

EDITORIAL

Current view of the immunopathogenesis in inflammatory bowel disease and its implications for therapy

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Received: November 16, 2007 Revised: January 15, 2008

Abstract

Although the aetiology of inflammatory bowel disease (IBD) remains unknown, the pathogenesis is gradually being unravelled, seeming to be the result of a combination of environmental, genetic, and immunological factors in which an uncontrolled immune response within the intestinal lumen leads to inflammation in genetically predisposed individuals. Multifactorial evidence suggests that a defect of innate immune response to microbial agents is involved in IBD. This editorial outlines the immunopathogenesis of IBD and their current and future therapy. We present IBD as a result of dysregulated mucosal response in the intestinal wall facilitated by defects in epithelial barrier function and the mucosal immune system with excessive production of cytokines growth factors, adhesion molecules, and reactive oxygen metabolites, resulting in tissue injury. Established and evolving therapies are discussed in the second part of this editorial and at the end of this section we review new therapies to modulate the immune system in patients with IBD.

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Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Tolerance; Cytokines; Mucosal inflammation

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Torres MI, Ríos A. Current view of the immunopathogenesis in inflammatory bowel disease and its implications for therapy. *World J Gastroenterol* 2008; 14(13): 1972-1980 Available from: URL: <http://www.wjgnet.com/1007-9327/14/1972.asp> DOI: <http://dx.doi.org/10.3748/wjg.14.1972>

INTRODUCTION

The intestinal mucosa constitutes an immunologic system in which oral tolerance and defence against harmful organisms develop^[1]. The mucosal immune system, which plays a pivotal role in host defence, is continuously exposed to large amounts of exogenous (i.e., dietary) and endogenous (e.g., bacterial) antigens^[2]. Activation of lamina propria (LP) T cells by lumen antigens may lead to the production of inflammatory cytokines and subsequent mucosal inflammation and tissue damage^[3,4]. Dysfunctions of the intestinal immune system and cross-reactivity against host epithelial cells have been implicated as major mechanisms by which inflammation occurs^[5]. In addition to immune factors as leukocytes, macrophages, polymorphonuclear cells, mast cells, B and T lymphocytes, other potential mediators of inflammation are involved in the disease: eicosanoids, biological amines, cytokines, nitrogen- and oxygen-reactive metabolites, platelet-activating factor have been noted to influence inflammatory processes^[6]. Among environmental factors, antigens to intestinal bacteria play an important role. The loss of tolerance to intestinal bacterial flora is manifested as an abnormal immune response^[7]. Accordingly, inflammatory bowel disease (IBD) could be considered to be an imbalance between pro-inflammatory and anti-inflammatory mediators^[3]. The following editorial summarizes the current view of the immunopathogenesis basis of IBD in relation to barrier disruption, immune deregulation genetic epidemiology and susceptibility to environmental dysregulation, triggers and its implications for therapies.

EPIDEMIOLOGY AND CLINICAL FEATURES

IBD like ulcerative colitis (UC) and Crohn's disease (CD), comprises a group of multifactorial intestinal disorders with high incidence throughout the human population^[8]. The highest incidence rates and prevalence have been reported in northern Europe and North America. The disease is characterized by cycles of clinical exacerbation and remission, with periods of improvement followed by relapse, and appears to be immunologically mediated^[12]. UC and CD show some overlapping clinical features, and in 10%-15% of cases it is not possible to differentiate between the two diseases. But also, differences exist in the nature and location of the lesion damage between UC and CD. While UC is restricted to the large intestine and is associated with continuous mucosal inflammation, including crypt abscesses as well as ulcers, which typically

Table 1 IBD immunopathogenesis

Immune dysregulation
Cytokines
Epithelial barrier function
Oral tolerance
Reactive oxygen species (ROS)
Antioxidant defence system

spread from the most caudal part of the rectum, CD can affect any part of the gastrointestinal tract and is characterized by segmental and transmural inflammation, fistulas, oedema and granulomas in whole intestinal wall^[13].

