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TOPIC HIGHLIGHT

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Insights from advances in research of chemically induced experimental models of human inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD), the most important being Crohn's disease and ulcerative colitis, results from chronic dysregulation of the mucosal immune system in the gastrointestinal tract. Although the pathogenesis of IBD remains unclear, it is widely accepted that genetic, environmental, and immunological factors are involved. Recent studies suggest that intestinal epithelial defenses are important to prevent inflammation by protecting against microbial pathogens and oxidative stresses. To investigate the etiology of IBD, animal models of experimental colitis have been developed and are frequently used to evaluate new anti-inflammatory treatments for IBD. Several models of experimental colitis that demonstrate various pathophysiological aspects of the human disease have been described. In this manuscript, we review the characteristic features of IBD through a discussion of the various chemically induced experimental models of colitis (e.g., dextran sodium sulfate-, 2,4,6-trinitrobenzene sulfonic acid-, oxazolone-, acetic acid-, and indomethacin-induced models). We also summarize some regulatory and pathogenic factors demonstrated by these models that can, hopefully, be exploited to develop future therapeutic strategies against IBD.

Key words: Inflammatory bowel disease; Experimental colitis; Dextran sodium sulfate; Trinitrobenzene sulfonic acid; Oxazolone; Pathogenesis

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INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), represents a chronic, relapsing and remitting inflammatory condition that affects individuals throughout life[1]. No completely effective therapeutic strategy has been established because the etiology of IBD remains largely unknown, although there has been extensive research on its pathogenesis. However, recent advances in the understanding of the pathophysiology of IBD have provided some clues for developing potentially helpful therapeutic tools.

Within the past two decades, several models of experimental colitis have been reported that demonstrate various pathophysiological aspects of human IBD. While no model serves as a complete surrogate for the human disease, some characteristically pathological features are open for investigation, depending on the method used to induce the experimental colitis. Experimental models of colitis enable us to dissect the pathogenic components during different phases of colitis, including acute, recovery and chronic phases. They also enable us to identify some pivotal immunological processes, as well as novel genes that are intimately involved in disease susceptibility.

In this review, we mainly focus on the role of functionally distinct factors, including immune cells, cytokines/chemokines, receptors/ligands, transcriptional factors, and enzymes/hormones, which maintain the homeostatic balance in the colon during the development of acute and chronic inflammation.

DSS-INDUCED COLITIS

The dextran sodium sulfate (DSS) model, originally reported by Okayasu *et al*[2] has been used to investigate the role of leukocytes in the development of colitis. Oral administration of 5% DSS in drinking water can induce not only acute, but also chronic colitis. One cycle of 3%-5% DSS administration for 5-7 d, followed by

regular water, results in extensive injury with complete crypt depletion (mainly basal crypt) and relatively slow regeneration of colonic epithelium. This regeneration is much slower than in other acute injury models, which use toxic substances such as acetic acid and ethanol[3]. The clinical features of this model include weight loss, loose stools/diarrhea, and rectal bleeding. Histopathological analysis typically reveals extensive crypt and epithelial cell damage, significant infiltration of granulocytes and mononuclear immune cells, and tissue edema, often accompanied with severe ulceration. In fact, because of the massive edema and subsequent ulceration during the acute phase, some researchers have wrongly used the DSS-induced colitis model by interpreting it as a model for human UC; however, this colitis is a simple model of acute chemical injury rather than chronic inflammation. Pathological scoring is generally performed on the distal segment of the colon, which is the most severely affected portion[3]. Histopathology, by hematoxylin and eosin staining, is scored based on three parameters: severity of inflammation (none, mild, moderate, severe), extent of inflammation (none, mucosa, mucosa and submucosa, transmural), and crypt damage (none, basal one-third damaged, basal two-thirds damaged, crypt lost but surface epithelium present, crypt and surface epithelium lost). It is noteworthy that long-term DSS administration produces colorectal carcinoma, which is similar to the dysplasia-carcinoma sequence seen in the course of cancer development in human UC[4].

Acute mucosal damage can be observed in both wild-type and severely combined immunodeficiency (scid) mice, which indicates that acquired immune responses are not involved in the induction of DSS-induced colitis[5]. The lesions observed in scid mice have been associated with increased production of macrophage-derived proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α. While the role of luminal bacteria in the pathogenesis of DSS-induced colitis is unclear, this colitis can be ameliorated by treatment with antibiotics that are clinically effective in patients with IBD[1], which suggests the importance of commensal bacteria in the development of colitis[6]. Although the earliest change of acute DSS-induced colitis is a progressive disruption of colonic crypts during the chronic phase (14 d after stopping DSS), macrophages and $CD4^+$ T cells are more prominent in areas of wound healing in the basal portions of the lamina propria (LP). These $CD4^+$ T cells secrete increased levels of interferon (IFN)-γ and IL-4, which suggests that chronic immune activation mediated by both Th1 and Th2 cells play a pathogenic role in chronic DSS-induced colitis[7].

