What is the origin of ulcerative colitis? Still more questions than answers

Milan Lukas, Martin Bortlik, Zdenek Maratka

Despite more than a century of existence as a clinical entity, the true origin of ulcerative colitis still remains elusive. Several factors probably contribute to the development of this condition. Recently discovered technologies have clarified the role of bacterial species, which may account for intestinal dysbiosis, as a factor triggering ulcerative colitis. Genetic susceptibility together with abnormal innate immunoreactivity probably comprise the essential prerequisites for the initiation and perpetuation of ulcerative colitis. Although the genetic background has been more clearly recognised in patients with Crohn’s disease than in those with ulcerative colitis, some candidate loci associated with ulcerative colitis have also been intensively studied. Additionally, environmental factors may interfere with inherent predispositions to ulcerative colitis, and either suppress or reinforce them. Whatever the origin, the search for the aetiology of ulcerative colitis must have the same goal: the improvement of treatment and the quality of life in patients with ulcerative colitis.

Ulcerative colitis, together with Crohn’s disease, is part of the spectrum of inflammatory bowel diseases (IBDs). It is a chronic inflammatory condition with unknown aetiology and only a partially understood pathogenesis. Starting from the rectum, the disease may affect the mucosa of the large bowel to varying lengths. A typical clinical course of ulcerative colitis consists of rectal bleeding and diarrhoea; in severe cases, however, a systemic inflammatory reaction also becomes apparent. Moreover, at least 11% of patients with ulcerative colitis have extraintestinal manifestations that include joint involvement (enteropathic arthritis), hepatobiliary disease (primary sclerosing cholangitis), and several types of eye and skin lesions.

Worldwide, the incidence of ulcerative colitis varies greatly from 0.5 to 24.5 per 100,000 inhabitants. Both the incidence and prevalence are related to the economic situation of a country, with the lowest rates in developing countries and the highest found in North America, as well as western and central Europe. At present, the incidence of ulcerative colitis seems to be increasing in central and eastern Europe, whereas it has been stable over the past 20 years in western Europe and the Scandinavian region.

AETIOLOGY

Although ulcerative colitis has been known as a clinical entity since 1859, the aetiological mystery has not yet been completely revealed. However, the incorporation of new molecular biology techniques has yielded considerable progress in the understanding of the aetiology of ulcerative colitis.

What is the role of the intestine’s bacterial contents in ulcerative colitis?

Some of the similarities between ulcerative colitis and infectious colitides have led many investigators to search for the unidentified microorganism triggering the chronic inflammation in the large bowel. However, until now, no single microbial agent has been associated, unequivocally, with the development of ulcerative colitis. Many arguments exist against an infectious aetiology of ulcerative colitis (box 1).

Over the past few years, we have gained considerable evidence that it is an abnormal mucosal immune reactivity, against enteric bacteria, that is the key event leading to intestinal injury in patients with IBD. Molecular biology techniques have shown that the intestinal space of an adult may contain >500 different bacterial species; some of them exert a protective role, whereas others are aggressive. The number of bacterial strains along the small bowel progressively increases, with the predominance of Gram-negative aerobes. The bacterial population in the large bowel reaches a density of around $10^{12}$ microbes per gram of luminal contents. More than 50% of the bacterial strains cannot be cultured under conditions currently available. In adults, the faecal bacterial composition is host specific and stable over time, with small fluctuations of the strains up to 20% (box 2).

The gut bacteria have an essential role in the development of the gut immune system, as they stimulate the lymphocytes to clonal expansion and also prevent lymphocyte apoptosis. Selective bacterial stimulation may occur, with Gram-positive bacteria preferentially stimulating interleukin (IL)12 production, whereas Gram-negative organisms induce IL4 production. Gram-negative bacteria and lipopolysaccharide are responsible for inducing oral tolerance.

