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Recent Approaches in Pathogenesis of Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD) commonly refers to ulcerative colitis (UC) and Crohn disease (CD), which are chronic inflammatory diseases of the GI tract of unknown etiology. This inflammatory response is most likely made possible by defects in both the mucosal immune system and the barrier function of the intestinal epithelium. Predominant Immune system components associated with Crohn's disease are CD4+ lymphocytes with a Th-1 phenotype typified by the production of INF-g and IL-2. In contrasts to this, ulcerative colitis is predominated associated with predominance of CD4+ and Th-2 phenotype which are characterized by the secretion of TNF-α and IL-5. In addition nuclear factor Kappa-B & toll like receptor NOD_2 are also actively involved in IBD. in reference to all above, here various avenues are focus which are responsible for the IBD.
Key Words: Inflammatory bowel disease, Cytokines, TNF-alpha.

INTRODUCTION:

Inflammatory bowel disease is a chronic inflammatory disease of gastrointestinal tract. It comprises the two conditions, Crohn's disease and ulcerative colitis, characterized by chronic recurrent ulceration of the bowel and of unknown etiology. The pathogenesis likely involves genetic, environmental, and immunologic factors.[1]

ULCERATIVE COLITIS:

UC is a condition in which the inflammatory response and morphologic changes remain confined to the colon. The rectum is involved in 95% of patients, with variable degrees of proximal extension. Inflammation is limited primarily to the mucosa and consists of continuous involvement of variable severity with ulceration, edema, and hemorrhage along the length of the colon. The characteristic histologic findings are acute and chronic inflammation of the mucosa by polymorphonuclear leukocytes and mononuclear cells, crypt abscesses, distortion of the mucosal glands, and goblet cell depletion.[2]

CROHN'S DISEASE:

CD in contrast to UC can involve any part of the gastrointestinal tract from the oropharynx to the perennial area. Diseased segments frequently are separated by intervening normal bowel, leading to the term "skip areas." Inflammation can be transmural, often extending through to the serosa, resulting in sinus tracts or fistula formation. Histologic findings include small superficial ulcerations over a Peyer's patch (aphthoid ulcer) and focal chronic inflammation extending to the submucosa, sometimes accompanied by noncaseating granuloma formation. The most common location is the ileocecal region, followed by the terminal ileum alone, diffuse small bowel, or isolated colonic disease in decreasing order of frequency.[2]

INCIDENCE & PREVALENCE:

The annual incidence of ulcerative colitis and Crohn's disease ranges from 1 to 10 cases per 100,000 people annually depending on the region studied[3-4]. The peak age-specific incidence occurs near 20 years of age, and a second, smaller peak occurs near age 50. The prevalence of ulcerative colitis and Crohn's disease

ranges from 10 to 70 per 100,000 people, but recent studies in Manitoba, Canada, and Rochester have shown prevalence as high as 200 per 100,000 people.[5-6] In the United States, males and females are equally affected.

ETIOLOGY AND PATHOPHYSIOLOGY [7]:

The IBD afflict more than a million individuals in the United States. Despite extensive studies and clinical experience over the past several decades, the etiologic factors responsible for these disorders remain substantially uncertain and understanding of their pathogenesis remains incomplete. As a result, therapy continues to be primarily aimed at the non-specific suppression of inflammation.

Although the exact cause of IBD remains undetermined. Various factors responsible for its occurrence are identified. Even though no one factor has been identified as the initial trigger for Inflammatory bowel disease, piece of the puzzle have been elucidated; fitting them together to create a complete picture remains to be accomplished.

(A) IMMUNE SYSTEM AND INFLAMMATORY MEDIATORS:

Differing cytokines & other inflammatory mediator profiles have been identified for UC & CD. The classic lesions of IBD, involving the mucosal layer with extensive epithelial damage, abundant neutrophils & crypt abscesses have led to a search for an immune mechanism to explain the epithelial damage.

The traditional view of the pathogenesis of inflammatory bowel disease is that intestinal inflammation is mediated by cells of the acquired immune system. In IBD, the tissue damage occurs in areas that are heavily infiltrated with activated CD4+T lymphocytes. These cells are recruited from the blood stream as a result of enhanced production of chemoattractants within the inflammatory microenvironment and regulated cytokines, which overcome the control mechanisms. Alternatively, IBD may result expression of adhesion molecules on vascular endothelium and integrins on Tcells. The chronic inflammation could result from overly aggressive activity of effector lymphocytes and proinflammatory from a primary failure of regulatory lymphocytes and cytokines, such as interleukin-10 to control inflammation and effector pathways[8, 9].

Presentation of intraluminal antigens to mucosal lymphocytes by antigen-presenting cells (*APCs*) leads to the generation of effector responses. As a result of an effector response, there is an over production of effector T cells (T_{eff}) leads to the inflammation by generation of inductive cytokines such as IL-12, INF-γ. Integrin & chemokine receptors are upregulated after stimulation allows degree of specificity of binding restricted to sites where there is ongoing injury.

In the normal gut, overt inflammation is prevented by controlling the activation of mucosal through at least 2 distinct mechanisms. First, regulatory T-cell subpopulations (T_{reg}) in the mucosal immune system suppress effector T-cell activity in part through the production of interleukin-10 and transforming growth factor-ß. Second control is also provided by eliminating T_{eff} by apoptosis, thereby preventing undesired over expansion. In individuals with IBD, both of these regulatory mechanisms seem to be defective (See figure 1).

As per above classic paradigm for cytokine involvement in the pathogenesis of Crohn's disease focuses on type 1 helper T-cell (Th1) cytokines, such as TNF-α, interleukin-12, and interferon-γ, which are thought to have a primary role in initiating the disease process. Conversely, type 2 helper T-cell (Th2) cytokines, such as interleukin-4 and interleukin-13, are considered to have a more prominent role in ulcerative colitis (figure 2).

The cytokine profile in UC patients provides more evidence of an exaggerated Th2 response & elevated interleukin-5 (IL-5) but no significant elevation of interferon-gamma (IFN-γ) and other cytokines associated with an overactive Th1 response[11]. Other researchers have reported elevated IL-8 in the mucosa of UC patients compared to controls or patients with CD[12]. Other cytokines associated with generalized inflammation-IL-1, IL-6, and TNF- α are found elevated in both inflammatory bowel conditions[13]. Table 1 compares cytokine profiles typically seen in UC and CD.