At the histological level, various abnormalities have been observed in patients with IBD and in experimental models of intestinal inflammation including the presence of a significant number of neutrophils within the lamina propria and the crypts, where micro-abscesses can form, the depletion of goblet cell mucin, induced by disturbed transformation of undifferentiated cells in an environment exposed to inflammatory cytokines, damage to the nervous system^[13,14] and hypertrophy of smooth muscle cells^[15]. Intestinal inflammation alters the contractile activity of intestinal smooth muscle, and the motility disorders induce abnormal growth of the intestinal flora, resulting in disturbance of the intestinal flora that can aggravate the pathogenesis of mucosal inflammation^[16].

GENETIC FACTORS

The discovery of susceptibility genes to IBD have shown the importance of (1) dysregulation of the innate immune response to enteric microflora or pathogens; (2) increased permeability across the epithelial barrier, and (3) defective regulation of the adaptive immune system of epithelial barrier function in disease pathogenesis. IBD is considered a complex polygenic disease and its susceptibility genes could interfere with the disease and with the response to different therapies.

Strong evidence for genetic factors has been reported contributing to IBD susceptibility^[17]. IBD is thought to be caused by the mutual reactions among host susceptibility genes (CARD15/NOD2, CARD4/NOD1, HLA, TLR4, DLG5, NF- κ B1), environmental factors including enteric flora and food antigens, and abnormal immune balance^[9-11]. The genetic contribution may be more important in CD than UC with multiple gene products contributing to risk^[18]. Identifying NOD2 as a susceptibility gene in CD and additional susceptibility loci have been implicated in IBD such as IBD5, IL23R and ATG16L1 among other loci^[19-21]. The number of potential gene continues to increase, additional novel loci map to chromosomes 16q24.1, TNFSF15, NKX2-3 and the intergenic region on chromosome 10q21.1 might contribute to the IBD^[22]. Future genetic research may include focus on phenotypes, control for environmental variables and gene-gene interactions.

PATHOGENESIS OF IBD

There is compelling evidence that dysregulation of the

mucosal immune system is a major factor contributing to the pathogenesis of IBD^[13]. The pathogenesis of these diseases is understood to represent the outcome of three essential, interactive cofactors: host susceptibility, enteric microflora and mucosal immunity^[12,13]. The basis of IBD is the presence of genetically determined alterations that result in a mucosal immune system that overreacts to normal intestinal microflora. These immune responses may be induced by defects in the epithelial barrier, and increased intestinal permeability, adherence of bacteria, and decreased expression of defensins^[12].

The mucosal immune system senses and interprets the local microenvironment, recognizing and avoiding reactions to commensal flora (tolerance), whilst retaining its capacity to respond to episodic challenge from pathogens^[1,2]. Increased synthesis and release of pro-inflammatory mediators such as cytokines, chemokines, eicosanoids, platelet activating factor, reactive oxygen and nitrogen metabolites, as well as other abnormalities have been in IBD^[6]. We described IBD as a result of dysregulated mucosal response in the intestinal wall facilitated by defects in epithelial barrier function and mucosal immune system with excessive production of cytokines growth factors, adhesion molecules, and reactive oxygen metabolites, resulting in tissue injury (Table 1).

DYSREGULATED IMMUNITY

Cytokines

Alterations in the production of many cytokines have been described in patients with active IBD^[23]. The significance of these findings in the pathogenesis of IBD remains poorly understood and controversy has continued as to whether these changes really represent a primary defect in the regulation of the immune system or are a secondary consequence of immune activation^[6].

