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REVIEW

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Animal models of intestinal inflammation: new insights into the molecular pathogenesis and immunotherapy of inflammatory bowel disease

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Abstract Inflammatory bowel diseases (IBDs) in humans are complex chronic inflammatory disorders of largely unknown cause. Several mouse models that in some respects resemble human IBDs have recently been developed and have provided new insights into immunoregulatory processes in the gut. Both genetic and environmental factors have been shown to be involved in chronic intestinal inflammation. In most of the models $CD4^+$ T lymphocytes have been identified as central mediators of inflammation. Inappropriate activation of T_H1-dominated cytokine pathways upon contact with luminal bacterial antigens and lack of tolerance appear to be crucial for intestinal pathology. We present a brief overview of important animal models of IBD and describe the recent progress in understanding the mechanisms that contribute to chronic intestinal inflammation. Furthermore, novel immunotherapeutic approaches derived from such animal models are discussed.

Keywords Inflammatory bowel disease · Animal models · Cytokines

Introduction

Crohn's disease (CD) and ulcerative colitis (UC), the prototypes of chronic intestinal inflammation in humans, are complex immunological disorders of largely unknown cause [1]. However, multiple studies in the past few years have led to the view that both environmental factors and genetic susceptibility contribute to pathological immunoregulatory events causing colitis [2]. Much of the recent progress in the understanding of mucosal immunity and pathophysiology in the gut has been achieved by the development of new experimental animal models of chronic intestinal inflammation [3, 4]. Although these models do not represent the complexity of human disease and do not replace studies with patient material, they are valuable tools for studying many important disease aspects in reproducible in vivo systems. In addition, questions that are difficult to address in humans, such as the pathogenesis of early phases of colitis and the effect of new therapeutic strategies, may be analyzed in well-defined animal models.

The healthy gastrointestinal tract is a place for nutrient uptake and a barrier to pathogenic antigens at the same time. A direct consequence of this physiological function is a very complex network of immunological interactions leading to a tightly controlled mucosal immune balance [5]. The development of new transgenic and gene targeting technologies over the past decade has allowed a more precise analysis of the interplay of different cell types and their soluble factors in health and disease and has marked a new age in the study of colitis. In this review we first present a brief overview of a wide variety of established and recently developed animal models of chronic intestinal inflammation (Tables 1, 2, 3). In the second part we discuss common mechanisms for immunopathology and therapy of chronic intestinal inflammation on the basis of results obtained from both animal models and patient material.

Animal models of intestinal inflammation can be divided formally into four categories: spontaneous models, inducible models in mice with a normal immune system, adoptive transfer models in immunocompromised hosts,

and genetically engineered models (transgenic mice, knockout mice). These models have led to a rapid progression in our understanding of mucosal immunopathology that is also based on the fact that more than 20 novel animal models of intestinal inflammation have been developed since 1993. Most of these models are adoptive transfer models and genetically engineered models of chronic intestinal inflammation, indicating that many of these models result from the availability of gene targeting/transgenic mouse technologies and a better understanding of the pathogenic role of certain cell populations with pathogenic function. Although most models have a very heterogeneous origin, many models result in a common phenotype: mucosal inflammation mediated by T_H1 T cells that are activated by bacterial antigens in the mucosa. This situation may be very similar to CD, where many different initiating factors and genetic susceptibilities may result in a T_H1-driven intestinal inflammation.

In spite of our better understanding of mucosal pathology none of the currently available models resembles in all aspects the human inflammatory bowel diseases (IBDs). In particular, none of the models so far has a truly chronic relapsing course with acute flares as in IBD or truly mimics the extraintestinal manifestations of IBD or the association of an UC-like lesion with sclerosing cholangitis. Thus, although considerable knowledge has been achieved in recent years, there are still many aspects of mucosal immunopathology that require a better understanding, and a more "ideal" animal model for human IBD must yet be developed.

Models of spontaneous colitis

IBD in humans is believed to occur in individuals with genetic predisposition after exposure to certain environmental factors. Animal models with spontaneous colitis (Tables 1, 2) could therefore offer some advantages over inducible models for defining genetic susceptibility factors of mucosal inflammation.

