**Chapter 1**

**CURRENT KNOWLEDGE IN INFLAMMATORY BOWEL DISEASES IMMUNOPATHOGENESIS**

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**ABSTRACT**

Ulcerative colitis (UC) is a chronic disease characterized by inflammation of the colonic mucosa. The etiology of this disease is not completely understood, but a multifactorial origin has been proposed, involving genetic, environmental and immunological factors. The genetic factor seems to be essential, based on both epidemiological and family studies. Environmental factors such as tobacco, NSAIDs, oral contraceptives, diet and exposure to pathogens have also been shown to play a role.

Genome-wide association studies (GWAS) have highlighted the association of several genetic polymorphisms with UC. The loci involved (IBD genes) encode molecules that directly interfere with both innate and acquired immunity. A recent meta-analysis showed an association of 47 loci with UC, 40% of which are specific for UC and the rest shared with Crohn’s disease (CD).

Some of these loci involve a greater risk of epithelial dysfunction, such as EMC1 (a mutated member of a transmembrane complex required for efficient folding of proteins in the ER), HNF4A (hepatocyte nuclear factor 4 alpha), CDH1 (encodes epithelial cadherin or E-cadherin), and LAMB1 (encodes laminin subunit beta-1). The DAP locus (Death-associated protein 1, which encodes a protein that acts as a positive mediator of
programmed cell death), involves impaired autophagy and apoptosis. PRDM1 (encodes PR domain zinc finger protein 1, also known as BLIMP-1), interferon regulatory factor 5 (a protein that in humans is encoded by the IRF5 gene), and NKX2-3 (homeobox protein Nkx-2.3) are associated with defects in the transcription process. Loci overlapping with CD include several genes from the interleukin 23 (IL-23) signaling pathway, and HLA genes that associated with autoimmunity.

The IL-33/ST2 axis is a new discovery in the pathogenesis of UC. This axis's role had been previously demonstrated in other chronic inflammatory diseases, and in 2010, IL-33 and its cognate receptor ST2 were shown to be upregulated in gut of UC patients. This proinflammatory axis has the ability to enhance Th2 pathogenic responses in gut-associated lymphoid tissues and seems to have an important role in the pathogenesis of UC. This review describes the current evidence on the pathogenesis of UC, including alterations in the intestinal barrier leading to dysfunction of the mucosa and acquired immune response.

The data support the multifactorial hypothesis, where, in a genetically predisposed individual, pathogenic bacteria initiate intestinal inflammation, and the inflammatory process is sustained by loss of tolerance to the commensal microbiota.

**Keywords:** Inflammatory bowel disease, immunopathogenesis, innate immune response

**INTRODUCTION**

Inflammatory bowel diseases (IBD) are a group of multifactorial diseases that primarily affect the gastrointestinal tract, characterized by inflammation of the small intestine and/or colon. The disease is manifest as recurrent diarrhea and abdominal pain [1].

IBD are characterized by their chronicity and limited response to therapy, evolving with relapses and complications. Treatment is based on inflammation modulators such as mesalazine or 5-aminosalicylic acid, steroids, immunosuppressants (mainly Azathioprine, 6-mercaptopurine (6-MP) and methotrexate), and biologic therapy (infliximab, adalimumab, certolizumab) [2].

Although the etiology of IBD is not yet fully understood, genetic, environmental and immunologic factors have been suggested as contributors to its pathogenesis (Figure 1).

Ulcerative colitis (UC) is a type IBD, along with Crohn's disease (CD) and a group called Indeterminate Colitis. UC was first described as a clinical entity in 1856 by Samuel Wilks, and even though it has been the subject of significant research since that time, the pathogenic mechanisms that lead to UC are not yet completely understood.

UC is the most frequent IBD, with an incidence of 1.2 to 20.3 cases per 100,000 persons per year, and its prevalence is 7.6 to 246.0 cases per 100,000 per year (as compared with an incidence of 0.03 to 15.6 cases and a prevalence of 3.6 to 214.0 cases per 100,000 per year for CD) [3].