The nature of the immune response and the cytokine profile generated are under genetic control and determine the features of the inflammatory process in IBD. In active IBD the balance of regulatory and effector cells is disturbed, predominating effector T cells (Th1, Th2) over regulatory T cells (Th3, Tr). CD has been associated with type 1 helper T-cell cytokines (Th1), such as interferon- γ , TNF- α and IL-12^[24,25]. In ulcerative colitis, the pattern of cytokine is less clear; there is a modified Th2 response associated with cytokines such as IL-15 and IL-10^[25,27]. Among the cytokines involved, Interleukin-10 is a regulatory cytokine which plays a crucial role in the balance of the mucosal immune system, promoting physiological activation and preventing the pathological inflammation that characterizes the inflammatory bowel diseases^[26]. The immuno-regulatory activity of IL-10 is based upon its ability to inhibit both cytokine synthesis and antigen presentation, with maintenance of intestinal immunoregulation and tolerance to components of intestinal flora, controlling the inflammatory responses to intestinal antigens^[26].

This pathophysiological concept for IBD is changing as a result of recent advances with the description of another type of effector immunologic response CD4+ Th pathway, namely interleukin-23/interleukin-17 axis. IL-23

is produced by antigen-presentation cells and promotes a population of T lymphocytes that produce IL-17, IL-6 and TNF- α (Th17 cells)^[27,28]. These IL-23-driven CD4+ T cells are highly inflammatory and elicit IL-17-dependent autoimmunity. IL-17 is an inflammatory cytokine expressed by activated CD4+ T cells and triggers the NF- κ B signalling cascade and MAP kinase pathway, leading to T cells proliferation and up-regulation of inflammatory molecules^[29]. Recent publications have reported that the IL-23/IL-17 pathway may have a pivotal role in intestinal inflammation^[30,31]. These findings demonstrate that IL-23, but not IL-12, is essential for the development of intestinal inflammation in IBD. In addition, levels of expression of IL-23 and IL-17 are increased in patients with CD^[32]. Recently, the study of Duerr *et al*^[33] reported a significant association between CD and a gene on chromosome 1p31 that encodes a receptor for IL-23 (*IL-23R*) that is highly expressed by memory T cells.

Also, the interesting works of Bamias *et al*^[34] and Prehn *et al*^[35], respectively, have described a novel TNF-like cytokine co-stimulator of IFN- γ , namely TL1A that play an important role in mucosal inflammation and in experimental ileitis. TL1A is expressed in dendritic cells and acts on CD4+ cells and provides co-stimulation for proliferation of IFN- γ and is up-regulated in patients with active IBD. A single nucleotide polymorphism in the gene encoding TL1A (*TNFSF15*) confers susceptibility to CD^[36].

Mucosal epithelial barrier function

The polarized epithelial cells provide a crucial barrier function, with high concentrations of dietary and bacterial antigens at the apical surfaces in the mucosa and with high concentrations of lymphoid cells at the basolateral surface^[37]. The intestinal epithelium is considered a constitutive component of the mucosal immune system. Intestinal epithelial cells (IECs) are connected by tight junctions, which are dynamically regulated in response to cytokines and are down-regulated by the junctional complexes in human IBD (E-cadherin and β -catenin)^[38]. The epithelium is in constant communication with luminal flora and the underlying network of innate and adaptive immune cells, and IECs constitutively express or can be induced to express costimulatory molecules^[39] and components of the human major histocompatibility complex (MHC)^[40], toll-like receptors (TLRs)^[41], NOD proteins^[42], inflammatory cytokines^[43], as well as antimicrobial peptides^[44].

IECs contribute to the initiation and regulation of innate and adaptive defence mechanisms by interacting with lamina propria dendritic cells (DC), lamina propria lymphocytes (LPL), intraepithelial lymphocytes (IEL) and mediators of the immune and the enteric nerve system^[45]. IECs such as non-professional antigen-presenting cells might interact with naïve T cells (Th0) through MHC II receptors, and produce co-stimulatory signals suppressing or inducing anergy in mucosal T cells^[46]. The epithelial barrier is leaky in IBD and has a lower epithelial resistance and increased permeability that enables the proliferation of non-pathogenic organisms (normal microflora) in close juxtaposition to elements of the mucosal immune system.