Although standard cultivation techniques are capable of detecting up to 30% of total microflora, new techniques (including analysis of the intestinal flora, new techniques (including analysis of

Abbreviations: IBD, inflammatory bowel disease; MDR1, multidrug resistance gene 1; NOD, nucleotide-binding oligomerisation domain; TLR, toll-like receptor
bacterial 16S ribosomal RNA, polymerase chain reaction, in situ hybridisation, flow cytometry and DNA microarray or chip analysis) have markedly increased the detection rate. The beneficial bacterial strains, such as bifidobacteria and lactobacilli, are generally absent from mucosa-associated bacterial flora in patients with active ulcerative colitis. On the other hand, an increased mucosal concentration of Gram-negative anaerobes, particularly Escherichia coli, Fusobacterium varium and bacteroïdes, along with a high frequency of Peptostreptococcus invasion, has been shown. Various authors have also shown severe bacterial invasions of the mucosa in most colonic specimens from patients with ulcerative colitis, contrary to that in healthy controls. 

The high bacterial mucosal invasion in patients with IBD corresponds well with titres of immunoglobulin G to bacterial antigens. Some of these can now be used for distinguishing ulcerative colitis (eg, anti-Peptostreptococcus anserobius antibody) and Crohn’s disease (eg, anti I2-from Pseudomonas fluorescens antibody or antibody to an outer membrane porin of E coli—anti-OmpC). Nevertheless, these differences in bacterial mucosal concentrations between ulcerative colitis and Crohn’s disease were not found by several investigators. The determination of our intestinal flora was previously proposed to be partially under genetic control. Changes in the faecal flora were also found among healthy relatives of patients with IBD. However, the question of whether the dysbiosis in patients with ulcerative colitis is the cause or the consequence of the disease still lacks a satisfactory answer.

The role of intestinal bacteria in the aetiopathogenesis of ulcerative colitis can be summarised as follows:

- Microbial flora in patients with ulcerative colitis differs considerably from that in controls, in both composition and spatial distribution (mucosal invasion).
- Some commensal bacterial strains exert an essential role in mucosal homeostasis and the maturation of the intestinal immune system.
- Commensal bacterial strains are required to induce chronic inflammation in genetically susceptible mice or rats, and different bacterial species have a variable ability to induce chronic intestinal inflammation in these animals.
- Evidence from intervention studies with probiotics (E coli strain Nissle 1917, VSL #3), helminths (Trichuris suis) or antibiotics (rifaximin) in patients with ulcerative colitis supports therapeutic gains from manipulation of the bacterial flora.

### Box 2: Factors modifying the intestinal bacterial profile
- Western type of diet
- Use of antibiotics and chemotherapeutics
- Modern infant nutrition
- Public health measures
- High hygienic standards and sanitation

### Role of epithelial cells
Over the past two decades, many abnormalities have been described in the epithelial cells of patients with ulcerative colitis (box 3). This, conceptually, is based on the anatomical distribution of inflammation, which in the case of ulcerative colitis is associated predominantly with the rectum. Why such abnormalities are seen in patients with ulcerative colitis still remains elusive. The question is whether luminal factors, autoimmunity or a genetic basis is the major contributor to the aetiology of ulcerative colitis, or whether some combination of any or all of them accounts for the development of the disease.

The newer approaches are focused on the interactions among epithelial cells and indigenous bacterial flora. The cells that comprise the intestinal epithelium have evolved sophisticated mechanisms for the identification of pathogens and counteractions against them, when necessary. These mechanisms include several recognition receptors with various locations on and in the cells, including toll-like receptor (TLR) and nucleotide-binding oligomerisation domain (NOD) receptor. Bacterial ligands binding to host cell receptors induce cellular signalling events, leading to the production of various molecules, including cytokines, eicosanoids and antimicrobial peptides. It has been hypothesised that disturbances in the recognition of molecular patterns on pathogens or commensal microflora might induce chronic and unrestricted inflammation. Members of the TLR family are variably expressed throughout the intestine and display compartmentalisation. TLRs were found to play a key part in the defence against infections by Gram-positive bacteria and fungi. To date, 10 mammalian TLRs have been identified, responsible for recognising conserved bacterial structures. TLR4, encoded by gene polymorphisms is suggested to be responsible for the aetiology and pathogenesis of ulcerative colitis (fig 1).