This disease is characterized by inflammation of the mucosal surface alone, mainly affecting the rectum. If the disease affects the rest of the colon, it typically extends continuously, although in treated patients sometimes limited segments are affected [4,5]. Histopathologically, there is a loss of normal architecture, depletion of goblet cells, erosions of variable degree in the mucosa, micro abscesses rich in neutrophils at the bottom of the crypts, and infiltration into the lamina propria [2].
Figure 1. Patterns of inflammatory bowel disease (IBD) are multifactorial in etiology. Intestinal inflammation in IBD results from the influence of environmental and/or host factors. Genetic factors can affect mechanisms of cellular defense, such as autophagy, UPR, barrier function and innate and adaptive immunity against luminal antigens.

**Etiology**

Although the etiology of IBD is unknown, studies suggest that CD and UC result from an interaction of genetic and environmental factors that cause a cycle of continuous inflammation of the gastrointestinal mucosa. The intestinal mucosa is a functional barrier between the host and the bacteria of the intestinal lumen. The constant presence of bacterial antigens maintains the mucosal immune system in a state of controlled inflammation. Mucosal injury, due to a breakdown of immunoregulation at this level, may be due to excessive immune response to bacterial antigens or deficient immune response after infection by a pathogen [4].

**Environmental Factors**

As in other inflammatory and autoimmune diseases, the *Hygiene Theory* has been proposed in relation to IBD. According to this theory, a lack of contact with pathogens at an
early age, because of improved sanitary conditions, reduces tolerance [6]. Tobacco has been consistently shown to confer some protection from UC. In patients with UC, tobacco exposure seems to slow disease evolution and reduce the need for colectomy [7], and tobacco cessation may even trigger a crisis. The mechanism by which cigarettes affect IBD is unknown, but it is likely the action of nicotine on local inflammatory processes. Studies have suggested a role for nicotine patches in treating patients with UC [8-10]. Another protective environmental factor is appendectomy, especially when surgery is performed in childhood for acute appendicitis (rather than appendectomy of a healthy appendix) [11,12].

Drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) can trigger a crisis, and oral contraceptives enhance the risk of microthrombosis in the mucosa and submucosa of patients with IBD [13,14]. Diets high in fat and sugar, stress, and high socioeconomic status have also been associated with IBD development [15].

**Bacterial Role**

Health depends largely on an interaction between host and microbes. This is especially true in the colon, the organ hosting the greatest number and diversity of microorganisms [16]. Characterization of intestinal microbiota in health versus disease has not yet been achieved and awaits the results of the Human Microbiome Project [17]. However, the consensus is that the microbiota is denser in patients with IBD, although it is unclear if density is disease-specific and therefore helpful in differentiating between UC and CD [18]. One study compared clone libraries, revealing statistically significant differences between the microbiota of CD and UC patients and those of non-IBD controls. A subset of CD and UC samples contained abnormal microbiota, characterized by depletion of commensal bacteria, notably members of the phyla *Firmicutes* and *Bacteroidetes* [19]. Another study performed molecular profiling of fecal bacteria to investigate quantitative differences in compositions of UC and Irritable Bowel Syndrome (IBS) patients compared to healthy controls and to identify individual bacterial species that contribute to these differences. This study revealed abnormalities of intestinal microbiota in UC and IBS patients and distinct patterns of particular *Bacteroidetes* species loss associated with UC and IBS [20].

There is increasing evidence that intestinal microbes influence the host's immune development, immune responses, and susceptibility to human diseases such as IBD, diabetes mellitus, and obesity. Conversely, host factors can affect microbes, which in turn modulate disease susceptibility [21]. The intestinal immune system is generally tolerant to the burden of microbiota. The breakdown of this tolerance has been postulated as central to the pathogenesis of IBD. This loss of tolerance has been demonstrated in animal models; however, there is little evidence in CD and almost none in UC [22].

The lifestyle of modern industrialized societies has altered the pattern of microbial exposure in the intestine and has important implications for development and education of the immune system. The loss of immune tolerance to luminal bacterial flora produces an altered immune response, which results in damage to the gastrointestinal mucosa. Studies have found that the microbiota of IBD patients has a higher concentration of bacteria adhering to the mucosa, more local immune instability, and reduced biodiversity of bacterial flora, as compared to healthy subjects [23].
At least 3 theories have been postulated to explain how the microbiota affects IBD pathogenesis, which are not mutually exclusive:

1. Involvement of a persistent pathogen.
2. Abnormally permeable mucosal barrier, allowing for excessive bacterial translocation.
3. Breakdown in the balance between protective and harmful bacteria, or dysbiosis, promoting inflammation [24].

