

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis and colitis indeterminate. They cause intestinal swelling, inflammation and bleeding (*Baumgart et al., 2007*).

Ulcerative colitis is a form of colitis that includes characteristic ulcers. The main symptom of active disease is usually constant diarrhea mixed with blood, of gradual onset, abdominal pain, and a variable group of "extra-intestinal" manifestations (such as arthritis, uveitis, skin changes), and the accumulation of inflammatory cells within the small intestine and colon (*Podolsky, 2002*).

IBD results from the interaction between environmental, genetic and immune factors. Although environmental factors might be the triggers for the disorder, the predisposition to the disease is denoted by genetic and/or immune factors. This has recently led to the identification of over 30 CD-associated loci and a number of UC-associated genes (*Achkar et al., 2009*). Several of the genes were identified, including IL-23R, IL10, nucleotide-binding oligomerization domain 2 (NOD2) gene, autophagy 16-like (APG16) and immunity-related GTPase family M (IRGM). These genes are involved in

controlling intestinal barrier function, bacterial invasion, autophagy, or activation of the mucosal immune system (*Achkar et al., 2009*).

IL-23 is produced by activated myeloid cells including macrophages and dendritic cells (DCs) following bacterial stimulation (*Becker et al., 2003*), or via CD40 signaling (*Uhlig et al., 2006*), and drives increases in a number of inflammatory cytokines in the intestine in the absence of T cells, including TNF α , IFN γ , IL-6 and IL-17 (*Cua et al., 2003*).

It was suggested that an important function of IL-23 may be to drive an autocrine loop within the innate immune system, leading to the production of a number of inflammatory mediators that contribute to the intestinal inflammatory response (*Duerr, 2006*).

IL-23-driven inflammation has primarily been linked to the actions of a new subset of T-helper cells namely T helper type 17. They not only play an important role in host defense against extracellular pathogens, but are also associated with the development of autoimmunity and inflammatory response such as inflammatory bowel disease (IBD) (*Abraham and Cho, 2009*).

IL-23 gene polymorphism is also identified as a susceptible gene for the development of multiple autoimmune diseases (*Agarwal et al., 2009*).

Interleukin 23 (IL-23) is a newly identified cytokine with increased expression in inflamed biopsies of colon mucosa in patients with ulcerative colitis (**Duerr et al., 2006**). It is a heterodimeric cytokine comprised of two subunits, p19 which is unique to IL-23, and p40, which is shared with IL-12.

Recently a novel role for IL-23 in controlling innate immunity in the intestine was suspected as T cell-independent colitis following intestinal bacterial infection was found to be dependent on IL-23 and not IL12 (**Hue et al., 2006**).

It is known that ulcerative colitis (UC) is severe intestinal inflammatory condition which is resulted from autoimmune and immune mediated phenomena (**Neuman, 2007**). It is suggested that UC is mainly mediated through T helper 2 and natural killer cells. IL-23 promotes the development T helper 17 cells from mechanisms that are distinct from those of T helper 1. It is usually considered as a cytokine mediating CD disease (**Andoh et al., 2008**); however recent studies have found increased expression of IL-23 in inflamed and noninflamed mucosa of patients with UC (**Kobayashi et al., 2008; Abraham, 2009**).

It could be hypothesized that UC is associated with increased levels of IL-23 that resulting from increased inflammation and autoimmunity (**Gyulveszi et al., 2009; Li et al., 2010**).

AIM OF THE STUDY

Our aim is to assess the relation of IL-23 to the severity of ulcerative colitis.

ULCERATIVE COLITIS

Inflammatory bowel disease:

Inflammatory bowel disease (IBD) commonly refers to ulcerative colitis (UC) and Crohn's disease (CD), which are chronic inflammatory diseases of the GI tract of unknown etiology (*Hyams, 2002*).

Ulcerative colitis is characterized by diffuse mucosal inflammation limited to the colon. It is classified according to the maximal extent of inflammation observed at colonoscopy, while Crohn's disease is characterized by patchy, trans mural inflammation, which may affect any part of the gastrointestinal tract, it may be defined by: age of onset, location, or behavior (*Silverberg et al., 2005*).

In particular, the definitions of ulcerative colitis and Crohn's disease acknowledge the revised Montreal classification which attempts to more accurately characterize the clinical patterns of IBD (*Satsangi et al., 2006*).

Unclassified (IBDU) is the term best suited for the minority of cases where a definitive distinction between UC, CD, or other cause of colitis cannot be made after considering clinical, radiological, endoscopic and pathological criteria, because they have some features of both conditions. **Indeterminate colitis** (IC) is a term reserved for pathologists to describe overlapping features in IBDU (*Satsangi et al., 2006*).

