL37 and other protective factors (e.g. mucus, trefoil factors and many others) in the intestinal tract helps to limit invasion and adherence of pathogenic and commensal bacteria. Defensins are endogenous antibiotics with microbicidal activity against Gram-negative and Gram-positive bacteria, fungi, viruses and protozoa [5]. While many defensins are mostly expressed in epithelial cells, defensin like peptides (elafin and SLPI) are of epithelial and Leukocyte origin [6]. All these molecules have similar biochemical properties like low molecular mass, cationic charge and disulfide-bonds. In their function as serine protease inhibitors, elafin and SLPI seem to be critical in maintaining tissue integrity by antagonising aggressive serine proteases like human neutrophil elastase (HNE) [7]. In addition they serve as antimicrobials with a broad spectrum against Gram-positive and Gram-negative bacteria, selected fungi as well as different viruses [6]. Another antimicrobial
peptide mostly directed towards gram-negative bacteria is bactericidal/permeability-increasing protein (BPI). Elegant functional studies revealed that epithelial BPI contributes significantly to lipid mediated bacterial killing and the attenuation of bacterial-elicited proinflammatory signals [8, 9].

In the gastrointestinal tract, defensins help regulate the composition and number of colonizing microbes, and protect the host from food-borne and water-borne pathogens. The proposed physiological functions of the intestinal defensins can be grouped into several overlapping categories. In the large intestine, the physiology is different from the small intestine, mostly because of the very high density of colonizing microbes [10]. It is remarkable that infections and translocation across the colonic mucosa by these bacteria are uncommon, considering that an epithelium with a single cell layer separates the bowel from the microbe-laden lumen. A leading hypothesis holds that the colon is a complex ecosystem with dynamic interactions between dense resident microflora, the colonic epithelial cells and the classical immune cells [11]. When the ecosystem is in balance, epithelial cells prevent microbial invasion by providing a strong chemo-mechanical barrier, including the constitutive human β-defensin HBD1 [12]. Only during inflammation or infection is the synthesis of additional defensins and other antimicrobial peptides by the colonic mucosa induced. In the latter case, defensins may prevent further bacterial entry into an already compromised epithelium and contribute to antimicrobial defense during inflammation at this site. Thus, it may be of relevance that the human β-defensin HBD2 is regulated by NF-κB-dependent pathways, because this transcription factor also regulates many proinflammatory cytokines [13]. Paneth cell metaplasia at various sites of inflammation along the gastrointestinal tract [14-16] seems to be an alternative “on-demand” mechanism that provides antimicrobial expression and protection.

In contrast, the number of bacteria is very low in the small intestinal tract. This seems to be due, at least in part, to the extremely abundant constitutive expression of α-defensins which are expressed by crypt Paneth cells [17] with almost exclusive physiological expression in the small intestine [18]. It should be emphasized that the exceptional expression of metaplastic Paneth cells (mentioned above) throughout the intestinal tract occurs at much lower levels. In addition, the Paneth cell defensins regulate the composition and number of luminal colonizing microbes present in the small intestine [19], and protect the host from food-borne and water-borne pathogens [20, 21]. Paneth cell antimicrobials, which are stored in secretory granules, are released into the intestinal lumen on stimulation with bacterial products including lipopolysaccaride (LPS) and muramyl dipeptide (MDP) [22], the specific ligand of NOD2 [23].