Also, IBD have disturbed innate immune mechanisms of the epithelial layer and mucosal epithelial cells have a different pattern of TLR expression^[47]. Also, an up-regulation of NOD2 in IECs and disturb in antigen recognition and processing by antigen-presenting cells are present in patients with IBD^[48].

Paneth cells secrete antimicrobial peptides, including α -defensins that play an important role in innate intestinal defences. The Paneth cell deficiency in α -defensins increases the risk of CD and polymorphism in the defensin gene associated with CD^[49].

Goblet cells are also an important component of the epithelium and are responsible for defence and epithelial mucosal repair in colitis. Defects in mucus production have been reported in IBD^[50,51].

The adaptive immune response in IBD failure to balance, and the DCs might be responsible for a dysregulated innate immune response^[52]. DCs are the primordial cells in controlling immunity against pathogens and tolerance towards commensals and are dominant subsets of antigen-presenting cells in the intestinal lamina propria^[53]. DCs penetrate their dendrites between epithelial cells to sample luminal antigens without altering the mucosal barrier and they contain components of commensal bacteria. Depending upon the nature of the antigen and the activation state of DCs, the end result may be immune activation or tolerogenic action^[54]. DCs also have an important role in mucosal inflammation through the production of cytokines, resulting in persistent activation of effector T cells^[55].

An increase in intraepithelial lymphocytes (IEL) appeared in IBD and the activation of these IELs could be responsible for: (1) defending the mucosal barrier against intraluminal microorganisms, (2) modulation on epithelial cells of the expression of MHC antigens, or (3) non-MHC as well as MHC-restricted cytotoxicity^[56]. The increase of IELs is known to be associated with an abnormal expression of class II MHC molecules on surface and crypt colon epithelial cells. Helper T cells could trigger an MHC-restricted immune mechanism.

Oral tolerance

In an antigenic environment like intestine, the mucosal immune system must maintain tolerance to commensal bacteria, food and self antigens and must be able to initiate defence responses to pathogens. Studies have suggested that IBD is a consequence of the breakdown of mucosal tolerance and tolerance to normal flora is broken^[57]. DCs in conjunction with antigen-specific T lymphocytes trigger the maintenance of immune tolerance. Activation of intestinal NKT cells by CD1d-expressing IECs and professional antigen presenting cells (DC cells) may contribute to induction of oral tolerance^[58,59].

In IBD, atypical antigen-presenting cells become potent effector-T-cell activators, and the IECs can act as antigen-presenting cells capable of stimulating primed T cells which acquire an activated phenotype with increased histocompatibility molecule expression in the presence of inflammatory cytokines^[60]. IECs might also activate T cells *via* non-classical MHC. Our research group has previously shown that intestinal epithelial cells expressing HLA-G at

Table 2 Medical management based on pathogenesis

Dietary nutrients
Polyunsaturated fatty acids (PUFAs)
Fiber
Probiotics
Prebiotics
Flavonoids
Antagonist platelet-activating factor (PAFs)
Biological therapies
Anti-inflammatory/Immunosuppressive
Immunomodulators
Generation regulatory T cells/Activation effector T cells
Inhibition of recruitment, migration, adhesion molecules
Epithelial repair/Restitution barrier function
Induction apoptosis
Autologous hematopoietic stem cell transplant

the apical surface of the epithelial layer and at crypt level in ulcerative colitis, but not in CD^[61]. HLA-G is a non-classical major histocompatibility complex class I, which is selectively expressed at the maternal-foetal interface of cytotrophoblast cells and protects the foetus from maternal rejection and creating a general state of tolerance^[62].