Colitis in C3H/HeJBir mice

C3H/HeJBir is a novel substrain of C3H/HeJ mice bred at the Jackson Laboratory [6]. These mice reproducibly develop a spontaneous pathogen-independent colitis at about 3 weeks of age with acute and chronic lesions and ulcerations mainly in the cecum and the right side of the proximal colon mucosa. $CD4^+$ T cells, immune reactive to antigens of enteric bacterial flora, but not to food antigens, have been identified as important components in the pathogenesis of colitis in these mice [7]. C3H/HeJBir mice have also been used in combination with inducible colitis models [8] and together with the parent strain may be valuable for studying and identifying genetic susceptibility factors.

Cotton-top tamarin colitis

The cotton-top tamarin (*Saguinus oedipus*) is a primate with unusual susceptibility to UC-like mucosal inflammation, subsequent colon cancer, and viral infections [9]. Environmental factors strongly affect the pathogenesis because a further increase in the number of animals with onset of colitis has been observed when they live outside a tropic climate. The monkeys have only a single MHC class I locus [10, 11] and it is thought that this genetic factor contributes together with environmental factors to the high incidence of colitis and viral infections in these animals. In addition, spontaneous development of colon cancer has frequently been observed in cotton-top tamarins, allowing investigation of the genetic basis for adenocarcinoma as a result of gut inflammation.

Although the efforts required for breeding them are substantial, the spontaneous gut inflammation in these primates is in some aspects likely to be more relevant to human IBD than rodent or rabbit models.

Inducible colitis models

Transient or chronic inflammation of the animal gut can be induced by various methods leading to mechanical or chemical disruption of the mucosal barrier. Probably the most important reason for the onset of colitis in these models is the activation of the mucosal immune system by contact with luminal antigens (Tables 1, 2). Studies in germ-free systems and in animals treated with antibiotics show that in some models the contact of the immune system with bacterial cell wall components triggers the inflammatory response.

Colitis induced by formalin/immune complexes

A transient (<5 days) mucosal inflammation in rabbits can be induced by administration of a diluted formaldehyde solution into the distal colon followed by systemic injection of immune complexes [12, 13]. Presumably, chemical damage of the epithelium and activation of the complement cascade in the lamina propria leads to an inflammatory response of infiltrating granulocytes and macrophages, which is characterized by cryptitis, crypt distortion, and mucosal necrosis. High levels of secreted mediators such as prostaglandin E_2, thromboxane B_2, leukotrienes B_4, and C_4 and interleukin (IL) 1 can be found in inflamed areas. Elevated IL-1 levels seem to play a major proinflammatory role since blocking its function with an IL-1 receptor antagonist results in a milder colitis [14, 15]. Additional studies have shown that prostaglandin E_2 and some sensory neuropeptides are necessary for healing of such colitis [16]. Taken together, the formalin/immune complex colitis model is

Table 1 Animal models of chronic intestinal inflammation: an overview

Spontaneous	Inducible	Adoptive transfer	Transgenic	Knockout
C3H/HeJBir mice	Formalin/immune complexes	$CD45RB^{High}$→scid	HLA-B27 (rats)	IL-2
Cotton top tamarin	Acetic acid	BMC→Cd3εTg26	STAT-4	IL-2Ra
Samp1/Yit mouse	Carrageeenan	Hsp60 specific $CD8^+$ cells→$TCR\beta^{-/-}$	Dom. neg. N-cadherin	IL-10
	Indomethacin		IL-7	CRF2–4
	Peptidoglycan-polysaccharide		HSV tyrosine kinase	TGF-β
	Dextrane sulfate sodium			$G_{i\alpha}2$
	Radiation			TCR-α
	Cyclosporin A			Trefoil factor
	Hapten-based			Mdr1a
	TNBS/DNBS			WASP
	Oxazolone			TNFΔARE