Antimicrobial peptides are positively charged polypeptides, <100 amino acids in length, which are implicated in the microbial activity associated with phagocytes, inflammatory body fluids and epithelial secretions. Two of them, cathelicidins and defensins, exert antimicrobial effects and communicate with the host immune system, including neutrophil chemotaxis and recruitment of mastocytes.
family). Substantial experimental evidence supports the NOD family receptors. Pathogenic gut bacteria stimulate the preformed membranous receptors (TLR) or by intracellular based on the rapid recognition of bacterial antigens, either by mucosa through the activation of an innate immunity. It is immune responses. Close contacts between the intestinal epithelial cells and bacteria preserve homeostasis on the immune system by using anti-bacterial strategies. The disturbances of intestinal mucosal immunity and defective interaction between commensal flora and immune compartments can lead to immunoregulatory disorders, including IBD. Owing to the high hygienic standards in developed countries, the contact between commensal bacterial flora and immunocompetent cells in the bowel is dramatically reduced in early childhood. Consequently, the loss of a tolerance to bacterial antigens may cause chronic intestinal inflammation later on. Such an explanation is called the "hygienic hypothesis".

Defensins are heterogeneous peptides, which are produced by epithelial cells (α subfamily) or by Paneth cells (β subfamily). Substantial experimental evidence supports the important role of a deficiency of defensins in patients with Crohn’s disease, and of disturbances in the secretion and harbouring of these peptides in the epithelial mucous layer in those with ulcerative colitis.

An understanding of the role of indigenous bacteria in promoting the development of healthy mucosal barrier function brings new light to the fundamental causes of ulcerative colitis. Manipulation of the intestinal microbial flora, by use of probiotics or antibiotics, may be to be a new and promising therapeutic modality in the near future.

**IS ULCEARATIVE COLITIS AN IMMUNOREGULATORY DISEASE?**

Bacterial content of the gut permanently stimulates epithelial cells and the gut lymphoid tissue in both local and systemic immune responses. Close contacts between the intestinal epithelial cells and bacteria preserve homeostasis on the mucosa through the activation of an innate immunity. It is based on the rapid recognition of bacterial antigens, either by preformed membranous receptors (TLR) or by intracellular NOD family receptors. Pathogenic gut bacteria stimulate the production of pro-inflammatory cytokines (eg, tumour necrosis factor α, interferon γ) by activating the transcription of relevant genes. In the case of invasion of non-pathogenic microbes into the mucosa in healthy people, the regulatory cytokines (eg, transforming growth factor and IL10) are produced by immunocompetent cells. It must be emphasised that some bacterial strains (Lactobacillus, E coi strain Nissle 1917) down regulate the release of pro-inflammatory cytokines and induce the apoptosis of activated lymphocytes.

Epithelial cells have an important role not only in the development of innate immunity but also in the induction of memory pathways of acquired immunity. The main places where the acquired immune response takes place are at Peyer’s patches and lymphatic follicles. The specialised dendritic cells transmit bacterial antigens to the lymphatic tissue to initiate the clonal expansion of T or B cells. The naïve T cells then undergo differentiation into Th1, Th2 or T regulatory cells (Th3, Tr1 or CD25+ CD4+). These subpopulations of lymphocytes have markedly different effector capabilities. The major determining factor for T cells still remains to be completely elucidated. During the 1990s, some insights into the cell-to-cell mediators (cytokines) were obtained with the conception of the “Th1 and Th2 paradigm” in Crohn’s disease (Th1) and ulcerative colitis (Th2). Nowadays, the reality seems to be much more complicated, and a strict differentiation between the two diseases, according to major cytokines, is far from perfect.

Both ulcerative colitis and Crohn’s disease have a complex genetic basis, with many associated genes and great heterogeneity, but the genetic influence is much better recognised currently in Crohn’s disease than in ulcerative colitis. Moreover, the disease phenotype is further modified considerably by gene interaction and by the influence of several external factors.

In the past decade, more than 10 genome-wide screening and various linkage studies have delineated at least nine IBD susceptibility loci (IBD1–IBD9). Many independent studies have shown that the NOD2/CARD15 polymorphism is not linked to ulcerative colitis, whereas Crohn’s disease susceptibility is increased in European and American Caucasian carriers of the NOD2/CARD15 polymorphism. Nevertheless, several other genes have been studied as candidate loci linked to ulcerative colitis. Experimental studies have shown that multidrug resistance gene 1 (MDR1)-deficient mice develop colitis. Additional clinical studies showed that two polymorphs (C3435T and G2677T/C) of the MDR1 gene are associated with ulcerative colitis. The human MDR1 codes for a P-glycoprotein that constitutes a barrier against xenobiotics. Polymorphism of this gene causes lower protein expression, and seems to be crucial in the defence against intestinal bacteria. However, other case–control studies did not confirm this finding. In the near future, outcomes of some ongoing studies on the IBD3 and IBD6 loci are expected. IBD3, located on chromosome 6p, contains the major histocompatibility complex genes.