2,4,6-TRINITROBENZE SULFONIC ACID (TNBS)-INDUCED COLITIS

In 1995, Neurath *et al* described a novel murine model of intestinal inflammation induced by intrarectal administration of hapten reagent TNBS in ethanol solution. Simultaneous administration of TNBS and ethanol is required to induce TNBS colitis, because ethanol disrupts the epithelial layer and exposes the underlying LP to bacterial components. Intestinal inflammation induced by intrarectal administration of TNBS has many of the characteristic features of CD in humans, including severe transmural inflammation associated with diarrhea, rectal prolapse, weight loss, and induction of an IL-12-driven inflammation with a massive Th1-mediated response[8]. Interestingly, prior oral administration of TNBS in the form of trinitrophenol-haptenated colonic protein (TNP-CP) prevents colitis induced by intrarectal administration of TNBS[9,10]. The preventive effect is due to the induction in the LP of regulatory cells consisting of $CD4^+$ T cells that produce transforming growth factor (TGF)-β after oral administration of TNP-CP[10].

The susceptibility to TNBS colitis varies between different mouse strains; SJL and BALB/c are susceptible, whereas C57Bl/6 and 10 mice are resistant. The susceptibility has been shown to be related to a genetically determined high IL-12 response to the lipopolysaccharide (LPS) locus on chromosome 11 in SJL/J mice[11]. In a recent study, te Velde and colleagues compared gene expression profiles in the colons of three different models of colitis (DSS, TNBS and $CD45RB^{high}$ T-cell transfer models)[12]. As a result, a restricted number of genes were either up- or down-regulated in the TNBS colitis (21 genes) model compared to DSS-induced colitis (387 genes) and $CD45RB^{high}$ transfer model (582 genes)[12]. Of the 32 genes known to change transcriptional activity in IBD (*TNF, IFN-γ, Lt*β*, IL-6, IL-16, IL-18R1, IL-22, CCR2* and *7, CCL2, 3, 4, 5, 7, 11, 17* and *20, CXCR3, CXCL1, 5* and *10, Mmp3, 7, 9* and *14, Timp1, Reg3*γ*, Pap, S-100a8, S-100a9, Abcb1,* and *Ptgs2*), two (*Mmp14* and *Timp1*) are up-regulated in TNBS, 15 (*IL-6, IL-16, IL-22, CCL2, 3* and *11, CXCL1* and *5, Mmp3* and *14, Timp1, Reg3*γ*, Pap, S-100a9,* and *Ptgs2*) are up- or down-regulated in DSS, and 30 (except for *CCL11 and Timp1*) are up- or down-regulated in the CD45RB transfer colitis models. The study suggests that the pattern of gene expression in these colitis models closely reflects altered gene expression in human IBD[12].

OXAZOLONE COLITIS

In contrast to TNBS, which leads to colitis driven by a Th1-polarized type of T-cell response, administration of another haptenating agent, oxazolone, leads to a colitis associated with a Th2-polarized type of response. This model is induced by the rectal administration of oxazolone suspended in an ethanol vehicle. Although the SJL/J strain of mice was utilized in the original description[13], over half of the later studies have been performed using the C57Bl/6 strain. The induction of colitis in the C57 strain requires a presensitizing treatment, since this strain is resistant to haptenating agents[14]. For presensitization, 4.5 mg - 6 mg of oxazolone in 100% ethanol is injected into the abdominal wall of mice, followed by intrarectal administration of various doses of oxazolone in 50% ethanol after 5 d.

Oxazolone colitis is limited to the distal part of the colon, in contrast to TNBS colitis that is characterized as pan-colitic. Microscopically, the inflammation of oxazolone colitis manifests as relatively superficial ulceration[13]. An IL-4-driven Th2-type of response is predominant and is

Table 1 Pathogenesis of IBD models in DSS colitis

Pathogenic factors	
Categories	Factors (References)
Chemokines/cytokines	Migration inhibitory factor[114], LIX[115], L-18[33], CCR5[116], IL-1[117]
Adhesion molecules	CD98[118], β2 integrins (CD18/11a)[83], Integrin α1β1[81], VCAM-1[119]
Transcriptional factors	STAT3[74]
Toll like receptors and ligands	CpG motifs[92], Flagellin/TLR5[90]
Enzymes	Chitinase 3-like-1[102], Carbonic anhydrase Ⅳ[100], Eosinophil peroxidase[120], Caspase-1[105]
Hormones	Adiponectin[112], Resistin-like molecule β[121], Leptin[113], Osteopontin[122], Activins[123]
Others	Galanin-1 receptor[124]
Regulatory factors	
Categories	Factors (References)
T cells	γδT cells[23,24]
Cytokines/chemokines	BFGF[51], FGF2[125], TGF-α[46], TFF2[53], ITF[54], HGF[47,49]
Transcription factors	SOCS3[74], Nrf2[126], PPARγ[76,77], PPARδ[76]
Adhesion molecules	B2 integrins (CD11β)[83]
Receptors	TLR4[87], PG receptor EP-4[95], Pregnane X Receptor[127]
Enzymes	COX-2[94,96], COX-1[94], Matrix metalloproteinase-2[128]
Hormones	Estrogen[129], Growth hormone[130], Adiponectin[110]
Neuronal factors	Vagus nerve[131], IRE1β[132], Neurotensin[133]
Lipid-associated molecules	Lipoxin A4[134], Apolipoprotein A-Ⅳ[135]
Others	Dietary glycine[136], Follistatin[123], Bacterial superantigens[137], Thioredoxin-1[138]