Table 2 Characteristics of animal models of chronic intestinal inflammation

Model	Species	Pathology	Affected site	Pathogenesis/remarks	Costs
Spontaneous models					
Cotton top tamarin	Primate	Acute, chronic mucosal	Colon	T cells/appropriate animal facility required, induction of colon cancer	High
C3H/HeJBir	Mouse	Acute, chronic transmural	Cecum, right colon	T cells reactive to bacterial antigens	Medium
Inducible models					
DSS	Mice	Acute, chronic mainly mucosal	Colon	Toxic intestinal damage plus activation of the mucosal immune system (T_H1/T_H2)/ addition of azoxymethane induces cancer development	Low
TNBS	Mice, rats, rabbits	Acute, chronic transmural	Colon	Activation of the immune system (T_H1-mediated; hapten-specific)/optimization of TNBS dose required, only certain strains	Low
Adoptive transfer model					
$CD45RB\ CD62L^+$ cell transfer into SCID mice	Mice	Acute, chronic transmural	Colon, duodenum	IL-12 driven T_H1 T cells/induction of colitis requires 6–12 weeks, appropriate animal facility for SCID mice required	High
Genetically engineered models					
IL-2 knockout mice	Mice	Acute, chronic mucosal	colon	IFN-γ producing T cells/colitis 6–15 weeks after birth, variability between mice	Medium
IL-10 knockout mice	Mice	Acute, l chronic transmural	Colon, sometimes jejunum/ileum	T_H1 cells in response to bacterial antigens/variability between mouse strains	Medium
STAT-4 transgenic	Mice	Acute, chronic transmural	Colon, ileum	T_H1 T cells in response to bacterial antigens/requires immunization of mice	Medium

very valuable for the study of pro- and anti-inflammatory processes in acute colitis, but is not suitable for long-term or therapeutic studies.

Acetic acid induced colitis

The intrarectal administration of diluted acetic acid into rodents or rabbits leads to epithelial injury and increased permeability followed by an acute mucosal/transmural inflammation in a dose-dependent manner [17]. This reproducible model is easy to use and valuable for studying early events of inflammation after mucosal injury and wound healing.

Carrageenan colitis

Degraded carrageenan polymers in the drinking water of guinea pigs and mice lead to mucosal inflammation of the cecum within a week, which extends to the left side of the colon within 3–6 weeks after treatment [18, 19].

Removing the polymers from the drinking water prolongs the colitis for 1–2 weeks, while prolonged treatment is lethal after 7–8 weeks (due to sepsis). Carrageenan affects epithelial cells and severely impairs the mucosal barrier. Several studies have shown that the presence of anaerobic bacteria (in particular *Bacteroides* species) is important for the development of mucosal lesions and ulcerations [20], although the exact pathophysiological mechanisms remain unclear.

Indomethacin-induced colitis

In rats subcutaneous injections or oral administration of indomethacin causes chronic ulcerations and transmural inflammation in the small bowel [21, 22]. Epithelial damage induced by indomethacin probably together with bile fluid seems to be an important factor, as well as specific inhibition of protective prostaglandins. Germ-free rats and rats treated with antibiotics do not show chronic inflammation, indicating a pivotal role of the enteric microflora for disease development.

Peptidoglycan-polysaccharide colitis

Intramural injection of the bacterial cell wall component peptidoglycan-polysaccharide (PG-PS) into the distal colon of rats induces transmural enterocolitis [23]. In genetically susceptible animals chronic granulomatous colitis with thickening of the colon wall and infiltrating lymphocytes, macrophages, and neutrophils develops after 3–4 weeks. PG-PS increases mucosal permeability and myeloperoxidase activity and enhances NO production and collagen synthesis. Treatment with recombinant IL-1 receptor antagonist [24] or IL-10 [25] attenuates disease, the latter particularly the chronic stages of inflammation. Data obtained from this model clearly show that cell wall components of nonpathogenic resident enteric bacteria are sufficient to induce acute and chronic colitis in a susceptible host when they penetrate into the colon wall.

Dextran sulfate sodium colitis

Feeding mice or rats for several days with dextran sulfate sodium (DSS) polymers in the drinking water induces an acute left-sided colitis with bloody diarrhea, ulcerations, histological damage, and infiltrations with neutrophils [26]. In susceptible strains the administration of DSS for several cycles (7 days DSS, 7 days water) results in chronic lesions with infiltrating macrophages, $CD4^+$ T lymphocytes, and fissuring ulcers [8]. Later phases of the disease are associated with increased levels of proinflammatory cytokines (IL-2, IL-4, IL-6) and leukotrienes – signs for involvement of the adaptive immune system. It has been shown that pretreatment of mice having DSS colitis with azoxymethane leads to the development of multiple colorectal tumors predominantly in inflamed regions of the colon [27]. Therefore experimental DSS colitis might be a valuable model for studying the molecular interplay of colitis and colorectal carcinogenesis.