However, this classic Th1-Th2 paradigm may be overly simplistic, and new immunologic models are proposed that involve both clusters of cytokines. Furthermore, individual cytokines may have diverse, and even opposing, functions in different clinical and immunologic scenarios.

In Crohn's disease, in which the inflammatory process appears to develop in two distinct phases — an initial, inductive phase and an effector phase characterized by chronic inflammation. Both Th1 and Th2 pathways may be involved in each phase, either concomitantly or sequentially. Cytokines involved in immune responses, such as TNF-α, interleukin-1, interleukin-6, and possibly interleukins 12 and 18, may play a key role in this phase. Once CD4+ T cells are activated, effector cytokines involved in the adaptive immune response, including TNF-α and interferon-γ, as well as interleukins 4 and 13, mediates the effector phase of the intestinal inflammatory response. Novel cytokines such as TL1A and interleukins 23, 27, and 31 may also contribute to the effector phase (figure 3).

FIGURE 1 THE TRADITIONAL PARADIGM FOR THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE (*IBD*).

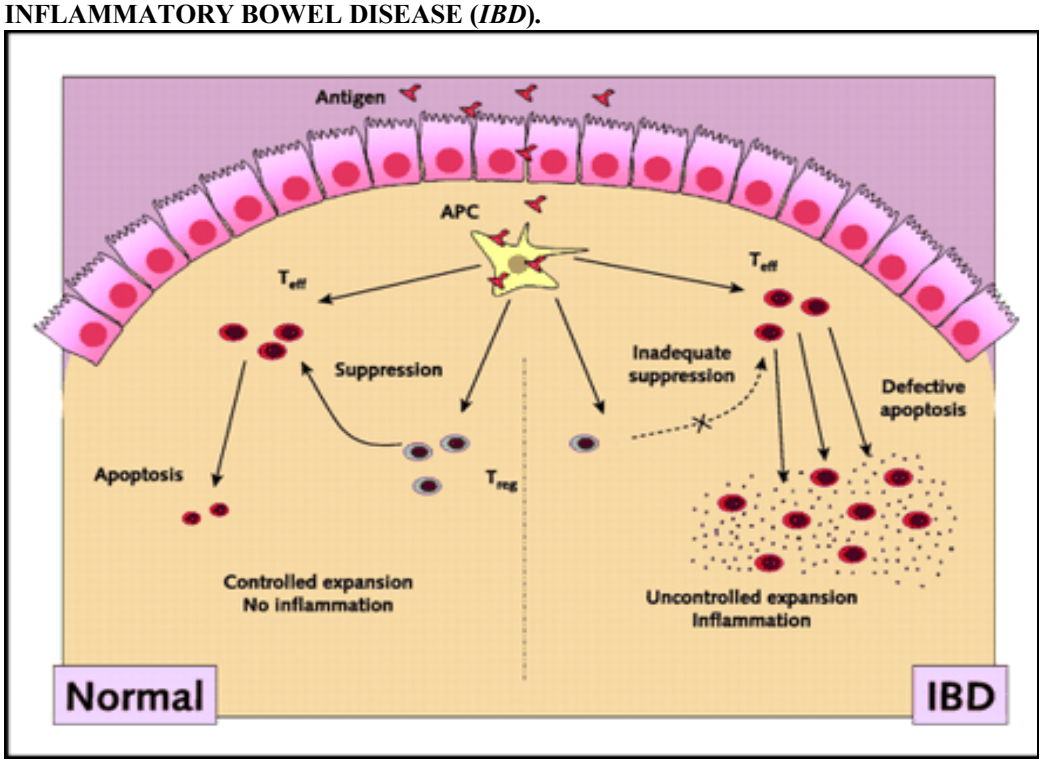
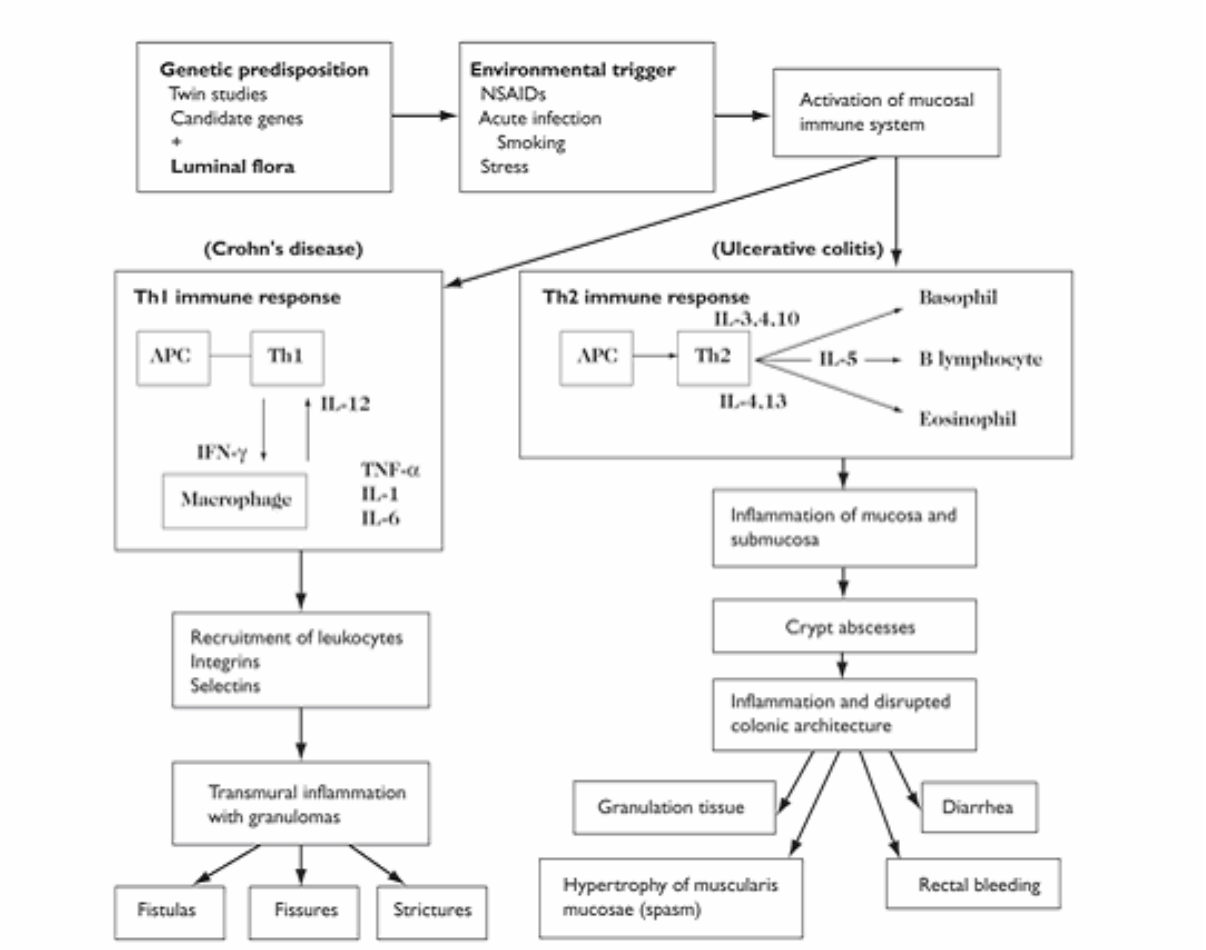


