Pathogenesis of inflammatory bowel disease (IBD)

S Jain, A Pithadia

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Abstract

The inflammatory bowel disease (IBD) is chronic inflammatory disease of gastrointestinal tract that include Crohn's disease and ulcerative colitis, characterized by chronic recurrent ulceration of the bowel and of unknown etiology. They have become important health problems. In present review, the pathophysiology of IBD is reviewed, with emphasis on the genetic predisposition and inflammatory cascades underlying the production of symptoms and the course of the disease.

INTRODUCTION

Inflammatory bowel diseases are chronic relapsing conditions. Epidemiology and etiology of the diseases remain consistent. Ulcerative colitis and Crohn's diseases are differing in extent of inflammation and site in gastrointestinal tract. Both diseases occur in adult and children. Crohn's disease (CD) is an inflammatory process that can affect any portion of the digestive tract, but is most commonly seen in the ileocecal region. It is the last part of the small intestine. It may affect any part of gastrointestinal tract including colon, small bowel (duodenum, jejunum and /or ileum), the anus, stomach or esophagus but not rectum which is involved in ulcerative colitis. UC is an inflammatory disease of the large intestine, commonly called the colon. UC causes inflammation and ulceration of the inner lining of colon and rectum. This inner lining is called the mucosa. The inflammation of UC is usually most severe in the rectal area with severity diminishing toward the cecum, where small and large intestine join. The inflammation often resulting in diarrhea, blood and pus. Some of the common systemic symptoms are anorexia, weight loss, lethargy and fever and others viz. Pyoderma gangrenosum, iritis, uveitis, arthritis, thrombocytosis, hepatobiliary disease.

ETIOLOGY AND PATHOPHYSIOLOGY

Inflammatory bowel disease is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora. This aberrant response is most likely facilitated by defects in both the barrier function of the intestinal epithelium and the mucosal immune system.

GENETIC FACTORS

Over the past 15 years, a wide variety of candidate genes have been studied. Most associations identified between specific candidate genes, including major-histocompatibility-complex loci, and inflammatory bowel disease have not been reproducible, have not shed new light on pathogenesis, or have not facilitated diagnosis [1]. However, substantial progress has now been made with the use of the less biased approach of genome-wide screening with microsatellite DNA markers. Detailed mapping of chromosome 16 has recently resulted in the identification of a gene responsible, at least in part, for this linkage [2]. This gene encodes a cytoplasm protein designated NOD2 (also referred to as CARD 15 [caspase activation and recruitment domain]), which is expressed in macrophages and may serve as a so-called pattern-recognition receptor for bacterial lipopolysaccharide, perhaps regulating nuclear factor-□B(NF-□B) activation and macrophage apoptosis. European and North American patients with Crohn's disease, including those without a family history of inflammatory bowel disease, are more likely to have variants of NOD2 than are persons without Crohn's disease. Paradoxically, these NOD2 variants appear to result in reduced macrophage activation of nuclear factor- B in response to lipopolysaccharide. Persons who are homozygous for variant NOD2 may have a 20-fold or more increase in susceptibility to Crohn's disease, with a particular predilection for ileal disease [3]. Heterozygotes are also at increased risk. However, fewer than 20 percent of patients with Crohn's disease are homozygous for these NOD2 variants. A putative locus associated with early-onset Crohn's disease appears to be present on chromosome 5 in the vicinity of genes encoding a variety of cytokine receptors

[4] .

ENVIRONMENTAL AND INFECTIOUS FACTORS

Accumulating evidence suggests that the luminal flora is a requisite and perhaps central factor in the development of inflammatory bowel disease [5] . Smoking may modify the phenotype, it protects against ulcerative colitis but increase risk of Crohn's disease [67] .Among myriad factors studied, and the most consistent are the use of nonsteroidal anti-inflammatory drugs which can lead to disease flares, possibly related to an altered intestinal barrier and early appendectomy which is associated with a reduced incidence of ulcerative colitis [89] . Many types of pathogens are involved in the pathogenesis of inflammatory bowel disease. However E. coli is the major microorganism found in the patients with ulcerative colitis [10] . Role of bacteria in the pathogenesis of inflammatory bowel disease is well understood [11] . Pathogenic bacteria secrete enterotoxins capable of altering gut permeability and causing systemic effects, elaborate immunosuppressive proteins that interfere with normal gut immune response and directly interfere with epithelial cell metabolism. A popular theory among researches is that ulcerative colitis is characterized by an abnormal host response to normal colonic bacteria i.e. a cross reactivity between antibodies produced against bacteria and mucosal proteins. The researchers further demonstrated a bacterial antigen could contribute to either an abnormal Th 1 or Th 2 response that progressed to colitis [12] .