Radiation induced colitis

MHC class $II^{-/-}$ mice spontaneously develop chronic colitis at 4–6 months of age [28]. In a recently published model lethally irradiated wild-type C57BL/6 mice reconstituted with bone marrow from MHC class $II^{-/-}$ mice displayed severe colitis within 2 months after reconstitution [29]. It can be speculated that radiation damage affects the epithelial barrier, allowing immune cells in the lamina propria to encounter luminal antigens. However, the reasons for onset of colitis only in the MHC class II deficient environment is poorly understood.

Hapten-based colitis models

Enemas of some contact sensitizing substances into the colon of mice and rats can induce acute and chronic intestinal inflammation. Although the exact mechanisms remain unclear, the inflammatory processes seem to be the result of delayed-type hypersensitivity immune responses against hapten molecules covalently bound to cellular proteins.

Trinitrobenzene sulfonic acid/dinitrobenzene sulfonic acid colitis

Colitis in susceptible strains of mice, rats and rabbits can be induced by luminal instillation of 2,4,6-trinitrobenzene sulfonic acid (TNBS) or dinitrobenzene sulfonic acid (DNBS) in 30–50% ethanol [30, 31, 32, 33, 34]. The development of acute, chronic, or lethal forms of colitis is highly strain dependent (e.g., Black 6 mice are resistant) and requires individual optimization of the administered TNBS concentrations, and sometimes multiple injections are necessary for chronicity. Acute colitis in rats is associated with mucosal permeability as a consequence of epithelial necrosis and elevations in colonic myeloperoxidase activity. A high damage score is observed, which is apparently related to an increase in the number of macrophages and granulocytes.

TNBS/ethanol-induced colitis in SJL/J mice is characterized by a transmural granulomatous inflammation with severe diarrhea, weight loss, and thickening of the bowel wall. The chronic stage is associated with an activation of the mucosal immune system and an increase in the number of infiltrating lymphocytes, espe-

cially $CD4^+$ T cells in the lamina propria [32]. The TNBS colitis model has been very useful in studying many important aspects of gut inflammation, including cytokine secretion patterns, mechanisms of oral tolerance [35], cell adhesion [36], and immunotherapy [37, 38]. In SJL/J mice with TNBS-induced colitis isolated lamina propria T cells produce significantly more interferon (IFN) γ and IL-2 than IL-4 and IL-5 after stimulation consistent with a T_H1 type response. Since treatment against tumor necrosis factor (TNF) α and anti-IL-12 ameliorates the disease, it has been suggested that a positive feedback loop between macrophages producing T cell activating IL-12 upon contact with bacterial antigens and T cells producing macrophage activating IFN-γ contributes to the chronicity of the inflammation. As in other models, transforming growth factor (TGF) β and IL-10 seem to play an important role for downregulation of the inflammatory process.

Many histopathological aspects of TNBS colitis and the increased gut levels of IL-12 and TNF-α are consistent with those observed in specimens of patients with CD. Interestingly, this model has been recently used to demonstrate that environmental stress factors affect mucosal permeability and can reactivate resolved DNBS colitis. This process is mediated and can be adoptively transferred by $CD4^+$ T cells [39]. It is important to note that induction of colitis in the TNBS model depends on the genetic background of the animal strain used and the individual microflora of the animal facilities. Since different TNBS lots show a striking variability in their capacity to induce colitis, initial studies are needed to find the optimal colitis-inducing TNBS/ethanol dose in a given microenvironment.

Oxazolone colitis

This model was initially developed in rats. Dark Agouti rats were skin-sensitized with oxazolone prior to an additional intrarectal luminal treatment with oxazolone dissolved in carmellose sodium/peanut oil [40]. The treatment induced inflammation with an elevated myeloperoxidase activity, epithelial damage, and ulcerations. A single rectal administration of oxazolone in 50% ethanol in SJL/J mice caused a severe colitis marked by weight reduction, diarrhea and marked loss of goblet cells, leading to death of half of the mice [41]. The inflammation affects only the distal colon and here particularly mucosal layers. Mice which survive recover from the wasting syndrome and diarrhea within 2 weeks after treatment. Histological features and elevated production of the T_H2 cytokines IL-4 and IL-5 of unstimulated and anti-CD3/anti-CD28 stimulated lamina propria T cells are in some aspects similar to characteristics of human UC. In contrast to several other models, treatment with anti-IL-4 antibodies ameliorates disease.