The possibility that IBD are infections has been discussed since these diseases were described. There are more pathogenic bacteria in the intestinal mucosa of IBD patients than in controls (adherent invasive E. coli, L. monocytogenes, Y. enterocolitica, Mycobacterium avium paratuberculosis and H. pylori among others) [25-27].

The development of infectious gastroenteritis, especially if caused by Campylobacter or Salmonella, has been closely linked with the subsequent development of IBD in cohort studies [27]. In addition, pediatric patients with IBD show elevated pathogenic bacteria (aerobic and facultative-anaerobic bacteria) or reduced commensal anaerobic flora in the intestine (in particular, Bacteroides vulgatus) [28], leading to the conclusion that the persistence of pathogenic bacteria in the gut could facilitate the development of IBD.

Antibiotics produce no benefit in UC, contrary to what has been seen in CD, which argues against a bacterial etiology [29].

Dysbiosis may be a key factor in the pathogenesis of IBD, as it may alter the immune response to commensal flora on the mucosal border. There is evidence that the overall dysbiosis observed in IBD patients relative to non-IBD controls might be a result of the disturbed gut environment rather than the direct cause of disease. Nonetheless, the observed shift in microbiota composition may be an important factor in disease maintenance and severity [30].

Dysbiosis promotes invasive growth of pathogenic bacteria and bacterial translocation through the intestinal epithelium into the mesenteric lymph nodes. Both phenomena contribute to an increase in the permeability of the epithelial barrier, which might lead to the activation of the immune response [1].

**GENETIC FACTORS**

Genetics seem to be crucial in the development of these diseases. Epidemiological studies have discovered geographic and ethnic patterns of disease development, familial forms of IBD, and high phenotypical concordance between monozygotic twins [31,32]. Data suggest that the genetic component is more important in CD than in UC.

In recent years, Genome-Wide Association studies have highlighted the association of specific gene polymorphisms and IBD. Results have been used to identify genes that may be implicated in the disease, called IBD genes [33, 34]. These genes encode molecules directly involved with both innate and acquired immunity.
A recent meta-analysis showed an association of 47 loci with UC, 40% of which are specific for UC and the others shared with CD. Thus, UC appears to be more heterogeneous, genetically speaking [35].

In UC, polymorphisms of HLA-DR have been associated with the presence of other autoimmune diseases (such as psoriasis, ankylosing spondylitis, multiple sclerosis, celiac disease and arthritis), particularly those genes related to Th1 and Th17 differentiation, such as IL-10, IL-17R, IL-23R and IFN-γ [36]. Both UC and CD have been associated with multiple genes linked to the IL-23 signaling pathway, including IL23R (IL23 receptor gene), IL-12B (gene encoding the p40 subunit of IL12) and STAT3 (signal transducer and activator of transcription 3) [36].

In UC, the C3435T mutation of MDR1 (multidrug resistance gene drug) has been associated with a more severe phenotype [37, 38]. This gene is involved in epithelial function, encoding a membrane transport glycoprotein. Its absence in mice generates spontaneous colitis. Studies have shown decreased MDR1 in patients with UC [38]. Some of these loci involve a greater risk of epithelial dysfunction associated with the potential development of UC, such as EMC1 (a mutated member of a transmembrane complex required for efficient folding of proteins in the ER), HNF4A (hepatocyte nuclear factor 4 alpha), CDH1 (E-cadherin 1) and LAMB1 (laminin subunit beta-1).

The DAP locus (Death-associated protein 1, which encodes a protein that acts as a positive mediator of programmed cell death), involves impaired autophagy and apoptosis. PRDM1 (encodes PR domain zinc finger protein 1, also known as BLIMP-1), interferon regulatory factor 5 (a protein that in humans is encoded by the IRF5 gene), and NKX2-3 (homeobox protein Nkx-2.3) are associated with defects in the transcription process [36]. Given the large number of genes involved, and the small additive effect of each, genetic screening for IBD risk is not recommended [24].

However, although the clinical implications of genetic testing are still limited, genetic research has enabled better understanding of the clinical heterogeneity and complex interactions between genetic and environmental factors in IBD [4].