### Defensins in inflammatory bowel diseases

Inflammatory bowel disease (IBD) is a chronic inflammation of the intestine. On the basis of its clinical features and histopathology it is often grouped into two major entities, ulcerative colitis and Crohn’s disease. In both forms of IBD, intestinal commensal microbiota are thought to trigger the disease in genetically susceptible individuals. Although the inflammation seen in patients with ulcerative colitis is typically restricted to the colon, that of Crohn’s disease occurs at many sites, most commonly in the small intestinal ileum and in the colon [24]. Our hypothesis of the key mechanism leading to Crohn’s disease is based on slow bacterial invasion due to compromised defense by mucosal peptide antibiotic including defensins. This concept is based on patient and confirmative mouse data and is not mutually exclusive to other more classical explanations which mostly hypothesize about a suggested primary role of a possibly dysregulated adaptive immune system. About a third of patients with Crohn’s disease have a mutation in the NOD2 gene, which encodes an intracellular bacterial pattern-recognition receptor (for a very recent review see [25]). Further clinical analyses have revealed that this mutation is associated with the clinical phenotype of ileal Crohn’s disease but not with the colonic type of Crohn’s disease (for review see [26, 27]). Recent lines of investigations demonstrated that these different clinical localizations of Crohn’s disease are associated with different deficiencies in epithelial and leukocyte antimicrobial peptide expression and function [5] (Table 1). As compared with ulcerative colitis, Crohn’s disease

### Table 1 Antimicrobial peptide expression in ulcerative colitis, colonic and ileal Crohn’s disease.

**Expression des peptides antimicrobiens dans la rectocolite hémorragique, la maladie de Crohn colique, et la maladie de Crohn iléale.**

<table>
<thead>
<tr>
<th>UC (colon)</th>
<th>CD (colon)</th>
<th>CD (ileum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal expression of beta defensin HBD1 and regular induction of HBD2, HBD3 and HBD4</td>
<td>attenuated induction of beta defensins HBD2, HBD3 and HBD4</td>
<td>specific reduction of ileal Paneth cell defensins (HD5 and HD6), even more pronounced in patients with a NOD2 mutation (in both cases independent of the grade of histological inflammation and not observed in inflammatory controls)</td>
</tr>
<tr>
<td>regular induction of antimicrobial antiproteases Elafin and SLPI</td>
<td>attenuated induction of antimicrobial antiproteases Elafin and SLPI</td>
<td>regular induction of BPI</td>
</tr>
<tr>
<td>regular induction of cathelicidin LL37</td>
<td>attenuated induction of cathelicidin LL37</td>
<td>overall reduced mucosal antibacterial activity</td>
</tr>
<tr>
<td>HD5 and HD6 expression due to metaplastic Paneth cells</td>
<td>HD5 and HD6 expression due to metaplastic Paneth cells</td>
<td>towards different bacteria</td>
</tr>
<tr>
<td>regular induction of BPI</td>
<td>regular induction of BPI</td>
<td>overall reduced mucosal antibacterial activity</td>
</tr>
</tbody>
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UC: ulcerative colitis, CD: Crohn’s disease
disease of the colon is characterized by an impaired induction antimicrobial antiproteases elafin and SLPI [28], the cathelicidin LL37 [29] and most importantly β-defensins [30-33]. As a consequence, the attenuated expression of antimicrobials, the colonic mucosa is compromised in their killing capacity towards different commensal bacteria. In contrast, ileal Crohn’s disease patients are characterized by a reduced antibacterial activity and a specific reduction of ileal Paneth cell defensins. This decrease is independent of the grade of histological inflammation and cannot be found in inflammation controls like UC ileitis in pouch (after colorectal removal). Some of these defects can be explained either by direct or indirect genetic mechanisms and appear to be primary. In the following, we will describe some of the known mechanisms which provide insights into relevant regulation of these antimicrobial defense molecules.

**Mechanism of β-defensin deficiency:**
Gene copy number polymorphisms

The first defensin to be identified in the human large bowel was the constitutively expressed HBD1 [12], and so far it is the only defensin known to be expressed in the uninfamed colon. Expression of HBD1 mRNA seems to be slightly reduced in the inflamed tissue of patients with IBD [30, 31]. In contrast to HBD1, the inducible β-defensin HBD2 is absent from the healthy colon [13]. Several studies have investigated the expression of HBD2 in ulcerative colitis finding a strong induction in case of inflammation [13, 30-32]. When comparing colonic HBD2 expression among patients with Crohn’s disease and ulcerative colitis there is a striking difference: whereas in ulcerative colitis patients strong HBD2 induction is observed, this induction seems to be attenuated in the inflamed tissue of Crohn’s disease patients [30, 31]. Two β-defensins with a different antimicrobial spectrum, HBD3 and HBD4, seem to follow this distribution pattern, although their mRNA expression levels are lower [30, 33].