Adoptive transfer models

Bowel inflammation is induced in adoptive transfer models by selective transfer of certain cell types to immunocompromised host animals. These models are versatile tools for unraveling many immunological and genetic factors contributing to disease and have provided outstanding new insights into the predominant role of T cells for mucosal immune regulation (Tables 1, 2).

$CD45RB^{High}$ transfer model

$CD4^+CD45RB^{High}$ T cells from wild-type donor mice transferred to immunodeficient SCID (severe combined immunodeficiency) or RAG (recombination activating gene) deficient recipient mice cause a wasting syndrome with transmural intestinal inflammation starting 5–8 weeks after cell transfer [42, 43, 44, 45]. Recipient mice repopulated with the entire $CD4^+$ T cell subset or $CD4^+CD45RB^{Lo}$ T cells do not develop colitis (or at least with delayed kinetics), although these cells also colonize the host gut. While regulatory cells within the $CD4^+CD45RB^{Lo}$ population have the potential to prevent such immune responses, many studies support the view that the bowel inflammation is caused by a proinflammatory IL-12-driven T_H1 response of $CD4^+CD45RB^{High}$ cells [46, 47]. $CD4^+CD45RB^{High}$ T cells obtained from mice deficient for the signal transducer and activator of transcription (STAT) 4, a key component in IL-12 signal transduction, develop a less severe disease upon transfer than wild-type cells [48]. Neutralizing antibodies to either IL-12, IFN-γ, or TNF-α ameliorate colitis and these cytokines probably play a pivotal role for pathogenesis in this model. In the case of IFN-γ there are two conflicting studies with $CD4^+CD45RB^{High}$ T cells from IFN-γ knockout donors. One group reported that mucosal inflammation in SCID recipients is abrogated in this case [49] while another group detected no dramatic differences to transfer of cells from wild-type donor mice [48]. Several studies identified IL-10 and TGF-β as central anti-inflammatory factors in this model. Regulatory T cells (Tr1 cells) which produce mainly IL-10 due to coculture with IL-10, prevent onset of gut inflammation and antigen-specific immune responses when cotransferred with pathological $CD4^+CD45RB^{High}$ T cells [50] as systemic administration of recombinant IL-10 or TGF-β do [47]. As in many other models of experimental colitis, bacterial antigens play a crucial role for pathology since treatment with antibiotics or germ-free breeding of recipient SCID mice is associated with significantly less severe bowel inflammation [51].

To avoid the requirement of an expensive FACS sorter, we recently developed a modified version of this model by isolation of T cells using magnetic cell sorting. In this transfer model $CD4^+CD62L^{High}$ (L-Selectin, MEL14) T

cells from BALB/c mice were isolated and transferred into CB.17 SCID mice. This cellular population induces a chronic bowel inflammation with similar disease manifestations and kinetics as transferred $CD4^+CD45RB^{High}$ cells. In this model chronic colitis could be effectively treated by blocking the IL-6 receptor signal transduction pathway, which is involved in T cell resistance to apoptosis [52].

CD3εTg26 transfer model

Mice with high copy transgenic expression of human CD3ε display an abnormal structure of the thymus, leading to a complete loss of both T and natural killer cells [53, 54]. Interestingly, adoptive transfer studies clearly demonstrate that these mice develop severe wasting disease and bowel inflammation after reconstitution with nonallogenic wild-type bone marrow depleted from T cells [53]. T cells that have undergone normal thymic selection can effectively inhibit development of such colitis. One striking feature that BM→Tg26ε model has in common with many other models is the predominant role of activated T cells secreting IFN-γ and TNF-α, consistent with a polarized T_H1 response.

Colitis induced by transfer of hsp60-specific CD8 T cells

Severe lethal intestinal pathology (predominantly in the small intestine) in this recently introduced mouse model is induced by adoptive transfer of a hsp60-specific $CD8^+$ T lymphocyte clone, preactivated by bacterial hsp60, into T cell receptor (TCR) $\beta^{-/-}$ or SCID mice [55]. Formation of colitis in these mice requires presentation of hsp60 on MHC class I and depends on a functional role of TNF-α as adoptively transferred cells do not induce colitis in TCRβ/TNF receptor I/tumor necrosis factor receptor II triple-knockout mice. In contrast to the findings obtained in many other models, intestinal inflammation in this model does not depend on the presence of the resident bacterial flora. Thus the results obtained by initial analysis of this model indicate that autoimmune hsp60 $CD8^+$ T cells that are reactive to cellular hsp60 mediate pathogenesis.