FIGURE 2 SCHEMATIC REPRESENTATION OF PATHOGENESIS OF CD & UC[10]:

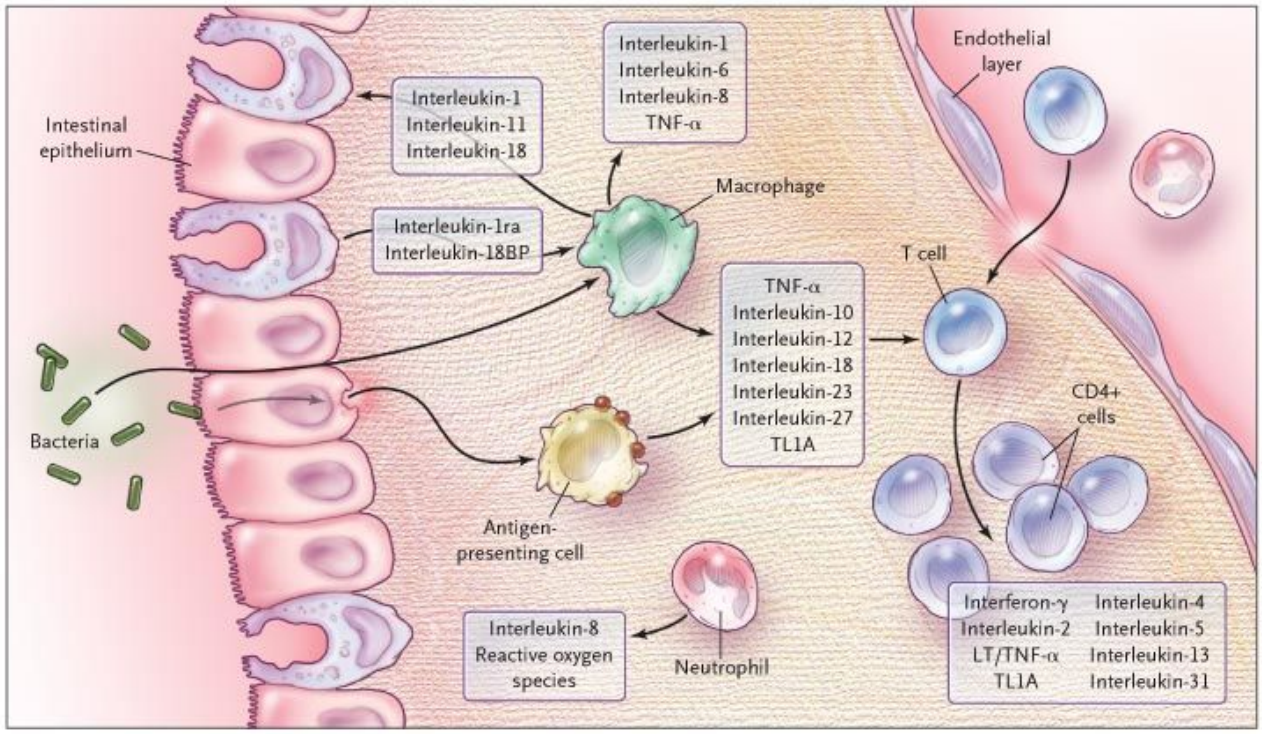


APC indicates antigen-presenting cell; IFN-γ, interferon γ; IL, interleukin; NSAIDs, nonsteroidal anti-inflammatory drugs; Th, T helper; and TNF-α, tumor necrosis factor α.

TABLE 1 CYTOKINE PROFILES: COMPARISON BETWEEN ULCERATIVE COLITIS AND CROHN'S DISEASE

Cytokine	Ulcerative Colitis	Crohn's Disease
IL-1	Normal in serum; raised in mucosa	Normal in serum; raised in mucosa
IL-2	Normal in serum and Mucosa	Raised in serum and Mucosa
IL-6	Normal in serum; raised in mucosa	Raised in serum and Mucosa
IL-8	Undetectable in serum; high in mucosa	Undetectable in serum; mucosa levels not reported
INF γ	Undetectable in serum; mucosa levels not Reported	Serum levels not known; high in mucosa
TNF-α	Serum levels high; mucosa levels high	Serum levels high; mucosa levels high
IL-4	Serum levels not known: Mucosa levels high	Not reported
IL-5	Serum levels not known: Mucosa levels high	Not reported
IL-12	Not reported	Serum levels not known: Mucosa levels high
IL-13	Serum levels not known: Mucosa levels high	Not reported

FIGURE 3 WORKING HYPOTHESES REGARDING THE ROLE OF CYTOKINES IN THE PATHOGENESIS OF CROHN'S DISEASE. BP DENOTES BINDING PROTEIN, RA-RECEPTOR ANTAGONIST, ROS-REACTIVE OXYGEN SPECIES & LT LYMPHOTOXIN.