Crohn’s disease of the colon is among the first diseases, with a known association of lower expression of a gene cluster [34]. Notably, the DNA copy number of the beta-defensin gene cluster on chromosome 8p23.1 is highly polymorphic within the healthy population, which suggested that the defective β-defensin induction in colonic CD could be due to low beta-defensin-gene copy number. We recently tested this hypothesis, using genomewide DNA copy number profiling by array-based comparative genomic hybridization and quantitative polymerase-chain-reaction analysis of the human beta-defensin 2 (HBD2) gene. We showed that healthy individuals, as well as patients with ulcerative colitis, have a median of 4 (range 2-10) HBD2 gene copies per diploid genome. In a surgical cohort with ileal or colonic CD and in a second large cohort with inflammatory bowel diseases, those with ileal resections/disease exhibited a normal median HBD2 copy number of 4, whereas those with colonic CD had a median of only 3 copies per genome. Overall, the copy number distribution in colonic CD was shifted to lower numbers compared with controls. Individuals with < or = 3 copies have a significantly higher risk of developing colonic CD than did individuals with > or = 4 copies (odds ratio 3.06; 95% confidence interval 1.46-6.45). An HBD2 gene copy number of < 4 was associated with diminished mucosal HBD-2 mRNA expression. In conclusion, a lower HBD2 gene copy number in the beta-defensin locus predisposes to colonic CD, most likely through diminished beta-defensin expression. Since HBD3 and HBD4 are on the same gene locus, it is likely that the expression pattern of these other inducible beta defensins is due to the same mechanism.

To elucidate possible functional consequences of this deficiency we investigated the antimicrobial activity in colonic mucosa from patients with inflammatory bowel disease and healthy controls. For that, we established a flow cytometric assay to quantitate bacterial killing [35] and tested the antibacterial activity of cationic peptide extracts from colonic biopsies taken from patients with active or inactive ileocolonic or colonic Crohn’s disease, ulcerative colitis and controls against clinical isolates of different bacteria (including *Bacteroides vulgatus*, *Enterococcus faecalis* as well as reference strains of *Escherichia coli* and *Staphylococcus aureus*). Consistent with the previous findings, there was a reduced antimicrobial effect in Crohn’s disease extracts which was most evident against *Bacteroides vulgatus* [36]. Also the antimicrobial effect against *Escherichia coli* and *Enterococcus faecalis* was significantly lower in Crohn’s disease compared to ulcerative colitis. Activity against *Staphylococcus aureus* disclosed a similar pattern although less pronounced. The differences were independent from the inflammation status or concurrent steroid treatment. Bacteria incubated with biopsy extracts from ulcerative colitis patients showed frequently a characteristic change in cell size and granularity, compatible with more extensive membrane disintegration, compared with bacteria incubated with extracts from controls or Crohn’s disease. Thus, Crohn’s disease of the colon, like that in the small intestine, is characterized by a diminished functional antimicrobial activity [19, 36] which is consistent with the reported low antibacterial peptide expression.

**Mechanisms of Paneth cell α-defensin deficiency**

**Pattern recognition receptor NOD2**

In the small intestinal mucosa, NOD2 is expressed in Paneth cells, which is consistent with a possible role for Paneth cell antimicrobials in Crohn’s disease [5]. Independent studies in humans and a rodent model substantiate a link between NOD2 mutations, Paneth cell defensins and Crohn’s disease [19, 37, 38].