IMMUNE RESPONSE AND INFLAMMATORY PATHWAYS

The aggregate effect of genetic, environmental, and other processes is the sustained activation of mucosal immune responses [13] .It remains unclear whether the immune system is activated as a result of an intrinsic defect (either constitutive activation or the failure of down-regulatory mechanisms) or because of continued stimulation resulting from a change in the epithelial mucosal barrier [1415] .Normal epithelium, with its highly evolved tight junctions and products of goblet-cell populations, most notably trefoil peptides and mucin glycoproteins, provides an effective barrier against luminal agents. The integrity of the barrier may be compromised by genetic variations in key molecular determinants, a diminished reparative response to injury, or exogenous agents, such as nonsteroidal anti-inflammatory drugs. Chronic, recurrent intestinal inflammation appears to result from stimulation of the mucosal immune system by products of commensally bacteria in the lumen. Antigens from dietary sources may also contribute. Stimulation may occur as a result of the penetration of bacterial products through the mucosal barrier, leading to their direct interaction with immune cells, especially dendritic cells and lymphocyte populations, to promote a classic adaptive immune response. Alternatively, bacterial products may stimulate the surface epithelium, possibly through receptors that are components of the innate immune-response system; the epithelium can, in turn, produce cytokines and chemokines that recruit and activate mucosal immune cells. Activation of classic antigen-presenting cells, such as dendritic cells, or direct stimulation through pattern-recognition receptors promotes the differentiation of type 1 helper T cells (Th1) in patients with Crohn's disease or, possibly, atypical type 2 helper T cells in patients with ulcerative colitis. The stereotypical products of Th1 promote a self-sustaining cycle of activation with macrophages. In addition to producing the key cytokines that stimulate Th1 (interleukin-12, interleukin-18, and macrophage migration inhibitor factor), macrophages produce a mix of inflammatory cytokines, including interleukin-1, interleukin-6, and most notably tumor necrosis factor, which target a broad variety of other types of cells. The latter include endothelial cells, which then facilitate the recruitment of leukocytes to the mucosa from the vascular space, as well as fibroblasts and epithelium, modulating their functional properties. Most important, these functions may be altered either by genetically determined variants, as exemplified by germ-line mutations in the gene encoding NOD2, the product of the IBD1 locus, in some patients with Crohn's disease, or by the environmental factors.

It remains unclear whether the immune system is activated as a result of an intrinsic defect (either constitutive activation or the failure of down-regulatory mechanisms) or because of continued stimulation resulting from a change in the epithelial mucosal barrier .Substantial progress has been made in characterizing immune-cell populations and inflammatory mediators in patients with inflammatory bowel disease and murine models [1617] . There is reasonable consensus that the mucosa of patients with established Crohn's disease is dominated by CD4+ lymphocytes with a type 1 helper-T-cell (Th1) phenotype, characterized by the production of interferon- and interleukin-2. In contrast, the mucosa in patients with ulcerative colitis may be dominated by CD4+ lymphocytes with an atypical type 2 helper-T-cells (Th2) phenotype, characterized by the production of transforming growth factor (TGF-) and interleukin-5 but not interleukin-4 [18] . In murine models, the effects of the activation of Th1 cells may be enhanced by the concomitant

decrease in subgroups of suppressor T cells, variously designated Th3 or Tr1, which produce the down-regulatory cytokines interleukin-10 and TGF-β [19].

In-depth characterization of murine lines suggests that the stereotypical Th1 cytokines activate macrophages, which in turn, produce interleukin-12, interleukin-18, and macrophage migration inhibitor factor and thus further stimulate Th1 in a self-sustaining cycle. The activation of central immune-cell populations is eventually accompanied by the production of a wide variety of nonspecific mediators of inflammation. These include many other cytokines, chemokines, and growth factors as well as metabolites of arachidonic acid (e.g., prostaglandins and leukotrienes) and reactive oxygen metabolites such as nitric oxide [1620]. These mediators enhance the inflammatory process itself and tissue destruction, which eventuate in the clinical manifestations of disease. Recruitment of additional leukocytes from the vascular space to sites of disease activity is especially important in maintaining inflammation and depends on the expression of adhesion molecules in the local microvasculature and counter ligands on the various leukocyte populations [2122].