**Box 4: Arguments supporting a genetic basis in ulcerative colitis**

- Familial aggregation of ulcerative colitis (inflammatory bowel disease (IBD))
- Association with rare hereditary syndromes (glycogenosis, Hermansky–Pudlak syndrome)
- Similar patterns of ulcerative colitis (IBD) in family members
- High incidence of ulcerative colitis (IBD) in some ethnic groups (eg, Ashkenazi Jews)

**GENETIC BACKGROUND OF ULCERATIVE COLITIS**

Increasing evidence suggests the importance of genetic susceptibility in the aetiology of IBD (box 4). Genetic susceptibility, bacterial antigens and disturbed mucosal immune response are the major factors of intestinal inflammation. Modifying factors may further serve as triggers or suppressors of the inflammation. HLA, human leucocyte antigen; IFN, interferon; IL, interleukin; MDR1, multidrug resistance gene 1; NF, nuclear factor; TNF, tumour necrosis factor; UC, ulcerative colitis.

**Figure 1** Schematic view of the current concept of the aetopathogenesis of ulcerative colitis and inflammatory bowel disease. Genetic susceptibility, bacterial antigens and disturbed mucosal immune response are the major factors of intestinal inflammation. Modifying factors may further serve as triggers or suppressors of the inflammation. HLA, human leucocyte antigen; IFN, interferon; IL, interleukin; MDR1, multidrug resistance gene 1; NF, nuclear factor; TNF, tumour necrosis factor; UC, ulcerative colitis.

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According to preliminary results, human leucocyte antigen alleles relevant to IBD seem to differ among ethnic groups (HLA-DRB1*0103). The IBDD locus encompasses the gene encoding integrin-binding membrane protein, which is crucial for immune cellular adhesion and trafficking.26 The close association between the polymorphism of members of the nuclear factor κB (NFκB) family and IBD has recently been described.27 This linkage study, focused on the polymorphism of the promoter region of the human NFκB1 gene on chromosome 4q (the most prominent member of NFκB family), which is involved in a variety of regulatory processes (including innate and adaptive immunity, cellular growth, apoptosis and cell differentiation), has also been carried out in patients with ulcerative colitis.31 The authors found an increased frequency of the −94ATTG deletion polymorphism of the NFκB1 promoter in Dutch Caucasian patients with ulcerative colitis as compared with controls. Furthermore, homozygotic patients with a −94ATTG deletion were younger at onset of ulcerative colitis than non-homozygotic patients. The exact mechanism underlying the NFκB1-related disease susceptibility to ulcerative colitis remains unknown. One explanation might be a poor innate immune response to bacterial antigens owing to the low level of transcriptional proteins, leading to an invasion of the bacterial strains into the mucosa and the induction of chronic inflammation. Also currently being studied intensively are the genes encoding TLR4 and TLR9 that modify responsiveness to intraluminal antigens in the gut.26 Despite all the new data mentioned above, genetic susceptibility to ulcerative colitis remains unknown. One explanation might be that emotionally negative life events (eg, bereavement, depression or divorce) can provoke relapses of ulcerative colitis.25–26 In contrast with these findings, no study (so far) has brought forward any evidence that therapeutic manipulation reducing stress in patients with IBD notably influences the number, duration, frequency or severity of relapses of ulcerative colitis.32 Obviously, well-designed, prospective clinical investigations, assessing the relationships between life events and ulcerative colitis patterns, are difficult to carry out.