characterized by increased IL-4/IL-5, but normal IFN-γ production. The inflammation is prevented by the systemic co-administration of intraperitoneal anti-IL-4 antibody. The proinflammatory Th2-dominant cytokine response is regulated by TGF-β, which limits both the extent and duration of the disease. The histological features and inflammatory distribution of oxazolone colitis resemble human UC[13].

OTHER CHEMICALLY-INDUCED COLITIS MODELS

In a search for novel experimental models of acute IBD, MacPherson and colleagues have found that intrarectal administration of 3%-5% acetic acid induces acute colitis in the distal part of the colon in rats[15]. The initial injury consists of epithelial necrosis and edema that variably extends into the LP, submucosa, or external muscle layers. Epithelial injury is mainly caused by organic acids specifically because hydroxyl chloride (pH 2.3) does not generally induce acute colitis[4]. In mice, administration of acetic acid within 4 h results in colonic epithelial destruction without inflammation, which is then followed by an influx of acute inflammatory cells, and reaches its maximum intensity at 12 h. The inflammatory response is caused by non-specific factors after disruption of the epithelial barrier. The chemical injury heals within days in mice or 2-3 wk in rats[16].

Whereas acetic acid produces acute inflammation restricted to the colon, another pro-inflammatory agent, indomethacin, has been used to induce acute ileitis. Fasted rats are treated subcutaneously with indomethacin 7.5 mg/kg in sterile sodium bicarbonate, which leads to an acute inflammatory response characterized by multiple deep, longitudinal ulcers in the distal jejunum and proximal ileum. This acute response reaches its maximum intensity at 24 h and is completely resolved within 7 d, whereas two daily subcutaneous injections of indomethacin produce a chronic inflammation that lasts at least 2 wk[17]. Luminal bacteria and their products significantly contribute to the exacerbation and perpetuation of the chronic phase of indomethacin-induced inflammation.

These models have the advantage of being easy to initiate and therefore would be useful in the initial screening of new drugs for acute epithelial injury. However, the injury in the first 24 h is nonimmunologic and thus is not suitable for drug therapy trials for human IBD.

FACTORS INVOLVED IN THE PATHOGENESIS OF THE MAIN CHEMICALLY INDUCED COLITIS MODELS

In the following section, we focus more on the factors involved in the fine balance between pathogenic and regulatory factors in the pathogenesis of DSS- (Table 1), TNBS- (Table 2), and oxazolone- (Table 3) induced colitis.

T cells

$CD4^+$ T cells play a key role in the development of most T-cell-mediated IBD models. For example, the increased production of IFN-γ, mainly produced by $CD4^+$ T cells, is detected in most models of Th1-mediated colitis[18]. By contrast, IL-4 and IL-13, produced by natural killer (NK) T cells, have been shown to play a key role in the pathogenesis of Th2-mediated colitis, including oxazolone-induced colitis[19]. NK1.1 positive lymphocytes are also essential for alleviation of TNBS-induced colitis in the presence of peripheral tolerance[20].

Although $CD8^+$ T cells represent a major T-cell subset, there is little information available regarding the role of $CD8^+$ T cells in the pathogenesis of colitis. $CD8^+$ T cell receptor (TCR)-positive $V\beta14^+$ T cells, which are increased in the LP and have a cytotoxic effect[21], have a pathogenic role in the development of TNBS-induced colitis.