**IMMUNOPATHOGENESIS**

A three-stage pathogenesis for IBD has been proposed [1]:

1. Penetration of luminal contents to the underlying tissues, which may be facilitated by environmental factors or inherent defects of the mucosal barrier.
2. Decreased clearance of foreign material in the intestinal wall, which may be due to deficiency in the secretion of proinflammatory cytokines or defects in innate immune response (IIR).
3. Inadequate acquired immune response (AIR), which leads to chronic inflammation and symptoms of IBD.

The main abnormalities at each level of the immune system identified in UC pathogenesis are described below.
**MUCOSAL EPITHELIAL BARRIER**

**Secreted Barrier Role**

The absence of secreted barrier elements, such as mucin, α-defensin and TFF3 (trefoil factor 3), does not generate spontaneous colitis in mice, but it does increase inflammatory cytokine production and intestinal permeability with an increase of chemically-induced colitis (e.g. with Dextran sodium sulfate or DSS) [39].

Secretion of mucin and α-defensins by Goblet and Paneth cells is decreased in IBD. Mucin deficiency, both in quantity and quality (non-glycosylated mucin), has been correlated with the severity of UC [39]. In addition, the use of microarray assay shows that the genes coding for mucin in the ileum and colon of these patients are under-expressed [40].

**Cellular Barrier Role**

Epithelial cells are the first line of defense against pathogens. Once the signaling pathways of TLRs (Toll-like receptors) or NOD2 are activated, they produce β-defensins (antimicrobial peptide) and express MHC (major histocompatibility complex) to trigger the mucosal AIR. Authors have reported that in patients with active UC, higher levels of β-defensin 2, 3 and 4 are secreted by these cells [1,41].

There is evidence that colonocytes are directly involved in UC pathogenesis, based on findings that inflammation occurs only in the mucosa of the colon. It is hypothesized that the colonic epithelium are diffusely abnormal, independent of inflammation, with abnormal expression of PPAR-γ (peroxisome proliferator-activated receptor γ), a nuclear receptor that regulates inflammation [42]. Paneth cells also express TLRs and NOD2, and once activated they secrete α-defensins. In UC, this protein is elevated, once thought due to mutations in NOD2, as in CD. However, current evidence suggests that α-defensins may be elevated in UC secondary to the inflammatory process and not a genetic disorder, unlike in CD [43-45].

In UC, goblet cells are reduced in size and quantity, both in affected and unaffected regions, resulting in decreased production and poor quality of mucin. This abnormality may be explained by the cytoplasmic vacuolization derived predominantly from endoplasmic reticulum (ER) and Golgi apparatus in goblet cells, leading to a non-glycosylated mucin.

This is due to a protein assembly error, secondary to ER stress or poor response of the individual to these abnormal proteins. UC is not related to bacterial translocation or changes in epithelial permeability, although these may occur secondary to secretion of cytokines [46].

Alterations in intraepithelial unions and their relationships with the cytoskeleton may be related to CD, but not UC [26].

**Innate Immune Response (IIR)**

Intestinal homeostasis requires a controlled innate immune response against the microbiota, which is recognized by Toll-like Receptors (TLRs) and Nucleotide Oligomerization Domain receptors (NOD-like receptors, NLRs) expressed by epithelial and
immune system cells [47]. The weakening of the barrier defenses leads to more frequent contact between the antigens of commensal flora and the mucosal immune system. An excess of this interaction can lead to loss of tolerance, via activation of dendritic cells (DC) [1].

Dendritic Cells

In IBD, DC are overactive at intestinal inflammation sites, inducing differentiation into effector T cells (CD4 and CD8) and other effector cells such as NK and NKT, at the expense of regulatory T lymphocyte (Treg) production. As a result, peripheral tolerance to the commensal flora is lost, and inflammation is perpetuated [48].

The over-activation of DC is due to polymorphisms in the TLRs (TLR1, 2, 4, and 6 genes) associated with increased IBD risk, as well as polymorphisms in NOD2 that lead to inadequate recognition of microbial antigens [49]. This finding is apparently inconsistent with previous observations, which reported correlations between NOD mutations and low NFκB activity. However, the mutation responsible may be Leu1007fs, which prevents the activation of NOD2 from inhibiting the TLR-NFκB pathway, resulting in increased production of proinflammatory cytokines in response to antigen pathogens [50]. DC function is also altered, expressed as production of low IL-12 concentrations. These abnormalities perpetuate inflammation by impairing ability eliminate the pathogen, resulting in a persistent inflammatory response.