Smoking and oral contraceptives
Ulcerative colitis predominantly affects non-smokers and former smokers. Smoking improves the course of ulcerative colitis and decreases the need for oral steroids and the colectomy rate compared with that in non-smokers. A meta-analysis of several large series of patients with ulcerative colitis showed an odds ratio of 0.57 (95% confidence interval (CI) 0.38 to 0.85) for total colectomy in current smokers compared with that in non-smokers.28 The putative mechanisms for the beneficial effect of smoking on ulcerative colitis include increased mucin synthesis, decreased production of pro-inflammatory cytokines, reduction of smooth-muscle tone in the gut and the modified intestinal permeability of macromolecules. The effects of nicotine and tobacco were studied experimentally as well as clinically in oral and local applications, with ambiguous results.29–30 Interestingly, the influence of cigarette smoking on both IBDs (beneficial in ulcerative colitis and harmful in Crohn’s disease) has been clearly shown.

An effect of contraceptive use on ulcerative colitis is unclear. Only inconsistent data indicate that oral birth control may act as a trigger for relapses of ulcerative colitis. A meta-analysis showed a notable, although a mild, relationship between the use of contraceptives and higher incidence of ulcerative colitis and Crohn’s disease.31 At present, however, we do not have an unequivocal evidence to advise patients with ulcerative colitis against the use of oral contraceptives.

Dietary factors
A high intake of dairy products or a low intake of dietary fibre may be associated with the relapse of ulcerative colitis.32 The strongest evidence for a dietary factor is that sulphur and sulphate may be implicated in relapses of ulcerative colitis. This may be accomplished by their direct toxicity on colonocytes, and also indirectly by altering protein function and antigenicity. Another study further supports the idea that nutritional factors associated with a “modern life style” influenced the increasing frequency of IBD in the last centuries.41–44

Appendicectomy
It has been found that people who underwent appendicectomy before the age of 20 years were less likely to develop ulcerative colitis thereafter. An inverse relationship between appendicectomy and ulcerative colitis has been confirmed in a meta-analysis of 13 case–control studies, where a pooled odds ratio of 0.31 (95% CI 0.25 to 0.38) suggested that appendicectomy at a young age provides an almost 70% reduction in the risk of developing ulcerative colitis.45 Again, the mechanisms of this prophylactic effect of appendicectomy are elusive. Some speculate that the removal of the appendix, with its abundant lymphoid aggregates, might alter the balance between the regulatory and effector T cells. This concept seems to be supported by experimental data suggesting a decreased rate of experimental colitis after resection of the caecum, and also by clinical observations showing that patients who are predisposed to ulcerative colitis might be less likely to develop appendicitis.46

PATHOGENESIS
The currently accepted model of the pathogenesis of ulcerative colitis is of an inappropriate immune response to host microorganisms in genetically susceptible people. The host’s intestinal bacteria profoundly influence the local and systemic immune responses. The balance between homeostasis and chronic inflammation is determined by the host’s genetically established immune response to luminal antigens.

A two-component hypothesis for pathogenesis of ulcerative colitis
This hypothesis was proposed based on experimental studies showing that intestinal microorganisms in severe ulcerative colitis are pathogenic, as evidenced by allergic and immunological reactions, proved by agglutination and skin tests.47 Similar results were obtained in other intestinal diseases,
which point to the existence of a non-specific inflammation owing to intestinal microorganisms acquiring pathogenicity. Such a process may be superimposed on primary lesions of various origins, including that in the disease “inappropriately” termed ulcerative colitis.

Comprehensive clinical studies, with special attention to the periodic course of the disease, started in 1948. Till 1984, 959 cases of idiopathic proctocolitis (ulcerative colitis) were observed (compared with 303 cases of Crohn’s disease). 55–56 The population described was Czech and diagnoses were predominately made depending on clinical course, irrigography and rigid proctoscopy. Infection was excluded in every patient who had negative results for microbiological cultivation of stool. On the basis of the laboratory and clinical studies, the two-component hypothesis was proposed in 1948,51 and developed further subsequently.52–54 According to the two-component hypothesis, the primary component of the disease called ulcerative colitis presents as a haemorrhagic–catarrhal inflammation of unknown aetiology, possibly related to genetics and immunopathology, as evidenced by circulating anticolon antibodies and autoantibodies. 55–56 It presumably related to genetics and immunopathology, as evidenced by circulating anticolon antibodies and autoantibodies.55–56 It is a relatively mild disease, with periodic recurrences primarily affecting the rectum, with possible extension to the adjacent colon. The secondary component is superimposed on the primary lesion due to non-specific infections by intestinal microorganisms. This is then responsible for the severe extensive ulcerative form, with local and systemic complications and sequelae. These suppress the type of periodicity and change the morphological picture of the primary process. This is the reason why advanced stages of colonic inflammations, of any nature, may have a similar ulcerative character, whereas typical histological changes are more distinct in the early stages.56