Non-typical antigen-presenting cells, as epithelial cells, might acquire an activated phenotype with increased expression of HLA-G in the presence of inflammatory cytokines as IFN-gamma and TNF-alpha and might activate T cells *via* non-classical MHC molecules as HLA-G^[61]. In UC the specific expression of HLA-G, considered as a molecule implicated in tolerance immunity will be of great importance in the maintenance of the tolerance to fed antigens and of gut microflora and support the notion that it may serve as a regulator of mucosal immune responses to antigens of undefined origin.

REACTIVE OXYGEN SPECIES (ROS)

The intestinal mucosa is vulnerable to oxidative stress from constant exposure to reactive oxygen species (ROS) generated by the lumen contents such as oxidized food debris, transition metals such as iron and copper, bacterial metabolites, bile acids and salivary oxidants^[63]. A balance is maintained between oxidant and antioxidant systems under physiological conditions, but it is impaired in pathological success. Oxidant-mediated injury plays an important role in the pathophysiology of IBD^[64]. It has been suggested that intestinal damage in IBD is related to increased free radical production and to impaired antioxidant defence systems^[65]. There are an increased number of activated inflammatory cells in lamina propria of IBD releasing reactive oxygen radicals that are highly produced by neutrophils, macrophages and DCs^[63], and exceeds the limited intestinal antioxidant defence system, contributing to intestinal oxidative injury in IBD^[64].

Our research group has undertaken to determine whether the small intestine is subjected to oxidative damage during experimental IBD induced by administration of TNBS, as well as, to examine the accompanying changes in antioxidant status, in order to understand its role in the pathogenesis of disease.

TNBS may be metabolized to yield superoxide anion (O_2^-), and hydrogen peroxide (H_2O_2), suggesting that TNBS-induced intestinal inflammation may be partially mediated by cytotoxic reactive oxygen metabolites generated by the oxidative metabolism of TNBS^[66]. We evaluated the activity of the antioxidant enzymes catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GR), glutathione transferase (GT) and superoxide dismutase (SOD), as well as the levels of total glutathione (GSH). We found that GSH levels and SOD activity decreased in animals administered TNBS. These result are in agreement with studies in human IBD, that have been reported a decreased superoxide dismutase activity, as well as low total glutathione levels.^[67] Decreased GSH in gut epithelial cells may increase susceptibility to oxidative injury and exacerbate degeneration of the intestinal mucosa^[28]. Therefore, the elevated activities of glutathione peroxidase (GPX) and catalase (CAT) enzymes observed suggest that TNBS led to the formation of high levels of peroxides, including H_2O_2 , increasing tissue injury^[68].

Nutritional deficiencies have been reported in IBD, such as lower levels of vitamins A, E and C, important natural antioxidants for the organism, as well as a decrease in trace elements such as zinc and selenium, which are crucial components of several antioxidant enzymes such as SOD^[69].

MEDICAL MANAGEMENT BASED ON PATHOGENESIS

The main goal of therapy for IBD is to induce a clinical remission and then maintain it for a long period of time, in order to realize the best attainable quality of life. Choice of therapy depends on the severity and location of disease, as well as side effects and other adverse events. Although 5-aminosalicylates, corticosteroids and immunosuppressive drugs are generally used in the treatment of IBD, there are an important numbers of the patients who are not controlled by these conventional therapies^[70], indicating a considerable need for develop new and more effective therapy. Treatment with anti-diarrhoeal agents, proper nutrition, antagonistics of activation platelets factors, flavonoids, probiotics and prebiotics can be efficient, but also, a growing number of new biological agents are under investigation, as monoclonal antibodies to antisense mRNA products, peptides and vaccines among others. In Table 2 we summarised medical management based on pathogenesis.

Dietary nutrients

Dietary management of IBD may be an interesting alternative to drug therapy if it proves to be effective without side effects and can be used as a remission induction and maintenance therapy^[71]. Nutrients may be involved in the modulation of the immune response, thus, as components of cell membranes, nutrients can mediate the expression of proteins involved in the immune response, such as cytokines, adhesion molecules, *etc*^[71].