IL-33/ST2 Receptor

The IL-33/ST2 axis has been implicated in several autoimmune and inflammatory diseases (asthma, atopic dermatitis, rheumatoid arthritis, lupus), and in recent years there has been speculation that is has pivotal role in IBD pathogenesis [52-57]. The IL-33/ST2 axis is proinflammatory and is activated in a wide variety of gut-associated immune cell subsets. Its activation can lead to chronic inflammation in the colonic mucosa. In active UC patients, IL-33 is localized primarily to intestinal epithelial cells. Production is elevated in damaged cells. Inflammatory ST2⁺ cells infiltrate the lamina propria (mast cells, macrophages, basophils, eosinophils, nuocytes, neutrophils, NK and NKT cells), which respond to IL-33 by preferentially inducing pro-inflammatory cytokine secretion (Figure 2) [52-57].

Serum IL-33 also increases in these patients, although the circulating IL-33 is a modified form; an extracellular protease inactivates the IL-33 to prevent systemic manifestations of inflammation such as anaphylactic shock [58]. An allergic airway inflammation model has shown that DC activated by IL-33 exacerbates lung inflammation.

These data demonstrate that IL-33 activates DCs during antigen presentation and thereby drive a Th2-type response with IL-5 and IL-13 production, but not IL-4, in allergic lung inflammation [58]. This mechanism's relationship to IBD has not been fully elucidated. However, this mechanism is plausible in IBD, especially UC, when one considers the upregulation of IL-33 in the colonic mucosa (in addition to the intestinal DC described above that express ST2), the characterization of UC as a Th2-type immune phenotype, and the pathogenic role of IL-13 [59].
Figure 2. Schematic representation of the variety of cell types of the innate and acquired immune involved in the effects of IL-33 in the inflamed intestinal mucosa. Colitis is triggered by multiple events (e.g. genetic susceptibility, environmental factors, pathogenic bacterial and dysbiosis, hyposcretion of mucins) leading to a damaged epithelium. Following injury, IL-33 is released and inflammatory cells are activated contributing to the persistent inflammation. Deregulated immune response owing to high cytokine production leads to the recruitment of adaptive immune cells into MALT.

It has also been observed that IL-33 is specifically expressed in activated subepithelial myofibroblasts, in direct relation to mucosal lesions in patients with UC and not CD, stimulating fibrosis dependent of the IL-13 [52,57]. Similar to IL-33, receptor ST2 was also found to be elevated in both the intestinal mucosa and serum of patients with IBD, although the main cellular origin of ST2 is not fully described.

To avoid exaggerated immune response, a soluble form of this receptor is secreted that sequesters its ligand IL-33 and thus prevents activation of this signaling pathway. Higher levels of soluble ST2 (sST2) have also been reported in UC, which may be related to disease activity level [59].

Measurement of plasma levels of sST2 may be to help in the differential diagnosis of IBD, predict disease progression, and evaluate disease activity, but more studies are needed [59]. The pathophysiological relevance of these findings is still being studied, and more mechanistic studies are needed to confirm the function of this interleukin in the pathogenesis of UC.
Cytokines

Production of proinflammatory cytokines such as IL-1β, IL-6, TNF-α and TLA1A (TNF-like ligand 1) is elevated in patients with IBD, but cytokine levels cannot discriminate between CD and UC [24]. This prolonged inflammation leads to recruitment of immune cells such as neutrophils and eosinophils, producing a large infiltration in the affected mucosa.

Eosinophils

The role of eosinophils in the etiology and pathogenesis of IBD is not completely clear. However, evidence shows an eosinophilic content 10 times higher in the colonic mucosa of UC patients versus healthy controls [51,60].

Adaptive Immunity Role

**T Helper Lymphocytes**

UC patients show an atypical Th2 pattern, in which IL-13, IL-5 and TGF-β are secreted [54]. Non-classical NKT is present in the colon, which secretes abundant IL-13. This interleukin mediates cytotoxicity in epithelial cells, along with apoptosis and epithelial barrier dysfunction [35,62].