Activation of the protean transcriptional regulatory factor nuclear factor-κB (NF-κB) is a common pathway central to cell activation and the production of diverse inflammatory mediators, including a variety of cytokines and chemokines [13]. It also modulates resistance to programmed cell death (apoptosis). Several inflammatory factors implicated in inflammatory bowel disease activate NF-κB by eventually stimulating an intermediate kinase such as NF-κ-B–inducing kinase (NIK) or mitogen-activated protein kinase kinase 1 or 3 (MEKK1 or MEKK3) or by binding to receptor-interacting protein 2. These lead to phosphorylation of the inhibitor of κB kinase (IKK) and subsequent dissociation of NF-κB (itself a dimer). NF-κB then travels to the nucleus, where it can effect gene transcription. The phosphorylated constituents are subject to degradation by proteosomes after ubiquitination. The spectrum of mediators that activate this pathway includes inflammatory cytokines such as interleukin-1 and tumor necrosis factor (TNF), which bind to their respective cell-surface receptors, as well as microbial products such as lipopolysaccharide, which bind to cell-surface receptors that are members of the toll-like receptor family of pattern-recognition receptors. The pathway is also activated by NOD2 (also referred to as CARD 15), an intracytoplasmic receptor that is activated by the entry, through mechanisms yet to be defined, of bacterial lipopolysaccharide into the cytoplasm. NOD2 is the product of the IBD1 gene; germ-line mutations, which are present in many patients with Crohn's disease, appear to alter the activation of the NF-κB pathway.

NF-κB was first identified as a regulator of the expression of the Kappa light chain gene in murine B lymphocytes but has subsequently been found in many different cells. Several different NF-κB proteins have been characterized. The activated form of NF-κB is a heterodimer, which usually consists of two proteins, a p65 and p50 subunit. In unstimulated cells, NF-κB is found in cytoplasm and is bound to IκBα and IκBβ, which prevent it from entering the nuclei when these cells are stimulated, specific kinases phosphorylate IκB, causing its rapid degradation by proteasomes. Activation of NF-κB involves the phosphorylation and subsequent proteolytic degradation of the inhibitory protein IκB by specific IκB kinases. The free NF-κB (a heterodimer of p50 and p65) then passes 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. P denotes protein, and mRNA.

ROLE OF PGD (PROSTAGLANDIN D), LTC (LEUKOTRIENE C¬) AND PAF (PLATELET ACTIVATING FACTOR)

Degranulation of mast cells is reported to be involved in active Crohn's disease [23]. It was reported that mast cells in the actively involved areas of ulcerative colitis released greater amount of PGD_2 in parallel to histamine and LTC_4 in a rat experimental colitis model [24]. This was accompanied by a significant granulocyte infiltration, indicating the likelihood of involvement of PGD_2 in inflammatory bowel disease pathogenesis. The increased secretion of PAF was detected in the stool of patients with active Crohn's disease which is not found in those of patients with irritable bowel syndrome [25].

ROLE OF OXIDATIVE STRESS, GLYCOSAMINOGLYCANS AND SULPHUR - BUTYRIC ACID CONNECTION

IBD is a multifactorial disorder of unknown etiology. However very good evidence from animal and clinical studies document that an enhanced formation of reactive oxygen or nitrogen species importantly contributes to the pathophysiology of IBD. It is reported that monocytes from patients with Crohn's disease [26] and polymorph nuclear cells from patients with ulcerative colitis [27] have an increased capacity to generate free oxygen radical which are involved

in the process of lipid peroxidation. Lipid peroxidation refers to the oxidative degradation of lipids. It is the process whereby free radicals "steal" electrons from the lipids in cell membranes, resulting in cell damage. This process proceeds by a free radical chain reaction mechanism. It most often affects polyunsaturated fatty acids, because they contain multiple double bonds in between which lies methylene $–CH_2-$ groups that possess especially reactive hydrogen. As with any radical reaction the reaction consists of three major steps: initiation, propagation and termination [28].

INITIATION

Initiation is the step whereby a fatty acid radical is produced. The initiators in living cells are most notably reactive oxygen species (or ROS), such as OH°, which combines with a hydrogen atom to make water and a fatty acid radical.

PROPAGATION

The fatty acid radical is not a very stable molecule, so it reacts readily with molecular oxygen, thereby creating a peroxyl-fatty acid radical. This too is an unstable species that reacts with another free fatty acid producing a different fatty acid radical and a hydrogen peroxide or a cyclic peroxide if it had reacted with itself. This cycle continues as the new fatty acid radical reacts in the same way.

TERMINATION

When a radical reacts it always produces another radical, which is the reason the process is called a "chain reaction mechanism." The only way to stop a radical reaction is for two radicals to react and produce a non-radical species. This is what happens when the concentration of radical species is high enough for there to be a high probability of two radicals actually colliding. Living organisms have evolved different molecules that catch free radicals and protect the cell membrane e.g. ascorbic acid and vitamin E.