By contrast, TCRγδ T cells are an evolutionarily

Table 2 Pathogenesis of IBD models in TNBS colitis

Pathogenic factors	
Categories	Factors (References)
T cells	Th1[8], $CD8^+$ TCR $V\beta14^+$ T cell[21], CEACAM1[27]
Cytokines/chemokines	IL-12[8,30], IFN-γ[8,34], IL-18[31,32,139], IL-6[73], IL-16[140], IL-17[38], TNF-α[29,141], MIP-α[142], MIP-3α[143]
Receptors	CD40[57,58], CD44v7[144], FcεRI[145], GITR[63,64], Complement receptor 3[146]
Transcription factors	NF-κB p65[65,67,147], RICK[69,70], MAPK p38[70], Smad7[72], Smad3[148]
Adhesion molecules	Integrinα1β1[80]
Enzymes	Poly (ADP-ribose) synthetase[149,150], Inducible nitric oxide synthase[151], Angiotensinogen[152], Vanin-1[107]
Hormones	Leptin[113], Ghrelin[153], Adiponectin[112]
Others	Geneticfactors[11], Glycolipid[154]
Regulatory factors	
Categories	Factors (References)
T cells	TCRγδ[25,26], NK1.1[20,155,156]
Cytokines/chemokines	TGF-β[10,44,45], IL-10[44,157,158], IL12 p40[34], IL12 p40-IgG2b[159], IL-2-IgG2b[160], IL-23[39], HGF[48], BFGF[51]
Receptors	PAR-2[61], TNFR1[56]
Transcription factors	STAT5b[161], Interferon regulatory factor-1[162], PPARγ[75]
Enzymes	Indoleamine 2, 3-dioxygenase[163]
Hormones	Adrenocortical hormones[164,165], NCX-101[166]
Neurotransmitters	Vasoactive intestinal peptide[167,168], μopioid receptor[169]
Lipid mediators	Lipoxin A4[170], Marine[171]
Bacteria and parasite related factors	Yersinia pseudotuberculosis[172], Lactic acid bacteria[173,174], Schistosome eggs[175], Cholera toxin subunit B[176,177]
Others	Galectin-1[178], Curcumin[179], Catalposide[180], Follistatin[123], Phex gene[181], FTY720[182], Matrine[183]

Table 3 Pathogenesis of IBD models in oxazolone colitis

Pathogenic factors	
Categories	Factors (References)
T cells	NKT[19], CEACAM1[27], Major basic protein[184], MHC class Ⅱ transactivator[185]
Cytokines/chemokines	IL-4[13], IL-13[19,40], EBI3[42]
Transcription factors	Smad7[72], NF-κB[67,68]
Others	Glycolipid[154]
Regulatory factors	
Categories	Factors (References)
T cells	Regulatory T cells[28]
Cytokines/chemokines	TGF-β[13]
Receptors	PAR-1[60]
Others	Budesonide[186]

conserved minor T-cell subset with characteristic properties that help maintain the homeostasis of epithelial cells, by providing a barrier between the luminal bacterial contents and underlying immune cells[22]. A regulatory role has been shown for TCRγδ T cells in DSS-[23,24] and TNBS-induced colitis models[25,26].

In addition to these populations, carcinoembryonic antigen-related cellular adhesion molecule 1 (CEACAM1; also known as CD66a) is a cell surface molecule that has been proposed to negatively regulate T cell function, and is associated with the regulation of T-bet-mediated Th1 cytokine signaling in TNBS- and oxazolone-induced colitis models[27].

Finally, regulatory T cells express the antigen non-specific suppressor factors transforming growth factor-β (TGF-β) and IL-10. Boirivant *et al* have shown that TNP-CP feeding cross-protects mice from an inflammatory response to a different hapten, oxazolone. This protective effect is associated with the appearance of mononuclear cells that produce regulatory cytokines[28]. This phenomenon of cross-protection could be exploited in designing novel treatments for IBD, because it demonstrates that an orally-administered antigen can induce production of regulatory cells that are able to suppress inflammation induced by a different type of antigen.

Cytokines/chemokines/growth factors

TNBS injection results in a transmural infiltrative colitis associated with an IL-12-mediated Th1-immune response[8]. In most cases, a single dose of TNBS is administered at the starting point of the experiment. In subsequent studies of IL-12, it has been reported that mucosal TNF-α is necessary for the initiation and perpetuation of TNBS colitis, since TNF-α-deficient mice are resistant to TNBS, and the colitis is extremely severe in mice that over-express TNF-α[29]. This result suggests that TNFα acts as a proximal co-factor for IL-12 or IL-18 production. One possible mechanism of amelioration by anti-IL-12 antibody treatment is through the induction of Fas-mediated apoptosis of Th1 cells[30].

Watanabe and colleagues have shown that TNBS-induced colitis is mediated by macrophage-derived IL-18[31]. In fact, neutralization with anti-IL-18 antibody results in dramatic attenuation of mucosal inflammation, and the administration of TNBS fails to induce significant colitis in IL-18 knockout (KO) mice. These results have been confirmed by another group who have demonstrated that recombinant human IL-18 binding protein isoform (rhIL-18BPa) leads to a significant reduction in TNBS-induced colitis, by decreasing local TNF-α production[32]. Interestingly, IL-18 is also a primary mediator of the inflammation in DSS-induced colitis, while neutralization of IL-18 attenuates intestinal damage in that colitis model[33].