Ulcerative colitis:

Ulcerative colitis is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in the developed countries of the world. The precise etiology is unknown and therefore medical therapy to cure the disease is not yet available (*Dignass et al., 2012*).

It is a chronic inflammatory condition causing continuous mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, which is characterized by a relapsing & remitting course (*Silverberg et al., 2005*).

Clinical disease activity is grouped into **remission, mild, moderate** and **severe**. This refers to biological activity and not to treatment responsiveness (*Rice-Oxley and Truelove, 1950*).

Response is defined as clinical and endoscopic improvement, depending on the activity index used. In general, this means a decrease in the activity index of >30%, plus a decrease in the rectal bleeding and endoscopy sub scores, but there are many permutations (*D'Haens et al., 2007*).

The term 'chronic active disease' has been used in the past to define a patient who is dependent on, refractory

to, or intolerant of steroids, or who has disease activity despite immunomodulators. Since this term is ambiguous it is best avoided. Instead, arbitrary, but more precise definitions are preferred, including steroid-refractory or steroid-dependence (*Van Assche et al., 2010*).

Steroid-refractory colitis if patients have active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks. **Steroid-dependent colitis** patients who are either unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or who have a relapse within 3 months of stopping steroids (*Van Assche et al., 2010*).

Immunomodulator-refractory colitis patients who have active disease or relapse in spite of thiopurines at an appropriate dose for at least 3 months (i.e. azathioprine 22.5 mg/kg/day or mercaptopurine 1- 1.5 mg/kg/day in the absence of leucopenia) (*Dignass et al., 2012*).

- **Epidemiology**

The peak age of onset for UC is 15 to 30 years old, although it may occur at any age. About 10% of cases occur in individuals <18 years old. UC has a bimodal age distribution, with a second, smaller peak occurring in individuals ages 50 to 70 years. Ulcerative colitis is

slightly more common in males, tend to occur in higher socioeconomic groups (**Andres and Friedman, 1999**).

Breakdowns by racial and ethnic subgroups indicate that higher rates of UC occur in people of Caucasian and Ashkenazic Jewish origin than in individuals from other backgrounds. The distribution of UC among ethnic and racial groups remains dynamic. In past decades, it was thought that UC occurred less frequently in ethnic or racial minority groups compared with whites. This gap has been closing, with an increased incidence in African Americans and in second-generation south Asians who have migrated to developed countries (**Loftus and Sandborn, 2003**).

- **Etiology**

It is likely that a number of factors contribute to the development of mucosal inflammation. Also, variations in influence may account for the clinical diversity seen in UC. For example, a single family may have multiple affected members, suggesting heightened genetic susceptibility. In contrast, sporadic disease, which accounts for the majority of UC cases, is more likely to be engendered by a unique environmental trigger or by a more subtle abnormality within the enteric immune system. Current etiologic theories concerning UC focus on environmental triggers, genetic factors, and immune-regulatory defects and microbial exposure (**Abreu, 2002**).

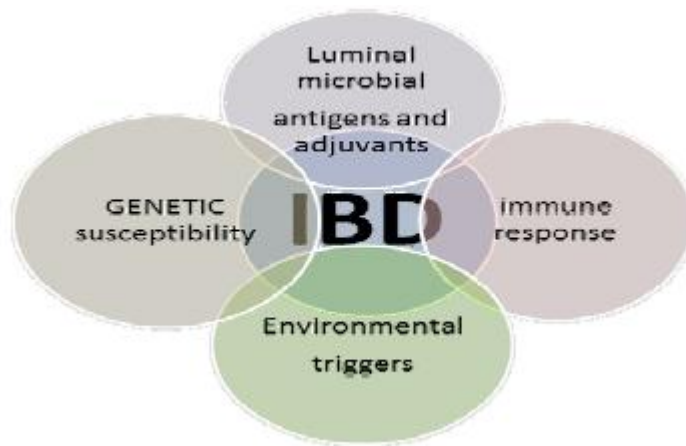


Figure (1): Interaction of various factors contributing to chronic intestinal inflammation in a genetically susceptible host. Genetic susceptibility is influenced by the luminal microbiota, which provide antigens and adjuvants that stimulate either pathogenic or protective immune responses. Environmental triggers are necessary to initiate or reactivate disease expression (*Sartor, 2006*).

So factors concerned with ulcerative colitis development include:

I. Environmental Triggers

A. Westernization

UC is most prevalent in developed regions, including the United States, United Kingdom, and Scandinavia. The higher incidence of UC seen in industrialized countries and the dramatic increase in cases during the 20th century support the theory that

environmental factors contribute to disease development (*Sandler and Loftus, 2004*).