Furthermore, advanced stages of bowel inflammation in humans and animals [2930] are associated with an enhanced (local) formation of NO (Nitric oxide) by inducible NO synthases.Introcolonic administration of DNBS(2,4-Dinitrobenzene sulphonic acid) and acetic acid were associated with immunohistochemical expression of nitrotyrosine, mostly localized on epithelial cells and in the area of infiltrated inflammatory cells. This suggests that peroxynitrile, other nitrogen derivatives and oxidants are formed in vivo and may contribute to tissue injury [31]. Immunohistochemical staining for nitrotyrosine was localized on epithelial cells in a DNBS model of guinea pig ileitis or rat colitis and in active Crohn's lesions in humans. The pathogenic role of nitrogen derived species such as peroxynitrile in IBD is further supported by fact that intracolonic administration of exogenous peroxynitrile induces a severe inflammation that mimics the feathers of both UC and CD [32]. Superoxide and peroxynitrile cause DNA single strand damage, leading to poly (ADP – ribose) synthetase activation and cell death. Some evidence exists to support the possible role poly (ADP – ribose) synthetase activation in IBD [33].

Ulcerative colitis yields a distinctly abnormal distribution of GAGs, with significantly greater amount of total glycosaminoglycans, heparan sulphate and hyluronic acid [34]. The composition of GAGs may significantly affect both the permeability of the colon and immune reactions. These alterations may contribute to the inflammatory process since hyluronic acid can interact directly with lymphocytes, inhibit macrophage response to cytokines and enhance phagocytosis. GAG content has been associated with alteration in the distributions of macrophages reactive to TNF -[35] .Butyric acid, a four carbon and short chain fatty acid and several other fatty acid including propionic acid and acetic acid are produced in a healthy colon by fermentation of fiber and other carbohydrates. Butyric acid produces the primary fuel for colonocytes. Proper ion transfer, mucus synthesis, phase II detoxification and lipid synthesis for cell membrane integrity in the coloncytes depend on butyrate oxidation. Impaired metabolism of SCF (short chain fatty acid) has been implicated as a factor in UC. Patients with active UC have significantly lower butyrate oxidation than the control patients. High concentration of sulfate reducing bacteria with concomitant elevation of hydrogen sulphide (H_2S¬¬) is responsible for the pathogenesis of UC. H_2S is potentially damage the gut mucosa by inhibiting the butyrate oxidation in the mitochondria essentially staving the colonocytes [36].

ROLE OF MAST CELLS

It was found that the histamine secretion rate was increased in patients with Crohn's disease compared with normal controls and the secretion of histamine was related to the disease activity, indicating strongly that degranulation of mast cells was involved in active Crohn's disease [37]. As a proinflammatory mediator, histamine is selectively located in the granules of human mast cells and basophiles and released from these cells upon degranulation. A total of four histamine receptors H_1, H_2, H_3 and H_4 have been discovered and first three of them have been located in human gut [38].

Histamine was found to cause a transient concentration dependent increase in short circuit current, a measure of total ion transport across the epithelial tissue in gut. These could be due to the interaction of histamine with H_1 receptors that increased Na [[[+]]] and Cl ions secretion from epithelium. H_1 receptor antagonist pyrilamine was able to inhibit anti lgE -induced histamine release and ion transport suggests further that histamine is a crucial mediator responsible for diarrhea in inflammatory bowel disease and food allergy. The ability of SR140-333, a potent NK1 (neurokinin 1) antagonist in reducing mucosal ion transport was likely due to its inhibitory actions on histamine release from colon mast cells [39].

Tryptase is a tetrameric serine proteinase that constitutes some 20 % of the total protein within human mast cells and is stored almost exclusively in the secretary granules of mast cells in a catalytically active form. The ability of tryptase to induce micro vascular leakage in the skin of guinea pig, to accumulate inflammation cells in the peritoneum of mouse and to stimulate release of IL-8 from epithelial cells [40]. However little is known about it actions in inflammatory bowel disease. Recently, proteinase activating receptor (PAR -2) a highly expressed receptor in human intestine was recognized as a receptor of human mast cells tryptase. Colonic administration of PAR-2 agonists unregulated PAR-2 expression, included granulocyte infiltration, colon wall edema and damage and increased paracellular permeability of colon mucosa. PAR-2 agonists were also able stimulate TNF-α secretion from mast cells and secreted TNF-α could then enhance PAR-2 expression in a positive feedback manner [41].

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Author Information

Sunita Jain, M.Pharm, Ph.D.Pharmacology
Department of pharmacology, L.M. College of Pharmacy

Anand Pithadia, M.Pharm, Pharmacology
Department of pharmacology, L.M. College of Pharmacy