In Th1-mediated colitis, the use of agents that block IL-12 secretion or activity provides the most direct approach for attenuating inflammation because IL-12 is critical for regulation of differentiation and activation of Th1 cells[8,30]. It has been demonstrated that IL-12p40 KO mice develop severe TNBS-induced colitis. Moreover, administration of IL-12p40 neutralizing antibody increases pathology in IL-12p35 KO mice, which suggests that IL-12p40, in contrast

to IL-12p70, exerts the major regulatory function in TNBS-induced colitis[34]. However, IL-12p40 forms heterodimers, not only with IL-12p35 (IL12p35p40; IL-12p70), but also with IL-23p19 (IL-23p19p40); a finding that raises the possibility that activity previously ascribed to IL-12 may be attributable to IL-23. Recently, it has been revealed that IL-23 is a key effector cytokine in the immune system of the intestine[35]. IL-23 specifically expands a pathogenic population of $CD4^+$ T cells called Th-17 cells, which produce IL-17A, IL-17F, IL-6 and TNF-α[36,37]. Indeed, IL-17R KO mice are protected against TNBS-induced colitis[38]. By contrast, Becker *et al*[39] have reported that IL-23 cross-regulates IL-12 production in T-cell-mediated TNBS colitis, since mice lacking the p19 subunit of IL-23 are highly susceptible to TNBS-induced colitis, and inhibition of IL-12p40 rescues IL-23p19 KO mice from lethal disease. These discrepancies regarding the role of IL-23 may result from different experimental models; therefore, further characterization should help in developing new therapeutic treatments for patients.

As for the Th2-type responses, oxazolone colitis is associated with increased production of IL-4/IL-5, and is prevented by the systemic co-administration of anti-IL-4 antibody[13]. Heller *et al*[19] have shown that IL-13, mainly produced by NK T cells, is a significant pathogenic factor in this model, since its neutralization by the decoy receptor IL-13Rα2-Fc prevents disease. As well, IL-13 induces TGF-β1, generally considered to be an anti-inflammatory cytokine, through IL-13Rα2 in oxazolone-induced colitis, and prevention of IL-13Rα2 expression leads to the marked down-regulation of TGF-β1 production and collagen deposition in bleomycin-induced lung fibrosis, during prolonged inflammation[40].

As an IL-12p40-related protein, it has been reported that Epstein-Barr virus-induced gene 3 (EBI3) dimerizes with a novel p28 subunit (which has homology to IL-12p35) to form the cytokine IL-27[41]. IL-27 has been shown to function as a proliferation factor for naïve, but not memory, $CD4^+$ T cells, and to synergize with IL-12 to stimulate IFN-γ production[41]. That EBI3 KO mice have been found to be resistant to oxazolone-induced colitis suggests that this molecule plays a crucial role in the induction of Th2-type immune responses[42].

Several families of growth factors regulate a wide spectrum of processes integral to IBD; including protection of the intestinal mucosa and activation, as well as regulation of the intestinal immune system. These factors mediate mucosal repair, restitution, remodeling and resolution of inflammation following tissue damage[43]. It is now widely accepted that TGF-β has an important function in regulating inflammation and tissue repair. Fuss *et al*[44] have elegantly demonstrated the relationship between TGF-β and IL-10 in the regulation of Th1-mediated inflammation in TNBS-induced colitis, by performing a study in which mice were fed a haptenated colonic protein and then administered either anti-TGF-β or anti-IL-10 antibody, at the time of subsequent rectal administration of TNBS. Anti-TGF-β antibody administration prevents TGF-β secretion, but leaves IL-10 secretion intact, whereas anti-IL-10 antibody administration inhibits both TGF-β and IL-10 secretion. Their data suggest that TGF-β alone is the primary mediator of counter-regulatory Th1-type mucosal inflammation, and that IL-10 is necessary as a secondary factor that facilitates TGF-β production, but does not act as a suppressor cytokine by itself. Interestingly, Kitani *et al*[45] have shown that single intranasal administration of DNA encoding active TGF-β prevents the development of Th1-mediated TNBS colitis. This study shows that following treatment, TGF-β-producing T cells and macrophages are found in the LP and spleen, in which they hypothetically act to prevent induction of TNBS colitis. Therapeutic strategies involving TGF-β-encoding DNA may provide beneficial effects in treating intestinal inflammation.

The role of TGF-α in the small intestine and colon has not been studied as extensively as it has been in the gastric mucosa. In DSS colitis, TGF-α is a mediator of protection and/or healing in the colon, which is demonstrated by the absence of disease in TGF-α-KO mice[46].

Hepatocyte growth factor (HGF) may be a critical regulatory factor in IBD since HGF activator-KO mice are unable to survive after DSS or acetic acid-induced colitis[47]. HGF promotes migration of gastrointestinal epithelial cells and accelerates wound repair by mucosal cells. The importance of HGF has been confirmed by the intrarectal administration of HGF-expressing adenovirus in TNBS-treated mice, which leads to significant improvements in mucosal damage[48]. The same group has also demonstrated the therapeutic effects of naked gene therapy of HGF in the DSS-induced colitis model[49]. Taking these results together, HGF gene delivery may be very useful as a therapeutic strategy for human IBD.

As well as HGF, basic fibroblast growth factor (bFGF or FGF-2) also improves mucosal damage by enhancing epithelial cell restitution and proliferation in the gastrointestinal tract[50]. In fact, rectal administration of human recombinant bFGF (hrbFGF) ameliorates DSS-induced colitis by significantly reducing the gene expression level of TNF-α[51]. Not only DSS-, but also TNBS-induced colitis is improved by the administration of hrbFGF, which not only enhances survival rate, but also up-regulates levels of cyclooxygenase (COX)-2, TGF-β, intestinal trefoil factor (ITF), and vascular endothelial growth factor (VEGF) in the colon[51].