The potential weakness of this hypothesis might be the experience that patients with severe ulcerative colitis do not need antibiotics for treatment. By using this hypothesis, it is also difficult to explain the abrupt line of demarcation between normal and inflamed mucosa of the colon seen in patients with ulcerative colitis.

In view of this hypothesis, and to avoid incorrectness in and ambiguity of the term ulcerative colitis, the term idiopathic proctocolitis was proposed for the disease entity.51–54 This term covers both the mild haemorrhagic and the severe ulcerative form of the disease, and aptly states its main characteristics—namely, the constitutional character and predilection for association of the rectum.

‘‘Hygiene’’ and ‘‘Old Friends’’ hypotheses

A high frequency of ulcerative colitis in the industrialised countries supports the idea that environmental factors have a dominant role in its aetipathogenesis. The “hygiene” hypothesis states in that raising children, an extremely clean environment negatively affects the development of the immune system and, thus, predisposes them to immunologically driven diseases, such as allergy or ulcerative colitis. An important role is assigned to the helminths, because until recently, the presence of infectious diseases might lead to an increased incidence of IBD and similar diseases. The multiple receptors of the innate immune system recognise old friends (lactobacilli, helminths, saprophytic mycobacteria and others) as harmless, as a consequence of their presence throughout mammalian evolutionary history. These antigens stimulate dendritic cells and cause their maturation. The immature dendritic cells may drive activation and exaggerated stimulation of regulatory cells, which then induce an imbalance between Th1 and Th2 subpopulations of lymphocytes, as well as between T regulatory and T effector cells. Two methods of mucosal immunoregulation are possible. The first possibility represents the normal situation, which is characterised as a “bystander regulation”, thanks to continuous exposure to the old friends. The second possibility represents an abnormal immune response due to a lack of exposure to the old friends early in life. This immunoreaction finally acts against specific components of the gut, giving rise to chronic inflammation.56

The switch from the immunotolerance to a specific immunoreactivity, owing to inappropriate activation of innate and adaptive immunity, is a crucial moment predisposing a person to ulcerative colitis. This knowledge of the important roles of harmful (dysmicrobial) or beneficial (probiotic) intestinal contents opens new horizons for medical treatment in the future. The clinical trials, where people with active IBD were exposed to helminths (eg, T suis), can provide therapeutic gains.59–61

CONCLUSIONS

Despite unequivocal progress in the past 20 years in both aetiology and pathogenesis with the application of modern therapeutic approaches on ulcerative colitis, most of the fundamental questions remain unanswered. The list of fundamental unknowns includes the following.

- Why does ulcerative colitis mucosal disease occur and why does the extent vary?
- What are the causes of relapses of ulcerative colitis?
- Why does microscopic colitis not develop into ulcerative colitis?

At the moment, it seems unlikely that any single therapeutic approach will be universally successful in patients with ulcerative colitis in the near future. Perspectives might lie in the application of individualised treatment, targeting the dominant stimulating antigen, correcting specific genetic defects, improving a destroyed mucosal barrier, eliminating luminal antigens due to manipulation with bacterial flora or delivering immunosuppressive molecules to block exaggerated mucosal immune reactivity. We hope that a wide application of probiotics, prebiotics, helminths or local antibiotics, as well as new molecules targeting pro-inflammatory mediators and biologicals, or new promising methods (leucocytoapheresis or stem cell transplantation) could provide a greater chance for higher therapeutic successes for ulcerative colitis in the near future.

Authors’ affiliations

M Lukas, M Bortlik, Gastroenterology Center, Fourth Medical Department, General Faculty Hospital, First School of Medicine, Charles University, Prague, Czech Republic

Z Maratka, Charles University, Prague Czech Republic

Competing interests: None declared.

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