This may also account for the north-to-south variation and higher frequency in urban communities compared with rural areas. Interestingly, increases in incidence have recently been noted in southern countries and Asia and among migrants to first-world countries. It is postulated that this is the result of "westernization" of lifestyle, such as changes in diet, smoking, and variances in exposure to sunlight, pollution, and industrial chemicals (*Loftus and Sandborn, 2003*).

B. Sanitation and exposure to infection

UC is a disease of cleanliness. In common with diseases such as asthma, multiple sclerosis, and rheumatoid arthritis, it demonstrates an inverse relationship with the degree of sanitation: poor sanitation appears to protect against UC. The propensity for infection associated with overcrowding may also be a factor. It is postulated that improved hygiene alters the intestinal flora by decreasing exposure to certain critical bacteria. There is an increased frequency of UC in higher socioeconomic groups (*Krishnan and Korzenik, 2002*).

C. Occupation

UC is more prevalent in white-collar compared with blue-collar occupations. Higher mortality from UC has been noted in managerial, clerical, and sales positions,

which typically involve sedentary, indoor work. In contrast, mortality resulting from UC is low among farmers and construction workers (**Sandler and Loftus, 2004**).

Sonnenberg suggests that employment involving outdoor air and physical activity is protective against IBD, whereas work in artificial venues confers an increased risk (**Sonnenberg, 1990**).

This theory could explain the higher risk for IBD in northern climates (e.g., more indoor exposure) and in immigrants to developed countries, as well as the varying rates among ethnic groups in different regions (**Andres and Friedman, 1999**).

D. Diet

Studies seeking to link diet and UC are generally inconclusive. There is some evidence that a higher intake of fatty acids increases the risk for UC (**Krishnan and Korzenik, 2002**).

Similarly, **Persson et al** suggests that frequent fast-food intake confers a 3- to 4-fold greater risk for UC (**Persson et al., 1992**).

E. Tobacco smoking

The relationship between UC and smoking is complex, Numerous case- control studies have shown that

current smoking is protective against UC (relative risk , 40% of that of nonsmokers), with results that are consistent across diverse geographic regions (**Sandler and Loftus, 2004**).

The decreased risk for UC in smokers appears to be dose dependent .Current smoking also is protective against sclerosing cholangitis and pouchitis. Paradoxically, ex-smokers are approximately 1.7 times more likely to develop UC than those who never smoked. Ex-smokers also have a poorer disease course, with more frequent hospitalization than current smokers; as a group they are twice as likely as current smokers and those who have never smoked to require colectomy (**Merrett et al., 1996**).

II. Familial and Ethnic Syndromes

There is an increased prevalence of UC in first- and second-degree relatives and a higher relative risk among siblings. The familial frequency of UC ranges from 20% to 30% in referral-based studies and between 5% and 10% in population surveys .The higher risk for IBD in the Jewish population suggests that genetic factors may play a larger role in some subgroups (**Satsangi et al., 2003**).

In families with a high incidence of IBD among first- degree relatives, 75% of those affected are concordant for either UC or CD, whereas 25% are not

concordant, with some members having UC and others having CD (*Binder, 1998*).

This finding indicates that multiple, overlapping genetic factors may contribute to disease pathogenesis. Further support for a genetic susceptibility comes from the finding of an association between IBD and other syndromes with a genetic predisposition (*Satsangi et al., 2003*).

Heritability studies indicate that there is a higher rate of concordance in monozygotic versus dizygotic twins for UC. For UC, reported concordance rates for monozygotic and dizygotic twins ranges from 6% to 17% and 0% to 5%, respectively, which is about the same as for non twin siblings (*Bouma and Strober, 2003*).