A potential relationship between components of the

diet and disease pathophysiology has been considered, and immunologic mechanisms have been postulated to link food antigens and the development of intestinal inflammation. Some reports have suggested that consumption of refined sugar might be a risk factor for CD, but not UC^[72]. Fat intake has been reported to be positively associated with UC, whereas fruit, vegetables, and fiber consumption seem to decrease the risk of IBD^[73].

Polyunsaturated fatty acids (PUFAs)

The composition of lipids in the cell membrane is modified by dietary changes and can influence cellular responses. Dietary lipids are one of the most active nutritional substrates modulating the immune response. The link between fatty acids and inflammation is that the eicosanoid family of inflammatory mediators is generated from PUFAs^[74]. Long chain n-3 PUFAs decrease the production of inflammatory eicosanoids, cytokines and adhesion molecules, inhibiting the arachidonic acid metabolism and altering the expression of inflammatory genes across effects on transcription factor activation and intraluminal bacterial content^[75].

Several studies have shown that patients with IBD had an abnormal plasma phospholipids fatty acid profile^[76,77]. The loss of the omega-3 fatty acids which increases the n-6. n-3 ratio, would lead to a predominance of proinflammatory eicosanoids. In an experimental model of IBD induced by rectal administration of TNBS when the animals received dietary n-3 PUFAs, they showed beneficial effect by competing with n-6 PUFAs for the production of lipid inflammatory mediators such as leukotrienes (LTB₄), thromboxane (TXA₂), Prostaglandins (PGE₂) and cytokines^[77]. The restoration of GSH levels after administration of the n-3 PUFAs demonstrated the decrease in oxidative stress. It was suggested that dietary PUFAs could affect mucosal adhesion sites for gastrointestinal bacteria by modifying the composition of the intestinal wall and as a result, the dietary PUFAs could modulate the probiotics action^[78].

Although LC-PUFA may be of interest in the dietary management of IBD, these fatty acids are highly susceptible to peroxidation, and indeed they may influence the antioxidant defence system. To overcome lipid peroxidation by products and cell damage from diets supplemented with PUFAs, appropriate antioxidants should be provided.

Dietary fiber

Several studies have shown that dietary fiber actively contributes to the intestinal anti-inflammatory effect, supporting its potential role in the treatment of IBD. Their therapeutic effect is associated with an increased production of short-chain fatty acids, mainly acetate, propionate and butyrate in the colonic lumen and with the promotion the use of these fatty acids, specifically butyrate by colonic epithelial cells^[79]. The result is the restoration of the metabolic function of the intestinal cells by aerobic ATP production after butyrate oxidation by epithelial cells that accelerate the intestinal repair preserving the integrity of the intestinal mucosa and downregulating the exacerbated immune response presented in IBD^[80].

The dietary fiber associated with the production of short-chain fatty acids, also can contribute to the inhibition of the production and release of proinflammatory cytokines, including IL-6, IL-8, TNF-alpha, and other mediators of inflammation as reactive oxygen and nitrogen metabolites (NO production)^[81].

Probiotics and prebiotics

IBD represent a malfunction of tolerance to the commensal microbiota, for this reason attention is focused on this relationship as a potential therapeutic action. Therapies such as prebiotic and probiotics that selectively manipulate the gastrointestinal microbiota present an attractive treatment in IBD with maintenance of remission and without major side effects. Some evidences support that the use of probiotics and prebiotics in IBD need to use standardized methodology to confirm their utilization as therapy^[82].

Probiotics

The human intestine contains different bacterial species, named intestinal microflora that plays a critical role in maintaining intestinal health. This intestinal microflora protects against pathogens and maintains the epithelial barrier integrity^[83]. The functions of these bacteria include control of proliferation and differentiation of IECs and development and balance of the immune system.