Lastly, the trefoil factor family is comprised of three peptides; trefoil factor family 1 (TFF1), spasmolytic polypeptide (SP also known TFF2), and ITF (also known as TFF3). TFF2 is a low-molecular-weight protein that is up-regulated in gastric tissues infected with *Helicobacter* or affected by other inflammatory conditions[52]. TFF2 KO mice are susceptible to DSS-induced colitis, with prolonged colonic hemorrhage and persistent weight loss[53]. The importance of ITF in the modulation of inflammation, wound healing, and protection of the intestinal mucosa is supported by experiments in ITF KO mice, which have shown increased susceptibility and delayed wound healing during DSS- and acetic acid-induced colitis[54].

Receptors

TNF-α plays a central role in the pathology of Th1-mediated colitis such as CD; however, the role of its receptors, TNF receptor-type I (TNFR1) and -type Ⅱ

(TNFR2) in mediating pathology has not been fully explored. TNFR2 expression and signal transducer and activator of transcription (STAT) 3 activation in colonic epithelial cells (CECs) are markedly up-regulated during the recovery phase of DSS-induced acute colitis[55]. Recently, it has been reported that TNFR1 KO mice lose more weight and have increased mortality compared with wild-type mice, while TNFR2 KO mice lose less weight and have an improved survival rate compared to wild-type mice in TNBS-induced colitis. These results suggest that TNF-α signaling through TNFR1, but not TNFR2, is protective in mouse models of IBD[56].

As for Th1-type responses, CD40L-CD40 interaction is crucial for the priming of Th1 cells *via* the stimulation of IL-12 secretion by antigen-presenting cells (APC) in TNBS-induced colitis. The administration of anti-CD40L antibody prevents IFN-γ production and TNBS-induced colitis, which suggests that the Th1 response may be mediated by CD40L-CD40 interactions[57,58].

Recent studies have demonstrated that the proteinase-activated receptors (PARs), a family of G protein-coupled receptors activated by serine proteinases, have an important anti-inflammatory role in the colon. PAR-1 and -2 are highly expressed in CECs and neuronal elements, and are involved in regulating secretion by the epithelial cells of salivary glands, stomach, pancreas and the intestine[59]. Intracolonic administration of PAR-1 agonist in oxazolone-treated mice efficiently inhibits colitis[59]. By contrast, the inflammatory responses in PAR1 KO or PAR-1 antagonist-treated mice are exacerbated in oxazolone-induced colitis[60]. As well, PAR-2 activation prevents the development of TNBS-induced colitis[61].

Finally, the glucocorticoid-induced TNFR (GITR)-related gene is a member of the TNFR superfamily that is constitutively expressed at high levels on $CD4^+$ $CD25^+$ regulatory T cells, and at low levels on unstimulated T cells, B cells and macrophages[62]. GITR signalling in $CD4^+$ T cells is involved in the development and progression of colitis[63], while deletion of GITR protects against TNBS-induced colitis by reducing innate immune responses and effector T-cell activity[64].

Transcription factors

Nuclear factor (NF)-κB is the key transcription factor for pro-inflammatory responses, and is thought to be important in the initiation and progression of both human IBD and animal models of colitis[65,66]. Disease activity in mice with TNBS-induced colitis is inhibited by antisense oligonucleotides that inhibit the p65 subunit of NF-κB, which suggests a critical role for NF-κB in mediating inflammatory responses[65]. Attempts to control mucosal inflammation by the use of agents that block the NF-κB pathway have had some success in murine models. For example, it has been shown that administration of NF-κB decoy oligodeoxynucleotides (decoy ODNs) encapsulated in a viral envelope prevents the development of TNBS- and oxazolone-induced colitis by inhibiting production of IL-23/IL-17[67]. De Vry *et al* have used a chemically modified, non-viral NF-κB decoy and have shown that the NF-κB decoy ameliorates disease severity in TNBS-, DSS- and oxazolone- induced colitis. These studies suggest that NF-κB decoy ODNs are effective in attenuating Th1- as well as Th2-mediated colitis, and this would be a potentially useful therapeutic strategy for human IBD[68]. In addition to NF-κB, mitogen-activated protein kinase (MAPK) p38 is also a crucial mediator of inflammation. Inhibition of NF-κB and MAPK p38 by SB203580 is able to attenuate the inflammatory response in TNBS-induced colitis models[69,70].

By contrast, TGF-β1 functions as a negative regulator of T-cell immune responses, signaling target cells through the Smad family of proteins. Smad7, an inhibitor of TGF-β1 signaling, is over-expressed in the intestinal mucosa and purified mucosal T cells isolated from patients with IBD[71]. Oral administration of antisense oligonucleotide of Smad7 also ameliorates inflammation in TNBS- and oxazolone-induced colitis, by restoring TGF-β1 signaling *via* Smad3[72].