III. Genetic Factors

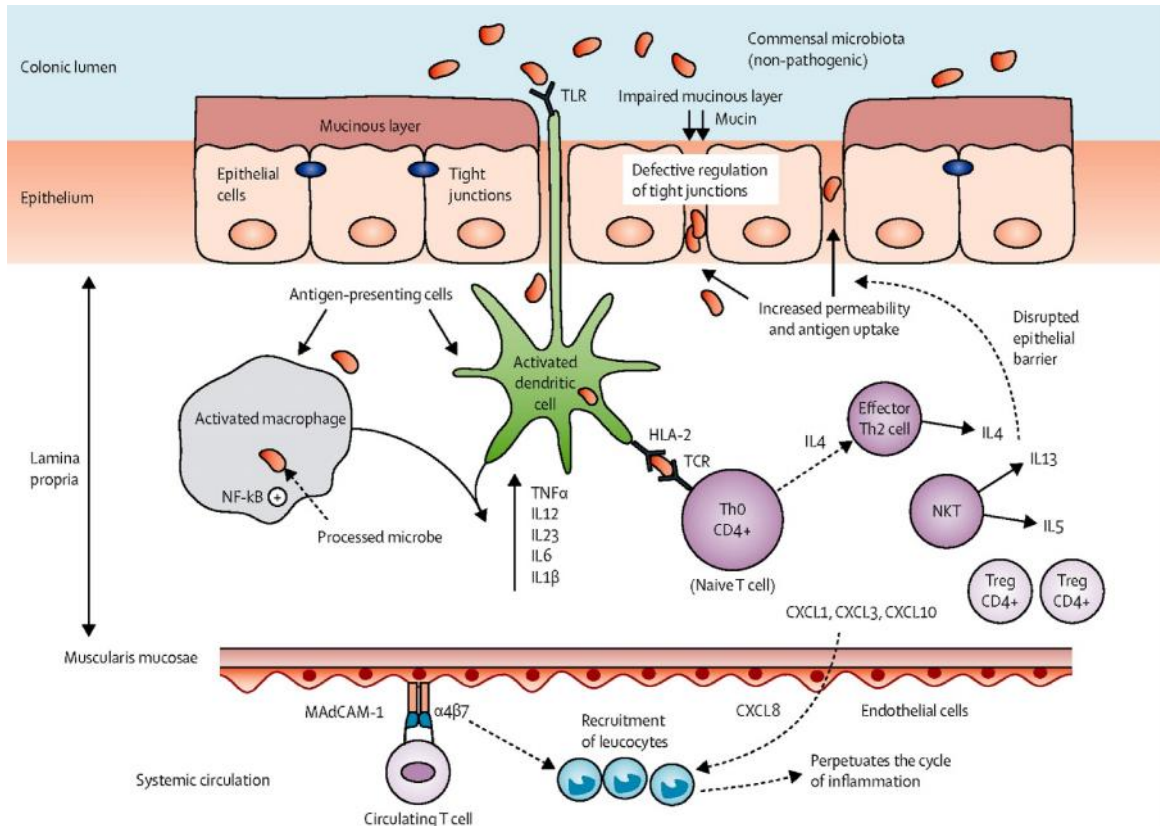
Epidemiological and family studies demonstrate that genetic factors play a role in the susceptibility to UC. The disease is however, genetically complex and cannot be explained by a single gene model alone. It is thought that UC may be heterogeneous polygenic disorders sharing some but not all susceptibility loci. Most likely, the disease phenotype is determined by several factors, including interaction between allelic variants at a number of loci, as well as genetic and environmental influences. Consequently, the presence of a mutated gene does not guarantee that UC will develop, nor does it predict who

will develop it, underscoring the importance of cofactors in precipitating the disease (*Satsangi et al., 2003*).

Genetic Background of Ulcerative Colitis

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 (*Silverberg et al., 2005*).

Nevertheless, several other genes have been studied as candidate loci linked to ulcerative colitis. Additional clinical studies showed that two polymorph (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 defense against intestinal bacteria (*Schwab et al. 2003*).



oFigure (2): Pathophysiology of ulcerative colitis: Disruption of tight junctions and the mucus film covering the epithelial layer causes increased permeability of the intestinal epithelium, resulting in increased uptake of luminal antigens. Macrophages and dendritic cells (innate immune cells), on recognition of non-pathogenic bacteria (commensal microbiota) through molecular pattern-recognition receptors (TLR), change their functional status from tolerogenic to an activated phenotype. Activation of NF- κ B pathways stimulates the transcription of proinflammatory genes, resulting in increased production of proinflammatory cytokines (TNF- α , interleukins 12, 23, 6, and 1 β). After processing of antigens, macrophages and dendritic cells present them to naive CD4 T-cells, promoting differentiation into Th2 effector cells, characterised by production of interleukin 4. Natural-killer T cells are the main source of interleukin 13, which has been associated with disruption of the epithelial cell barrier. Circulating T cells bearing integrin- α 4 β 7 bind to colonic endothelial cells of the microvasculature through the mucosal vascular addressin-cell adhesion molecule 1, whose expression is enhanced in the inflamed intestine, leading to increased entry of gut-specific T cells into the lamina propria. Upregulation of inflammatory chemokines, such CXCL1, CXCL3, and CXCL8, leads to recruitment of circulating leucocytes which perpetuates the cycle of inflammation. TLR=Toll-like receptor. HLA=human leucocyte antigen. IL=interleukin. TNF=tumour necrosis factor. NF- κ B=nuclear factor- κ B. Th=T-helper. NKT=natural killer T-cell. CXCL=chemokine. Treg=regulatory T cell. MAdCAM-1=mucosal addressin-cell adhesion molecule 1 (**Ordás et al., 2012**).