A decrease of Paneth cell α-defensin, i.e. HD5 and HD6, mRNA and protein has been shown in patients with Crohn’s disease of the small intestinal ileum. Interestingly, even though essentially all patients with ileal Crohn’s disease had diminished HD5 and HD6 levels, this decrease was most pronounced in patients with a NOD2 mutation. In the same patients the mRNA expression levels of proinflammatory cytokines TNF-α and IL-8 were independent of NOD2 status. By contrast, ileal levels of Paneth cell α-defensins from patients with Crohn’s disease of the colon were unchanged. In a further study in German and U.S. patient populations the decreased expression of Paneth cell α-defensins was confirmed both for mRNA and protein, whereas the
expression of other Paneth cell products either remained unchanged or increased when compared with controls [19]. The specific decrease of α-defensins was independent of the degree of inflammation in the specimens and was not observed in either Crohn’s disease of the colon, ulcerative colitis, or most importantly pouchitis, as an inflammatory control of non-Crohn’s ileitis. The functional consequence of the low α-defensin levels was a diminished antibacterial activity in ileal mucosal extracts [19].

In a subsequent study using a rodent model, Kobayashi and colleagues reported a decrease of Paneth cell α-defensin (cryptdin) mRNA expression in mice lacking the NOD2 gene [38]. The NOD2 knockout mice were unable to detect muramyl dipeptide, the ligand for NOD2. Most interestingly, these mice were more susceptible to an oral, but not systemic, infection with the pathogenic bacterium L. monocytogenes, supporting the importance of NOD2 in epithelial antimicrobial function [38]. Taken together, these results suggest that there is a link between NOD2 function and α-defensin expression, but the mechanistic details are still obscure. Furthermore, the studies of patients with ileal Crohn’s disease suggest that reduced Paneth cell defensins is ultimately linked to disease. Possibly, inadequate activation of proHD-5 is another mechanism contributing to compromised antibacterial activity [39].

Epithelial stem cell differentiation mediated by Wnt signaling

As mentioned above, NOD2 mutations provide one relevant mechanism for the decrease of Paneth cell defensins. Since this decrease is found in essentially all patients with ileal disease and only about a third have NOD2 mutations, there must be other mechanisms. Paneth cells derive from a compartment of progenitor cells located just above their crypt base location. Accordingly, their migration from these stem cells is downwards as opposed to the upward migration of the absorptive epithelial cells towards the villus tip. Wnt signalling which is transduced through β-catenin/Tcf-4 has been shown to maintain the undifferentiated state of the progenitor cells [40] and, paradoxically, also induces maturation of Paneth cells in intestinal crypts [40]. In elegant studies the group of Hans Clevers in Utrecht clearly demonstrated that a Paneth cell gene program is critically dependent on Tcf-4 embryonic mouse intestine [41]. This pathway is also disturbed in ileal Crohn’s disease patients [42]. We recently reported a reduced expression in ileal Crohn’s disease of the Wnt-signaling pathway transcription-factor Tcf-4, a known regulator of Paneth cell differentiation. Within specimens, the levels of Tcf-4 mRNA showed a high degree of correlation with both HD5 and HD6 mRNA. The levels of Tcf-4 mRNA were decreased in patients with ileal disease irrespective of degree of inflammation, but were not decreased in colonic Crohn’s disease or ulcerative colitis. As a functional indicator of Tcf-4 protein, quantitative binding analysis with nuclear extracts from small intestinal biopsies to a Tcf-4 high-affinity binding site in the HD-5 and HD-6 promoters showed significantly reduced activity in ileal CD. Furthermore, a causal link was shown in a murine Tcf-4-knockout model, where the comparably reduced expression of Tcf-4 in heterozygous (+/) mice was sufficient to cause a significant decrease of both Paneth cell α-defensin levels and bacterial killing activity. Notably, the association between Paneth cell α-defensins and Tcf-4 was found to be independent of NOD2 genotype. This new link established between a human inflammatory bowel disease and the Wnt pathway/Tcf-4 provides a novel mechanism for pathogenesis in patients with ileal Crohn’s disease [42].