As per reference 14 & 15 found unexpected results from animal models of intestinal inflammation, which have led investigators to reject traditional pathogenetic concepts of IBD. As per reference 16 & 17 says that, there is emerging evidence that defects in the innate immune system may play an equal or even more important role in IBD. It is the body's nonspecific defense against pathogens; may be equally important, especially in the inductive phase of disease. It responds immediately or within the first few hours after a challenge. Innate immune system is commonly considered the first line of defense and includes such physical barriers as the skin and the intestinal mucosa as well as immune cells that identify and remove foreign bodies. The innate immune system reacts to the chemical properties of the antigen rather than to the specific antigen itself. The acquired immune system, however, responds specifically to antigens. The antigen is processed and recognized, and immune cells that are specific to that antigen are then selectively proliferated. The intestinal epithelium, which is considered to be part of the innate immune system, plays an active role in the maintenance of mucosal homeostasis[18]. Consequently, dysfunction of epithelial cells can contribute to and may even be the primary defect in IBD. Epithelial cells form a tight, highly selective barrier between the body and the intraluminal microenvironment. Failure of this barrier may result in intestinal inflammation, most likely through exposure to fecal antigens leading to inappropriate activation of the mucosal immune system. as per reference 19 & 20 proved that the mice with genetically introduced defects in intestinal permeability develop intestinal inflammation.

Within the intestinal mucosa, there is constant cross-talk between the epithelium and cells of the immune system[21]. Epithelial cells can act as antigen-presenting cells because they are able to take up and process antigens and present them to cells of the immune system, along with appropriate activating stimuli. Aberrant communication, therefore, has the potential to create inappropriate signals that activate effector cells and lead to inflammation.

Epithelial cells are avid producers of chemokines, which regulate recruitment of acute and chronic inflammatory cells within the intestinal mucosa. In addition, many cytokines that are considered central to the pathogenesis of IBD, such as TNF-α, interleukin-1, and interleukin-6, are expressed in the intestinal epithelium. Aberrant secretion of these proinflammatory chemokines and cytokines by epithelial cells is an integral part of the dysregulated immune response that initiates or perpetuates intestinal inflammation[22,23].

In chronic inflammatory diseases, such as inflammatory bowel disease, several cytokines recruit activated immune and inflammatory cells to the site of lesions, thereby amplifying and perpetuating the inflammatory state[24]. These activated cells produce many other mediators of inflammation. As per reference 25 that there is greatly increased production rates of nitric oxide (NO) into the colonic lumen of patients with inflammatory bowel disease and provided evidence for the hypothesis that the enzyme, inducible NO synthase (iNOS), is the source of excess NO production. Several cytokines including TNF-α and IL-1β**,** IL-6 have been shown to be upregulated in IBD and serve to amplify and perpetuate tissue damage. Furthermore, chemokines are also upregulated, thus providing a continuous signal for the influx of leukocytes[26].

The production of IL-1β, TNF-α, IL-6, granulocyte, macrophage and many chemotactic cytokines (chemokines) is increased in patient's inflammatory bowel disease. All these cytokines have important roles in the inflammatory process.

(B) GENETIC FACTOR:

Studies have shown evidence for a genetic predisposition to IBD. First-degree relatives of patients with IBD have a 4- to 20-fold increased risk and a 7% absolute risk[27]. Among family members with CD, there is strong concordance within disease category and disease location. However, despite the evidence supporting a genetic predisposition, most patients with IBD have no close relatives with IBD[28]. Monozygotic twins have a significantly higher concordance rate than dizygotic twins. The genetic contribution appears to be greater in CD than in UC[29]. Overall, the genetic predisposition to CD and UC appears to be multifactorial, as opposed to being linked to one specific gene (Table 2).

(i) NUCLEAR FACTOR-KAPPA B

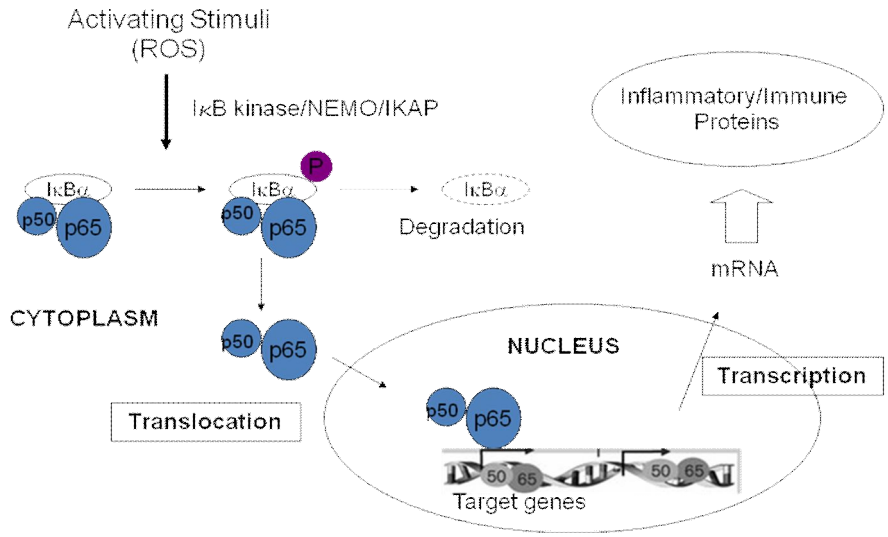
NF-kappa B is a transcription factor. In unstimulated cells, NF-κB is found in cytoplasm and is bound to IκBα and IκBβ, which prevent it from entering the nuclei[30] . When these cells are stimulated, specific kinases phosphorylate IκB, causing its rapid degradation by proteasomes[31,32]. The release of NF-κB from IκB results in the passage of NF-κB into the nucleus, where it binds to κB sites in the promoter regions of genes for inflammatory proteins such as cytokines, enzymes, and adhesion molecules(See figure 4).