**Th17/IL-23 Axis**

LTCD4+ Th17 (CD4+ CD25−) are a new group of effector T lymphocytes that are elevated in IBD. They are induced by IL-23 in the presence of TGF-β and IL-6 and secrete inflammatory cytokines IL-17A, IL-17F, IL-6, IL-21, IL-22 and TNF-α, especially in response to extracellular bacteria [62-64]. This group shares a common pathway with regulatory T cells (Treg), and the development of one type inhibits the other [62].

Genetic association studies have linked the gene for IL-23 receptor (IL23R) with IBD pathogenesis. Its contribution is likely through altered production of antimicrobial peptides such as β-defensins and the promotion of the pro-inflammatory Th17 profile. IL-23 leads to the development and expansion of pathogenic memory cells and ensures the survival of Th17 clonal expansion [64,65].

**Role of Regulatory T Cells (LTreg)**

LTreg concentration is elevated in IBD, but levels are insufficient to control inflammation. It is believed that this increase is due mainly to natural LTreg with preserved functioning [37,62]. This is explained by the common "ancestor" of Th17 and inducible LTreg, where the inflammatory condition caused by defects in innate immunity form a cytokine environment that favors the Th17 profile from naive LTCD4, with decreased inducible LTreg [62].
Humoral Immune Response

Elevated levels of IgA, IgG and IgM are common in both IBDs, but only UC is associated with a disproportionate elevation of IgG1 [66]. This finding might represent an autoimmune component in the pathogenesis of UC, supported by circulating IgG1 antibodies (Ab) against an antigen of the colonic epithelium also shared with skin, eye, joints and biliary epithelium. Because these are the sites of extraintestinal manifestations of UC, the finding suggests cross-reactivity of antibodies, causing damage to these organs. The antigen allegedly involved is Tropomyosin 5, a structural protein, but there is still a lack of evidence to show organ-specific autoimmunity in UC [66, 67].

In both IBDs, there is a large plasma cell infiltration in the mucosa. Local levels of IgG1, IgG2, IgM and IgE are high, while IgA is low [67, 68].

Over-stimulation of B lymphocytes leads to the production of autoreactive IgG antibodies directed against antigens of commensal bacteria. This suggests that IgA (protective) is shifting to IgG, which contributes to the maintenance of intestinal inflammation [69-71]. The only antibody associated with UC is an atypical p-ANCA (perinuclear antineutrophil cytoplasmic antibody), which recognizes a neutrophil nuclear antigen that may cross-react with a bacterial antigen [33]. The atypical p-ANCA pattern is characterized a lack of nuclear extension with widespread perinuclear extension, and both the ANA (antinuclear antibodies) test and ELISA for myeloperoxidase (MPO) are negative. The atypical p-ANCA antibody is frequently seen in patients with chronic inflammatory diseases: 60-80% in UC, 88% in Primary Sclerosing Cholangitis, 82% in Autoimmune Hepatitis, and 5-25% in CD [70].

In patients with UC, a positive atypical p-ANCA is correlated with increased risk of pouchitis after surgery [70]. A potentially pathogenic role has been described for atypical p-ANCA in relation to UC, in which neutrophils lose the ability to recognize antigens [71,72].

Just as p-ANCA is associated with UC, ASCA (anti-Saccharomyces cerevisiae antibody) is mainly associated with CD. However, these markers coexist in patients with CD and UC, and therefore its value in differential diagnosis is limited [72-75]. Multiple studies have identified antigens that could be markers for IBD, but these works cannot be homogenized because they use different diagnostic criteria, cut-off points and techniques to identify the antigens. Additionally, many of these antigens (G-catalase, elastase, histones) are present in bacteria [71].

CONCLUSION

Despite having been described over 150 years ago and having been the subject of extensive research since that time, the pathogenesis of IBD is only partially understood. There is evidence for certain abnormalities at different levels of the pathogenesis, but the full immunopathogenic mechanism for the disease is still unknown. Several factors, both environmental and host are involved. A complex interaction between genotype, the immune system, and commensal and pathogenic microbiota may be the basis for the development and evolution of the disease. The intestinal immune system is normally tolerant to the microbiota, and it has been postulated that a breakdown and loss of this tolerance to commensal bacteria is the central axis in the pathogenesis of the UC. Genetic susceptibility may lead to abnormal
processing and presentation of antigens to the intestinal effector cells, which may mount an inappropriate adaptive response, amplifying and maintaining inflammation.

REFERENCES

Current Knowledge in Inflammatory Bowel Diseases Immunopathogenesis