It has been demonstrated that cytokines exert their biological functions through Janus tyrosine kinases and STAT transcription factors. An experiment blocking the IL-6 receptor has demonstrated that IL-6 plays an important role in the development of Th1-mediated TNBS-induced colitis by activating the STAT3 signaling pathway[73]. Indeed, STAT3 was most strongly tyrosine-phosphorylated in human UC and CD patients and in DSS-induced colitis in mice[74]. These results suggest that the IL-6/STAT3 pathway plays a crucial role in the development and perpetuation of DSS-induced colitis.

Lastly, peroxisome proliferator-activated receptor γ (PPARγ) is a lipid-activated transcription factor, and PPARγ heterozygous mice are highly susceptible to TNBS-[75] and DSS-induced colitis[76]. It has also been reported that mice with a targeted disruption of PPARγ in macrophages display an increased susceptibility to DSS-induced colitis[77]. Therefore, activation of PPARγ may potentially protect against human IBD.

Adhesion molecules

Trafficking, activation and retention of leukocytes within inflamed tissues are mediated by several classes of specialized adhesion glycoproteins[78]. Collagens represent the most abundant extracellular matrix protein, and the major cell surface receptors for collagens are integrins[78,79]. The collagen-binding integrin α1β1 mediates inflammation in TNBS-[80] and DSS-induced colitis[81], which suggests the importance of α1β1-mediated adhesive leukocyte/matrix interactions in regulating mucosal inflammatory responses. Leukocyte β2 integrins are heterodimeric adhesion molecules consisting of a common β subunit (CD18) and different α subunits (CD11a-d)[82]. In DSS-induced colitis, leukocyte function-associated antigen-1 (LFA-1, CD11a/CD18) seems to have a pathogenic role, whereas Integrin alpha M (Mac-1α, CD11b/CD18) serves in a regulatory capacity[83]. Much attention has been focused on the role of α4 integrin in IBD, but it has recently been reported that neutralization therapy may result in undesirable complications such as multifocal leukoencephalopathy[84].

Toll-like receptors (TLRs) and their ligands

It is widely suspected that IBD arises from a dysregulated mucosal immune response to luminal bacteria. TLRs,

which are pattern-recognition receptors expressed by both immune and non-immune cells, play a pivotal role in host/microbial interactions and have two distinct functions-protection from infection and control of tissue homeostasis, depending on the recognition of pathogens or commensals[85-88]. TLRs send intracellular signals in response to intestinal commensal or pathogenic microbes that contain or release conserved molecular patterns, such as LPS, bacterial lipoprotein, bacterial cytosine-guanosine dinucleotide (CpG) DNA, and bacterial flagellin. Activation of TLRs results in the activation of the innate and/or adaptive immune response[85]. In this context, TLRs play an important role in the maintenance of intestinal homeostasis. TLR4 recognizes LPS, and transduces a proinflammatory signal through the adapter molecule myeloid differentiation marker 88 (MyD88)[86]. DSS treatment of TLR4 KO and MyD88 KO mice has been shown to induce earlier and more severe colitis compared to that in wild-type mice, which suggests that TLR4 signaling through MyD88 is an important suppressor of the inflammatory response to chemical injury[87].

Bacterial flagellin specifically stimulates TLR5 and activates MAPK and NF-κB-related signaling pathways, which leads to the production of macrophage inflammatory protein 3α (MIP3α) and IL-8[89]. Flagellin exposure exacerbates inflammation in DSS-induced colitis, but not in the intact colon[88]. By contrast, a TLR2 specific agonist, peptidoglycan or lipoteichoic acid, does not cause any inflammatory response[90].

Lastly, TLR9 is critical for the recognition of the CpG motif of bacterial DNA[91]. DSS-induced colitis is less severe in TLR-9 KO mice[92], and treatment of mice with an adenovirus expressing CpG-ODN that is known to block CpG effects results in significant amelioration of DSS-induced colitis[92], which indicates that ODN inhibition of the immune-stimulating properties of bacterial DNA may offer a novel and specific tool for the treatment of IBD.

Enzymes

Although intestinal epithelial cells constitutively express COX-1, COX-2 is induced only during inflammatory conditions. Enzymatic activity of these COX isoforms produces prostaglandins (PGs) that have proinflammatory roles mediating fever, hyperalgesia, vascular permeability and edema. However, PGs also have a protective role against gastrointestinal injury[93]. The linkage between COX-2 and PGE2 for protection against colitis has been highlighted in various studies. For example, COX-2 KO mice are more susceptible to DSS-induced colitis, which correlates with their inability to produce PGE2[94]. Kabashima *et al*[95] have used mice deficient in prostaglandin receptor EP4 and examined the roles of prostanoids in DSS-induced colitis; their mice developed severe colitis, which suggests that EP4 maintains intestinal homeostasis by keeping mucosal integrity and down-regulating immune responses. It has also been shown that COX-2-derived PGE2 is important in TLR4-related mucosal repair[96], and that COX-2 has a protective effect against acetic-acid-induced colitis[97,98]. These results suggest that COX-2 has a pivotal role in the maintenance of mucosal homeostasis. However, there is controversy about whether COX-2 inhibitors worsen symptoms of human IBD[99].