Genetically engineered models

The use of molecular biology techniques, in particular transgenic mice and gene targeting technologies, in the gastrointestinal tract is responsible for many recent advances in our functional understanding of mucosal inflammation [56] (Tables 1, 2). Such mice allow the precise molecular dissection of immunoregulatory pathways and are useful in identifying specific therapeutic strategies. Mutant strains can often be used together with the colitis models described above, and intercrossing of mutant strains allows further gradual analysis.

Transgenic mouse models

Colitis in HLA B27 transgenic rats

Rats transgenic for human HLA-B27, a molecule involved in human spondylarthropathies, and β_2-microglobulin develop a spontaneous inflammatory bowel disease which affects the stomach, ileum, and in particular the entire colon [57]. Crypt hyperplasia and mucosal infiltration of mostly mononuclear inflammatory cells characterize the disease. A functional role of activated T_H1 type lymphocytes (presumably from an aberrant antigen presentation via B27) for pathogenesis has been suggested [58]. This model has been used extensively to study the effect of resident intestinal bacteria for acute and chronic stages of gastrointestinal inflammation. Selective colonization of the gut of germ-free bred transgenic rats, which do not develop colitis, with certain bacterial species of the normal intestinal microflora has shown that different resident bacteria (e.g., *Bacteroides* spp.) have different proinflammatory potentials [59]. In addition, these studies have demonstrated that various bacterial species can induce diverse types of pathology, for example, colitis and gastritis, in these rats [60].

STAT-4 transgenic mice

STAT-4 is a regulatory transcription factor specifically associated with IL-12 receptor signaling [61]. Transgenic mice for STAT-4 under control of a cytomegalovirus promoter system which express highly elevated nuclear STAT-4 levels in $CD4^+$ T cells after systemic administration of dinitrophenyl–keyhole limpet hemocyanin have been shown to develop chronic transmural colitis [62]. Infiltrating lamina propria $CD4^+$ T cells after stimulation with αCD3/αCD28 produce in vivo and in vitro predominantly TNF-α and IFN- γ, but not IL-4, consistent with a T_H1-type cell response. This demonstrates that an abnormal activation of the IL-12 driven T_H1 pathway can be sufficient to destroy the mucosal immune balance. Interestingly, this suggestion is supported by the finding that colitis in these mice can be adoptively transferred to recipient SCID mice by $CD4^+$ T cells that have been primed with antigens from the autologous bacterial flora.

Transgenic mice for dominant negative N-cadherin

An elegant approach, which emphasizes clearly the importance of an intact epithelial barrier in the gut for mu-

cosal homeostasis, was the establishment of N-cadherin transgenic mice [63]. Cadherins are important mediators of cellular adhesion. Altered intercellular adhesion by tissue specific expression of a dominant negative mutant of N-cadherin in transgenic mice by using a small intestinal epithelial cell specific promoter results in the development of chronic inflammatory bowel disease with some similarities to CD. Human colitis is strongly associated with altered cell-cell interaction and adhesion processes, but the role of adhesion molecules, such as cadherins, in IBD is poorly understood. The differential tissue-specific expression of normal or mutated cadherins in transgenic mice can therefore contribute to a better understanding of epithelial cell functions in colitis.

IL-7 transgenic mice

IL-7 synthesized in intestinal epithelial cells regulates proliferation and differentiation of lymphocytes within the gut mucosa and has been found to be upregulated in the serum of patients with UC [64]. The expression of IL-7 in the colonic mucosa of IL-7 transgenic mice is associated with chronic colitis caused by infiltrating $CD4^+$ T cells [65]. The results of this study suggest an important role of a destructive T cell response for intestinal pathology. Another group has reported the importance of IL-7 for the development of colitis by using IL-$7^{-/-}$ deficient mice in a non-T/non-B cell (RAG-$2^{-/-}$) colitis model [66]. In this system the lack of IL-7 prevents a strong pathogenic myeloid cell response against the bacterial flora.