Therapeutic implications

Knowledge about defensins and other antimicrobial peptides could have a substantial influence on future therapeutic strategies. For the treatment of IBD, future strategies might aim to strengthen protective innate immunity. Some interesting experimental observations leave room for speculation. For example, zinc depletion has a crucial impact on Paneth cell integrity and antimicrobial function [43,44]. Conversely, supplementation with zinc significantly reduces mortality in childhood diarrhea [45]. A possible explanation for this clinical observation is that zinc may bolster Paneth cell function by as yet unknown mechanisms.

As discussed above, Paneth cell-derived antimicrobials are decreased in patients with ileal Crohn’s disease. In this context, the reported efficiency of Trichurus suis therapy in Crohn’s disease provokes the testable question of whether the stimulation of Paneth cell defensins by parasitic worms might be an explanation for their therapeutic effect [46]. Probiotic bacteria like E. coli Nissle 1917 and Lactobacilli, have been shown to induce antimicrobial peptides strongly [47]. In case of E. coli Nissle, this induction is mediated by a specific Flagellin [48] and further work will elucidate additional stimulators in other strains. E. coli Nissle 1917 (Mutafior®) is the oldest known (in use since World War I, 1917) and probably the best studied probiotic strain. Its efficacy in maintaining remission in ulcerative colitis (as effective as standard treatment with mesalazine) has been shown in different placebo controlled, double blinded studies and this strain is now recommended as a guideline therapy by the Deutsche Gesellschaft für Gastroenterologie (DGVS) [49-51]. Even though this strain is clearly effective in ulcerative colitis (and probably other probiotics too), probiotic treatment in Crohn’s disease seems to be limited and less useful. A possible but speculative explanation could be a general defect in the upregulation of defensins and other protective host molecules. We believe this might be an important mechanism to help the mucosa to prevent bacterial invasion. Probiotic bacteria are the first therapeutic agents for IBD that we know bolster the production of antimicrobial peptides but it is likely that other therapeutic agents like worm eggs, specific bacterial, food or artificial components could have similar effects (Figure 1).

Conclusion

Almost hundred years after the pioneer Fleming described antibiotic activity of lysozyme in mucosal secretions, the paramount importance of other antimicrobial peptides is becoming slowly accepted. The gastrointestinal tract is a particularly critical site because it has a large surface area that is heavily colonized with microbes. Defensins
and other antimicrobial peptides provide a critical mucosal defense. Defensins have a potent protective activity against a wide range of microbes and can also signal to the various components of the innate and adaptive immune systems. A complex and finely tuned system of regulation and function of intestinal antimicrobial peptides probably contributes to the maintenance and balance of commensal flora in a healthy gut. Disruption of this critical balance could lead to gastrointestinal infection and disease. We believe that this knowledge will result in new therapeutic avenues in the near future.

**Conflict of interest:**

Jan Wehkamp, Eduard Stange and Klaus Fellermann have no conflict of interest.

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**Figure 1** Proposed model for the role of intestinal bacteria and host defensins in the pathogenesis and disease progression of Crohn's disease. The healthy intestinal tract is characterized by a sensitive balance of host antimicrobial peptides and intestinal microbes (above). In Crohn's disease this balance is disturbed. Owing to insufficient expression and function of antimicrobial defensin molecules intestinal microbes are able to invade the mucosa. With further progression of disease the bacterial influx provokes an inflammatory response. Figure reproduced with permission from Wehkamp et al. (www.nature.com) [52].

**Rôle potentiel des bactéries intra-luminales digestives et des défensines intestinales dans la pathogénie de la maladie de Crohn.** L'intestin sain est caractérisé par un équilibre fin entre les micro-organismes présents dans la lumière digestive et les peptides antimicrobiens produits par certaines cellules de la muqueuse intestinale (en haut). Cet équilibre est perturbé dans la maladie de Crohn : du fait d’un défaut d’expression et d’anomalies fonctionnelles des défensines antimicrobiennes, certaines bactéries deviennent capables d’envahir la muqueuse intestinale et de susciter progressivement une réponse inflammatoire et immunitaire muqueuse. Figure reproduite avec autorisation (www.nature.com) [52].