Through the use of DNA microarray analysis, our group has demonstrated that several detoxification-associated molecules, which contribute to the prevention of inflammation by regulating physiological balance under normal conditions, are highly down-regulated in CECs in chronic colitis[100]. Among the up-regulated detoxification-associated molecules, carbonic anhydrase (CAR)-Ⅳ is an important enzyme involved in the suppression of acidification, by regulating mucosal bicarbonate concentration[101]. Unexpectedly, inhibition of CAR-Ⅳ suppresses the severity of DSS-induced colitis but enhances CEC proliferation, which raises the possibility that CAR-Ⅳ may have a pathogenic role under inflammatory conditions. Microarray analysis also identifies chitinase 3-like-1 (CHI3L1) as being specifically up-regulated in inflamed mucosa[102]. The expression of CHI3L1 protein is detectable in LP and CECs in several murine colitis models, and also in IBD patients, but is absent in normal controls. Anti-CHI3L1 antibody administration significantly ameliorates DSS-induced colitis, which suggests that inhibition of CHI3L1 activity may be a novel therapeutic approach for IBD. Our group is currently investigating this possibility by utilizing murine models of chronic colitis.

As well, IL-1β-converting enzyme (ICE), also known as caspase-1, is an intracellular protease that cleaves the precursors of IL-1β and IL-18 into active cytokines[103,104]. ICE deficiency results in protection from DSS-induced colitis, accompanied by the reduced release of the proinflammatory cytokines IL-18, IL-1β and IFN-γ[105].

Lastly, recent studies have identified Vanin-1 as being involved in the regulation of innate immunity. Vanin-1 is an epithelial ectoenzyme with pantetheinase activity, which is involved in the metabolic pathway of pantothenate (vitamin B5), and provides cysteamine to tissues[106]. Vanin-1 deficiency protects from TNBS-induced colitis. Additionally, by antagonizing PPARγ, Vanin-1 promotes the production of inflammatory mediators by intestinal epithelial cells[107]. This study suggests that Vanin-1 is an epithelial sensor of stress that exerts control over innate immune responses in tissues. As such, it has been proposed as a potential new therapeutic target for IBD.

Hormones

It has been demonstrated that adipose tissue secretes a variety of biologically active molecules[108]. Adiponectin (APN) is an adipose tissue-derived hormone and is considered to be a member of the expanding family of adipokines[109]. APN has a protective role against DSS-induced murine colitis, but not TNBS-induced disease[110], by inhibiting the production of chemokines such as monocyte chemoattractant protein-1 and MIP-2 in CECs, and the subsequent inflammatory response. However, a proinflammatory role for APN in synovial fibroblasts[111] and CECs[112] has recently been suggested. APN exerts proinflammatory activity in the colon by producing proinflammatory cytokines and inhibiting the bioactivity of protective growth factors such as bFGF and heparin-

binding epidermal growth factor. It is interesting to note that APN KO mice are highly protected from both DSS- and TNBS-induced colitis[112].

Finally, leptin, a regulator of food intake and energy expenditure, can also modulate immune and inflammatory responses. Leptin-deficient (ob/ob) mice exhibit less severe colitis compared to wild-type mice in DSS and TNBS models, while replacement of leptin in ob/ob mice converts disease resistance to susceptibility, which indicates that leptin deficiency accounts for the resistance to acute DSS- and TNBS-induced colitis[113]. It has also been shown that phosphorylation of STAT3 and induction of COX-2 are absent in the colon of ob/ob mice[113]. Therefore, leptin represents a functional link between the endocrine and immune systems.

CONCLUSION

Dysregulated immune responses initiated by microbial-host interactions contribute to the development and perpetuation of both murine colitis and, most likely, to human IBD. In this process, intestinal epithelial cells play important roles linking innate and acquired immune responses. In this review, we have focused primarily on the role of functionally distinct factors in the pathogenesis of chemically-induced models of intestinal inflammation during acute, recovery and chronic phases. The increasing clinical use of biological therapy in human IBD illustrates the potential benefits that may be derived from molecular analysis of immunopathogenesis. However, the long-term effects of such therapy have still not been determined, and concerns regarding potentially increased risks of infection or tumor development have been raised, given the essential roles of innate and acquired immunity in host defense. In this respect, topical treatment would have the advantage of selectively targeting local immune responses while sparing systemic immune protective mechanisms. Therefore, we need to find agents that have more targeted effects or take advantage of local delivery systems that target diseased lesions, such as is seen with oligonucleotide-based therapeutics. The different animal models provide an easy means to study factors involved in pathogenesis and to test new therapeutic agents for human IBD.

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