Probiotics are living microorganisms that upon ingestion in specific numbers have beneficial effect and exert their therapeutic effects to modulate the barrier function, the inhibition of pathogenic bacteria, the intestinal production of cytokines, with anti-inflammatory properties and enhancement of the digestion and absorption of food^[83,84].

Prebiotics

Prebiotics are selectively fermented short-chain carbohydrates that allow specific changes in the composition and activity of the microbiota in the gastrointestinal tract and confers health benefits, these include fructo-oligosaccharides and galacto-oligosaccharide^[85,86]. Prebiotics have been shown to enhance the immunoregulatory bacteria of lumen, to reduce the activity of pro-inflammatory transcription factors and attenuate the inflammation. In this sense prebiotics produce butyrate and acetate that inhibit, mucosal inflammation, acting on epithelial and DCs function^[87].

Flavonoids

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin and exert antimicrobial, antiviral, antineoplastic, antihepatotoxic, hypolipidemic, antiallergic and anti-inflammatory features^[88]. Biochemical investigations of flavonoid mechanisms have demonstrated that these compounds inhibit a wide variety of enzymatic systems. Variations in the heterocyclic ring C give rise to flavonols, such as morin.

Morin (2',3,4',5,7-pentahydroxyflavone, flavonol) is a yellowish pigment extractable from the wood of *Chlorophora tinctoria* and acts as a broad-spectrum and non-toxic antioxidant^[89]. Our laboratory analyzed the effects of morin on experimental TNBS-induced IBD

in rats. Oral administration of morin, at doses ranging from 10 to 200 mg/kg, significantly reduced the mucosal damage by 20%-40% induced by the TNBS experimental model of IBD, although these beneficial effects were not dose-related. Morin reduced the enzymatic activity of myeloperoxidase (MPO) (marker of neutrophil infiltration) and can be interpreted as a manifestation of this anti-inflammatory property^[89]. Also, significantly inhibited LTB₄ synthesis, and this inhibition was maximal at the highest dose of morin assayed (200 mg/kg). Also, morin reduces colon oxidative stress induced in the TNBS model. This reduction may be explained on the basis of its ability both to inhibit free-radical production and to scavenge free radicals once they have been released and by inhibition of colon LTB₄ synthesis.

Antagonistic platelet-activating factor

Sulphasalazine, a diazo compound with 5-aminosalicylic acid (5-ASA) linked to sulphapyridine that acts as a carrier, has been used as therapy for IBD. This agent is useful in maintaining remission by prevention of relapses in patients with IBD^[90]. Unfortunately, long-term administration of sulphasalazine is accompanied by a considerable number of side-effects, either dose-dependent such as nausea, vomiting, headache, *etc.*, or allergic such as cutaneous rashes, exanthema, fever, *etc.*

Several mechanisms have been postulated as being involved in the intestinal anti-inflammatory effect exerted by 5-ASA derivatives, including antioxidant and/or radical scavenging properties, inhibition of leukocyte chemotaxis and inhibition of IL-1 synthesis^[91]. It has been shown that colon mucosa from patients with IBD produces high levels of platelet-activating factor (PAF) with an important role in the pathogenesis of IBD, its inhibition by specific antagonists may have a potential therapeutic benefit in the treatment and management of these inflammatory diseases^[91].

UR-12746 is a compound which combines 5-ASA and UR-12715 through an azo link, and possesses antagonist PAF activity. We demonstrate the therapeutic efficacy of UR-12746 when administered orally at doses of 50 and 100 mg/kg in acute and chronic stages of the TNBS model of IBD^[92]. The intestinal anti-inflammatory effect of UR-12746 was associated with a decrease in leukocyte infiltration in the colon mucosa and with a reduction in myeloperoxidase activity. This effect was higher than that seen with sulphasalazine, when assayed at the same doses and in the same experimental conditions. This result suggests that the intestinal anti-inflammatory activity of UR-12746 by inhibition of leukotriene B₄ synthesis in the inflamed colon, improvement of the altered colon oxidative status, and reduction of colon IL-1 β production. Treatment with UR-12746 was able to ameliorate the altered colon oxidative status by significantly increasing glutathione content and by reducing the colon malonyldialdehyde levels^[92].