TABLE: 2 GENETIC ASSOCIATIONS IN INFLAMMATORY BOWEL DISEASE:

Loci Designation	Chromosome Location	Disease Association	Candidate Genes	Phenotype Correlation
IBD1	16q12	CD	CARD15/NOD2	Earlier disease onset, small intestinal localization and strictures
IBD2	12q13	Indeterminate colitis and terminal ileal CD	VDR, NRAMP2, STAT6, and MMP-18	Not reported
IBD3	6p13	CD and UC	Major histocompatability complex and TNF	Not reported
IBD4	14q11	CD	TCRα/δ, leukotriene B4 receptor, and major histocompatability complex type I, antigen presentation–associated proteosome cluster	Not reported
IBD5	5q	Indeterminate colitis and colonic and ileal–colonic CD	Cytokine cluster (IL-3, IL-4, IL-5, and IL-13; IRF-1; and CSF-2)	Perianal disease and early onset
IBD6	19p	CD	ICAM-1 and DDXL	Not reported
IBD7	1p	CD and UC	Mucin 3, EGFR, and HGF	Not reported

* CARD = caspase-activating and recruitment domain; CD = Crohn disease; CSF-2 = colony-stimulating factor isoform-2; DDXL = DEAD/DEAH box helicase; EGFR = epidermal growth factor receptor; HGF = hepatocyte growth factor; IBD = inflammatory bowel disease; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; IRF-1 = interferon regulatory factor isoform-1; MMP = matrix metalloprotease; NRAMP2 = natural resistance-associated macrophage protein 2; STAT = signal transducer and activator of transcription; TCR = T-cell receptor; TNF = tumor necrosis factor; UC = ulcerative colitis; VDR = vitamin D receptor.

FIGURE 4 SCHEMATIC DIAGRAM OF NF-κB ACTIVATION



The activated form of NF-κB is a heterodimer, which usually consists of two proteins, a p65 (also called relA) subunit and a p50 subunit. Other subunits, such as rel, relB, v-rel, and p52, may also be part of activated NF-κB, and it is likely that the different forms of NF-κB may activate different sets of target genes. Stimuli like oxidative stress, cytokines (IL-1, IL-6, TNF-α), bacteria and viruses can release NF-kappaB from their inactive cytoplasmatic form to the nucleus.

As per reference 33 showed a genetic association of IBD with the activation of NF-κB.

NF-κB plays a critical role in the expression of many genes for cytokines, enzymes, and adhesion molecules in chronic inflammatory diseases[34,35,36,37]. One such gene is that for inducible nitric oxide synthase, the expression of which is increased in colonic epithelial cells in patients with ulcerative colitis[38]. Interleukin-1β and TNF-α may influence the severity of disease, possibly by the persistent activation of NF-κB.

(ii) NOD2 MUTATIONS IN CROHN'S DISEASE:

Intracellular NOD receptors and transmembrane Toll-like receptors (*TLRs*) are important molecules for the recognition of pathogen associated molecular patterns, activation of the innate immune system, and maintenance of mucosal homeostasis. Muramyl

dipeptide, a component of the bacterial cell wall, binds to CARD15/NOD2(first gene that has been described as conferring susceptibility to Crohn's disease used by cells of the innate immune system), which then activates nuclear factor-κB (*NF-κB*)(**See Figure 5).** NOD2 is expressed in macrophages (*right*) and in Paneth cells at the base of intestinal crypts (*left*). An epithelial-oriented "loss of function" pathway may be associated with inability to effectively clear intraluminal microorganisms, as a result of decreased antibacterial peptide (defensins) secretion by Paneth cells (*left*). Alternatively, the "loss of function" may also affect the ability of NOD2 to attenuate signaling through TLR-2 in macrophages, the net result being enhanced NF-κB activation and proinflammatory cytokine production (*right*). An alternative hypothesis describes a "gain-of-function" phenotype, that is, direct MPD/NOD2-mediated increase in NF-κB signaling, with a similar end result of increased secretion of proinflammatory cytokines and chronic intestinal inflammation.

(C) ENVIRONMENTAL FACTOR[39] :

Environmental factors unquestionably play a major role in the pathogenesis of IBD. The major environmental factors implicated in the pathogenesis of IBD are shown in below **figure 6.** All these factors ultimately leads to the stimulation of the immune system & production of various cytokines cause IBD

FIGURE 5 FUNCTIONAL SIGNIFICANCE OF NOD2 GENE MUTATION IN CROHN'S DISEASE

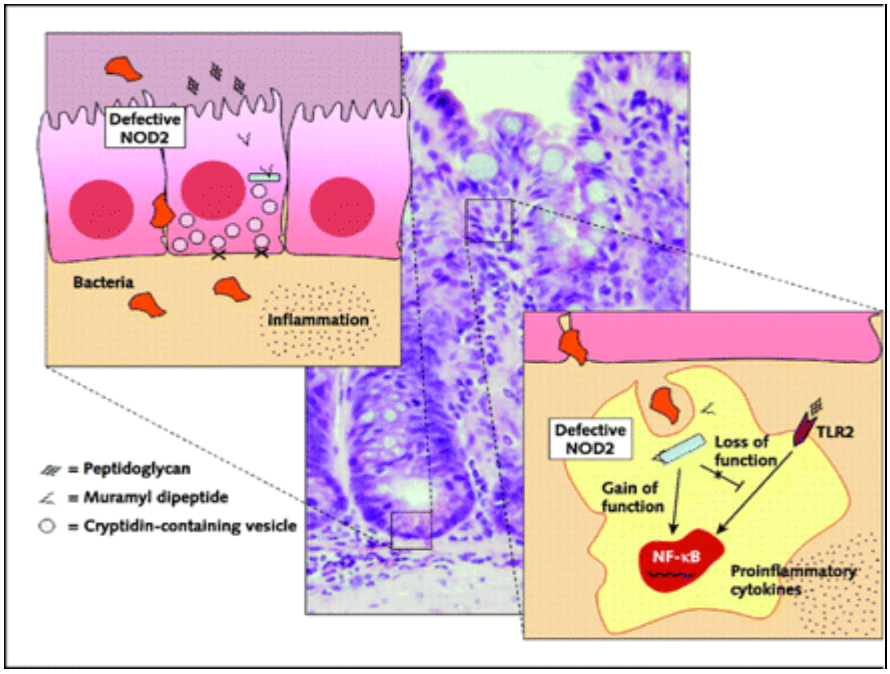


FIGURE 6 DIFFERENT ENVIRONMENTAL FACTORS ASSOCIATED WITH IBD:

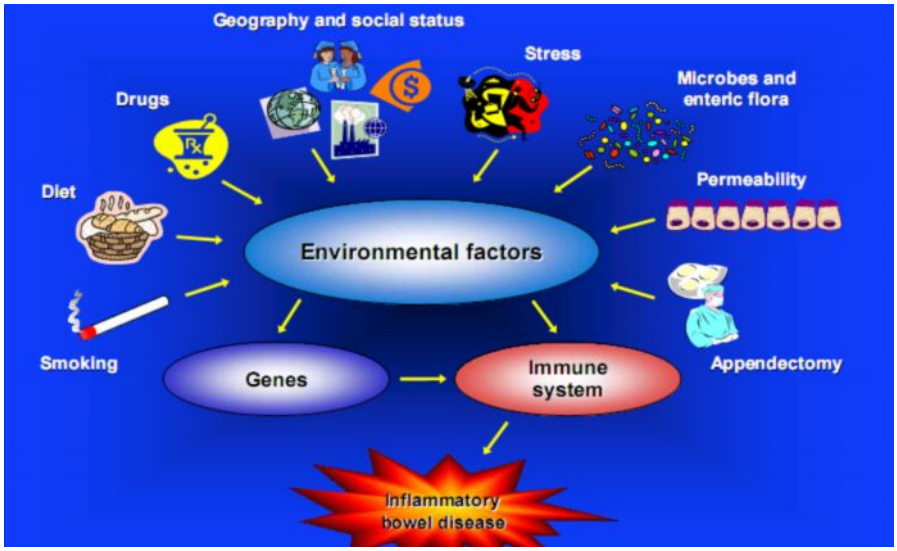


TABLE 3 ASSOCIATION OF BACTERIA WITH IBD

Variable	Evidance for association
Mycobaterium avium	May be the causative factor ia a subset of patients with CD
Echerichia coli	Increased incidence in postopeative CD recurrence
Helicobactor species	The presence of *H. Bilis* & *H. Hepaticus* results in more severe colitis in mice
Commensal bacteria	Overall, very strong evidence has led to the "no bacteria, no IBD" theory.

(A) RISK OF SMOKING IN IBD:

Smoking is an important environmental factor, having different effects in ulcerative colitis (UC) and Crohn's disease CD). A recent meta analysis partially confirmed previous findings that smoking was found to be protective against ulcerative colitis and, after onset of the disease, might improve its course, decreasing the need for colectomy. However, smoking increases the risk of developing Crohn's disease and worsens its course, increasing the need for steroids, immunosuppressant and re-operations. Smoking cessation aggravates ulcerative colitis and improves Crohn's disease. Data are however, largely conflictive as well as the potential mechanisms involved in this dual relationship are still unknown. The link between smoking & IBD was first made in 1982 as per reference 40 noticed a low proportion of ulcerative colitis patients were smokers. Two years later a case control study as per reference 41 & reported that the relative risk of developing crohn's disease was in those who smoked before disease onset, and for those with a current smoking habit. Relative risk of UC was also higher in former smokers & current smoking decreased the risk of UC. Interestingly in patients with who stopped smoking, UC develop in 52% of patients, in the first three years after cessation, as reported as per reference 42 in concordance with other studies[43]. In contrast active smoking in early childhood was associated with a gradually increased risk for developing UC[44].

The reason behind the opposite effect of smoking observed in CD & UC remains obscure. Nicotine is thought to be the most important agent responsible for the effect of smoking. Smoking cigarettes results in a fast absorption of nicotine and subsequent distribution over all tissues followed by accumulation and simultaneously started degradation. Nicotine binds to acetylcholine receptors located both in the central nervous system and the peripheral nervous system. Presynaptic stimulation results in the release of neurotransmitters and local hormones, which in turn attributes to either suppression or not of the immune system[45]. Nicotine has an inhibitory effect on eicosanoid production. As eicosanoids are considered to be mainly secondary mediators of inflammation, they will only modulate the course of the inflammation initiated by other bio-active pro-inflammatory mediators, such as the cytokines TNF α or IL- 1β.

In UC, the colonic mucosal layer is thin or absent, in contrast to CD where it is significantly thicker[46], with nicotine having been shown to increase mucin synthesis[46,47]. Smokers with IBD having significantly reduction in mucosal cytokines levels, specifically IL- 1β & IL- 8 in patients with UC, & IL- 8 in patients with CD[48]. Beneficial effect of nicotine in active UC may be associated with a decreased in IL- 8 expression. Hypoperfusion of the rectum & of acutely damaged colonic tissue may play an addition role[49] on the contrary, in CD, several plasma antioxidant parameters are altered, the total radical-trapping antioxidant potential is decreased[50], & abnormalities are present in the micovasculature[51]. Smoking through increased carbon monoxide concentration might amplify the impairment in the vasodilation capacity of chronically inflamed micro vessels, resulting in ischemia & perpetuating ulceration & fibrosis[49].

After smoking rectal blood[52] flow in UC was diminished, whereas both gastric acid secretion and motility[53] are enhanced in man. It also has been suggested that nicotine tightens the gut, which consequently leads to a diminished permeability and less availability of mediators of inflammation[54] although increased permeability mainly is found in the ileum, more or less resembling Crohn's disease. The diminished availability of inflammatory mediators therefore could be the result of local changes in blood flow and subsequent disturbed distribution in the gastrointestinal tract.

(B) DIET:

Diets that are low in fiber and high in refined sugars could possibly contribute to the development of Crohn's disease (Drug digest). High sucrose intake was associated with risk for both UC and CD, while fat (especially animal fat) was associated with increased risk for UC only.