Future in therapy: Modulation of the immune response and biologic therapies

Advances in the understanding of IBD pathogenesis have allowed the development of novel therapies, which at least

theoretically represent a more specific management of the disease with fewer side effects. The real future in therapy should be to develop an approach to prevention of the initiation and perpetuation of the inflammatory status before tissue damage success, involving the induction of tolerance, commensal flora, generation of regulatory T cells and gene transfer, among others. Between these therapeutics factors, the immunosuppressors like calcineurin inhibitor (tacrolimus and cyclosporine), that suppresses pro-inflammatory cytokine production and T-cell activation, have been used to treat inflammatory bowel disease, especially in refractory ulcerative colitis, and to treat an extra-intestinal manifestation of IBD^[93]. Understanding the role of cytokines has been an important advance in IBD therapies, along with the monoclonal antibody technology, which made possible the targeted inhibition of specific disease related cytokines. Also, it has been possible to give inhibitory cytokines as therapeutic agents^[94]. The blockage of proinflammatory cytokine TNF-alpha (anti-TNF- α monoclonal antibody) serves as a model for development of new therapy^[94]. In this sense, the use of infliximab inhibits the bioactivity of TNF-alpha by directly binding to the cytokine and also modulates the function of TNF-alpha-producing cells^[95]. Many case reports have been published on the use of infliximab for treating patients with extraintestinal manifestations of IBD^[96].

Other potential modes of therapeutic actions in IBD include the induction of the anti-inflammatory cytokines IL-10 or TGF-beta *via* retrograde signalling or induction of a certain subset of regulatory T cells^[97]. The IL-23 pathway has been a target of antibody blockade^[40]. Further research is needed to know how the *IL-23R* gene and the IL-23/IL-17-mediated inflammatory axis contribute to disease susceptibility and will lead to therapeutic interventions.

The process of T-cell activation, by enhancing regulatory T cells as opposed to inhibiting effector T cells could be considered to be effective for the treatment of IBD. Various populations of T cells exert a downregulatory effect on immune responses, including Tr1 cells (IL-10 secretion), Th3 cells (TGF-beta) and CD4+CD25+ T regulatory cells, in which inhibition is through direct cell contact. The earliest work of this therapy may involve the selection and engineering of T cells delivering IL-10^[98].

Lymphocyte-endothelial interactions mediated by adhesion molecules are important in leukocyte migration and recruitment to sites of inflammation in IBD, a selective inhibition of these adhesion molecules offers many potential targets for specific intervention against inflammation^[99] to treat CD. In the next years, the role of anti-CD3 drugs (visilizumab), which induces apoptosis in activated T cells, the epithelial repair, and autologous hematopoietic stem cell transplants^[100] will be established.

Ultimately, the future therapy for IBD should be individualized and directed at induction of remission over a long period of time with the avoidance of important side-effects and maintaining the patient's quality of life.

CONCLUSION

Relevant advances in the understanding of the molecular

pathogenesis of IBD have been made, discovering susceptibility genes, identification of environmental factors implicated, and dysregulation of immunity in disease pathogenesis. Although the precise mechanisms underlying the development of IBD are not known, sufficient data have been collected to suggest interplay between genetic predispositions, accompanied by the importance of epithelial barrier function, and innate and adaptive immunity. Current therapies generally involve combinations of pharmacologic agents such as aminosalicylates, azathioprine, steroids, with dietary manipulation. Newer agents including monoclonal antibodies targeted to specific proinflammatory cytokines, to adhesion molecules, and the induction of anti-inflammatory cytokines and T-cell activation, have emerged and provided clinical benefit in the treatment and relapse of IBD.

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