Interestingly, fructose intake was negatively associated with risk for IBD[55]. A case-control Netherlands study of 43 recently diagnosed (within the previous six months) UC patients and 43 age and gender matched controls examined dietary intakes for five years prior to the study using a cross-check dietary history method. In this study, high intakes of vitamin B6 and mono and polyunsaturated fats were associated with increased risk. The most significant finding was an increased relative risk for IBD associated with fast food consumption. Eating fast food twice weekly resulted in a relative risk of 3.9 for UC.

(C) CERTAIN MEDICATIONS:

Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs that reduce pain, fever, and inflammation. Popular NSAIDs such as ibuprofen, aspirin, and naproxen (if used excessively) can help to tear down the mucus protective lining of the digestive tract thereby promoting IBD.

(D) GEOGRAPHY & SOCIAL STATUS:

IBD is more prevalent in northern region compared with southern region & it is more prevalent in western countries than in developing countries. In other words higher economic status increases the risk of IBD. The main reason behind this is "Hygiene theory": Higher socioeconomic status is associated with less frequent helminthes infections during childhood. This result in a lack of mucosal TH2/anti-inflammatory or regulatory cytokines or both & leaves poinflammatory effector mechanisms unopposed[56].

(E) STRESS:

Stress will cause neuroendocrine response which will decrease the mucus secretion and thereby weaken the mucosal barrier & increases the permeability. Thus increases the risk of developing IBD (**See Figure 7).**

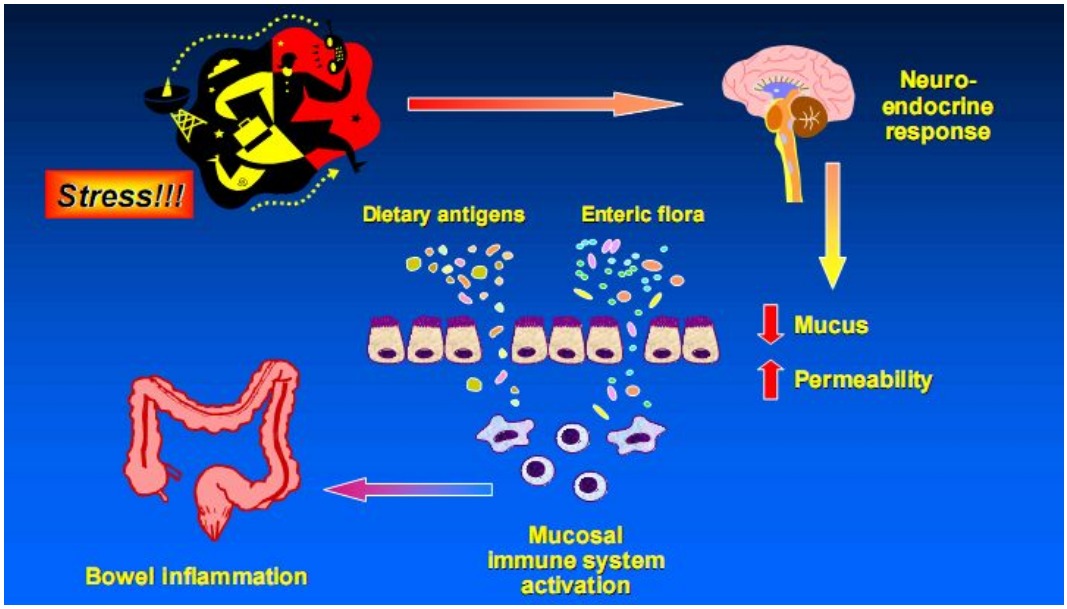
(F) BACTERIAL FACTOR:

Bacterial factor considered as an antigen, leads to the activation of intstinal immune system & epithelial cells. Activated immune system leads to the secretion of Cytokines, reactive oxygen species, nitric oxide, proteases & ecosanoids. Release of these inflammatory mediators causes local mucosal damage. In Table-3 certain type of bacterias & their association with the disease is highlighted.

(G) GUT PERMEABILITY

An impaired colonic mucosal barrier leading to increased intestinal permeability has been demonstrated in patients with UC. Local leaks due to apoptosis of colonic epithelium comprise the primary lesion in mild UC. Moderate to severe UC is characterized not only by extensive local leaks but also by highly permeable ulcerous lesions[57]. Patients with UC have also demonstrated decreased colonic mucin. An in vitro study demonstrated a possible interaction between bacterial peptides and the mucosa in UC, resulting in depletion of mucus secretion by goblet cells[58]. Medical therapy leading to remission not only results in decreased inflammation but also improved gut barrier integrity[59].

FIGURE 7 ROLE OF STRESS IN IBD



(H) APPENDECTOMY:

Patients who have been appendectomized have a lesser risk of developing UC. Moreover, in the few appendectomized patients who develop UC, disease course is less severe, with a decreased need of colectomy compared to non-appendectomized[60,61]. In Crohn's disease, the effect of previous apendectomy remains debated. Some series reported an increased risk of Crohn's disease after appendectomy[62,63] and others did not[64,65]. An increased risk of surgery for Crohn's disease was observed only in patients with perforated appendicitis[63]. In contrast to smoking, appendectomy has no effect on Crohn's disease severity. The response of IBD to the only environmental factors clearly documented so far but smoking and appendectomy is quite different in UC and in CD.

(4) OXIDATIVE STRESS:

Signs of increased oxidative stress are in evidence in the intestinal mucosa of patients with ulcerative colitis and may be secondary to inflammation. One study examined signs of oxidative stress and plasma antioxidant levels in controls compared to patients with UC and CD. Oxidative DNA damage was noted in both IBD groups compared to controls, measured by production of 8-hydroxy-deoxy-guanosine (8-OHdG). Other researchers have also found increased oxidative stress in ulcerative colitis patients. Mucosal biopsies of UC patients were analyzed and shown to have increased reactive oxygen intermediates & DNA oxidation products (8-OHdG). Decreased levels of endogenous antioxidant superoxide dismutase were also observed. This supports the theory that free radicals can produce damage to mucosal proteins in IBD. A theory proposed by several researchers involves TNF α produces reactive oxygen species (ROS); ROS in turn activate nuclear factor- kappa B (NF-kB), which then enhances further TNF α production, propagating a vicious cycle **(Figure 8).**

(5)THE ROLE OF GLYCOSAMINOGLYCANS

The gastrointestinal (GI) extra-cellular matrix is composed of the proteins collagen and elastin, and ground substance that include glycosaminoglycans (GAGs). GAGs are abundant in the basement membrane, lamina propria, and submucosa of the GI tract. The composition of GAGs may significantly affect both the permeability of the colon and immune/inflammatory reactions. Analysis of diseased, resected colons yielded altered GAG content in the colon of patients with IBD and colonic neoplasia compared to tissue from undiseased colons. In histologically normal colon tissue the majority of GAG content con-sists of chondroitin and dermatin sulfate, with smaller amounts of hyaluronic acid and heparan sulfate. Ulcerative colitis yielded a distinctly abnormal distribution of GAGs, with significantly greater amounts of total glycosaminoglycans, heparan sulfate, and hyaluronic acid than control tissue. Colonic neoplasias were also found to contain these abnormal GAG profiles, but to a greater extent than UC tissue[66].

Other researchers report the alterations are limited to the mucosa in UC, with substantial loss of GAGs from the subepithelial basal lamina. It is hypothesize that alterations in negatively charged sulfated compounds could significantly affect the passage of substances through the colonic mucosa, contributing to leakage of proteins and fluids, thrombosis, and extensive remodeling observed in UC and other inflammatory bowel conditions. Some researchers hypothesize these alterations may contribute to the inflammatory process since hyaluronic acid can interact directly with lymphocytes, inhibit macrophage response to cytokines, and enhance phagocytosis. GAG content has been associated with alteration in the distribution of macrophages reactive to TNF-α [67].

FIGURE 8 THE POTENTIAL ROLE OF REACTIVE OXYGEN SPECIES IN INFLAMMATION

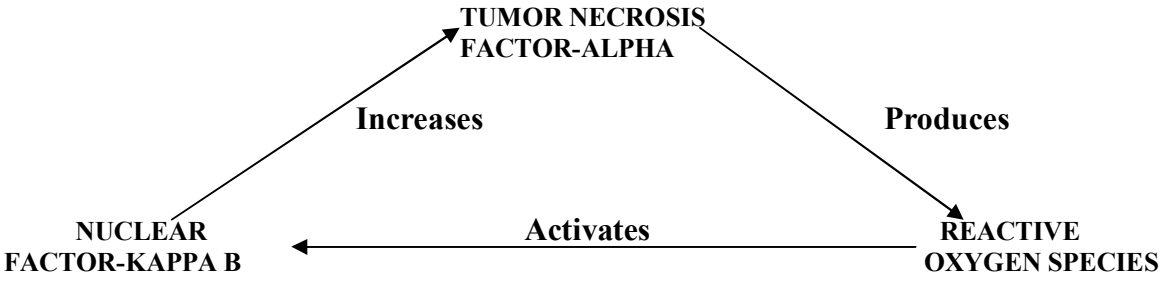
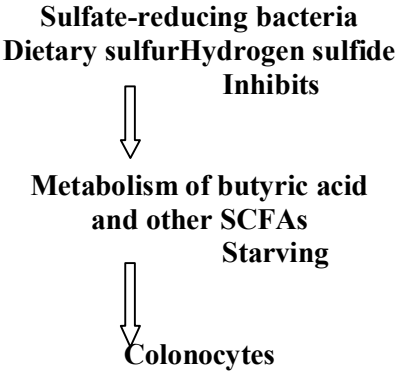


FIGURE 9 A POTENTIAL MECHANISMS FOR HYDROGEN SULFIDE TOXICITY



(6)THE SULFUR-BUTYRIC ACID CONNECTION TO IBD:

Butyric acid, a four-carbon short chain fatty acid (SCFAs) and several other SCFAs, including propionic and acetic acids, are produced in a healthy colon by fermentation of fiber and other carbohydrates. Butyric acid provides the primary fuel for colonocytes. Proper ion transfer, mucus synthesis, phase II detoxification, and lipid synthesis for cell membrane integrity in the colonocytes depend on butyrate oxidation[68]. Impaired metabolism of SCFAs has been implicated as a factor in UC. As compared with reference 69 butyrate metabolism in healthy controls with that of hospitalized patients with severe ulcerative colitis and UC patients in remission. They measured butyrate metabolism after rectal instillation of C-labeled C0 in the breath. Patient's butyrate by measuring with active UC had significantly lower butyrate oxidation than patients in remission (who had normal butyrate oxidation) or controls. Three patients with inactive disease had decreased butyrate oxidation and interestingly, all three relapsed within a few weeks. Perhaps decreased oxidation of SCFAs is a good predictor of possible relapse and occurs before other signs of inflammation. Because normal oxidation was observed in patients in remission, faulty SCFA oxidation is likely to be a result rather than a primary cause of ulcerative colitis.

Other researchers compared the rate of butyrate, glucose, and glutamine oxidation to carbon dioxide in colonoscopy biopsy specimens from 15 patients with quiescent or mild colitis to specimens from 28 controls with normal colonic mucosa. Butyrate, but not glucose or glutamine, oxidation was significantly impaired in the UC patients compared to controls, even though the disease was mild. High concentrations of sulfate-reducing bacteria with concomitant elevation of hydrogen sulfide have been noted in patients with UC. Hydrogen sulfide can potentially damage the gut mucosa by inhibiting butyrate oxidation in the mitochondria, essentially starving the colonocyte (Figure 9). In experiments on human colonocytes isolated from colectomy patients, hydrogen sulfide and other sulfur compounds inhibited butyrate oxidation by 75 percent in the distal colon and 43 percent in the ascending colon. The authors of the study conclude that the ìmetabolic effects of sodium hydrogen sulfide on butyrate oxidation along the length of the colon closely mirror metabolic abnormalities observed in active ulcerative colitis[68].

CONCLUSION:

In light of above evidence there are new targets like NF kB receptor, NOD_2, inflammatory mediators, PDE4 inhibition, COX-2 inhibition are the new avenues for better treatment of inflammatory bowel disease. Future development in this new areas can give better fight against IBD.

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