Jejunoileitis in herpes simplex virus tyrosine kinase transgenic mice

This model is useful for investigating the functional role of enteric glia in the gut. Transgenic mice expressing herpes simplex virus (HSV) tyrosine kinase under control of the astroglial cell specific glial fibrillary acidic protein promoter develop lethal inflammation of the ileum and the jejunum after elimination of bowel astroglial cells by a 2-week treatment with the antiviral drug ganciclovir [67]. The mechanism by which the loss or dysfunction of enteric glia in the gastrointestinal tract may contribute to chronic intestinal inflammation remains unclear. However, these mutant mice may be very helpful in studying the functions of the enteric nervous system in mucosal immunity.

Gene knockout models

IL-2/IL-2Rα knockout mice

Depending on the genetic background of the strain IL-2 knockout mice develop multiorgan disease, including inflammatory bowel disease [68]. Although large numbers of T and B lymphocytes infiltrate the colon, these are not essential in the formation of colitis since IL-$2^{-/-}$/$JH^{-/-}$ double-knockout mice, which lack B cells, do not fail to develop disease [69]. In the inflamed colon there are increased levels of proinflammatory cytokines such as IFN-γ, TNF, and IL-1β, suggesting an activation of the T_H1 pathway. IL-$2^{-/-}$ mice do not develop severe colitis under germ-free conditions [70, 71]. Although the exact role of IL-2 in mucosal immunity still remains unclear, the analysis of this extensively studied IBD model indicates that a dysregulated T_H1 response of $CD4^+$ T lymphocytes against components of the luminal bacterial flora is essential for intestinal pathology. Despite its well-known role as a growth factor for T cells, IL-2 seems to be at the same time a critical component of mechanisms leading to tolerance of T cells against autologous bacterial antigens in the gut.

IL-10/CRF2-4 knockout mice

IL-10 is a well-known suppressor of T_H1 cells and macrophage effector functions. Mice with targeted deletion of the IL-10 gene spontaneously develop chronic enterocolitis with massive infiltration of lymphocytes, activated macrophages, and neutrophils [72, 73, 74]. The disease is accompanied by a T_H type 1 cytokine response, which can be ameliorated by neutralizing antibodies to IL-12 and to a lesser extent IFN-γ or systemic administration of recombinant IL-10 [75]. Studies with B cell deficient IL-$10^{-/-}$ mice have shown that colitis is not dependent on this cell type. Germ-free bred IL-$10^{-/-}$ deficient mice have no evidence of colitis or immune system activation in the gut, suggesting that resident enteric microflora or their products are probably important for initiation and perpetuation of intestinal pathology [76]. Further evidence of the outstanding immunoregulatory role of IL-10 in the gastrointestinal tract was obtained by analysis of CRF2-4 targeted mice. CRF2-4 (type II cytokine receptor family) was recently identified as essential element of the IL-10 signal transduction pathway [77]. Macrophages of CRF2–$4^{-/-}$ mice are unresponsive to IL-10 after stimulation with lipopolysaccharides and develop chronic intestinal inflammation with similarities to the disease in mice lacking IL-10.

Colitis in $G_{i\alpha}2$–deficient mice

Heterotrimeric G proteins are involved in signal transduction processes via adenylate cyclase. Mice with targeted disruption of the α-subunit of G_i2, which is expressed in many cell types including intestinal epithelial cells and lymphocytes, display a severe chronic colitis and high incidence of adenocarcinomas with some clinical and histopathological features similar to UC in humans [78]. T lymphocytes from these mice show in vitro elevated pro-

liferation upon stimulation via the T cell receptor and produce high amounts of proinflammatory T_H1 type cytokines (IL-2, TNF-α, and IFN-γ), presumably as a result of altered thymocyte maturation and function [79]. In the inflamed colon there are markedly increased numbers of memory $CD4^+$ T cells and IgG-producing B cells in the lamina propria, and in addition to elevated IFN-γ and TNF-α levels, there is greater production of IL-12 p40 mRNA than in wild-type mice. While development of the disease depends on the genetic background of the used inbred strain, environmental factors seem to be less important, since breeding under specific pathogen-free conditions does not ameliorate the inflammation.

TCR-α chain knockout mice

Mice deficient for the TCR-α chain (TCR-$\alpha^{-/-}$) spontaneously develop mucosal inflammation at 12–16 weeks of age with some characteristics similar to UC in humans [28]. Colitis in these mice is associated with increased numbers of aberrant T_H2-type $CD4^+TCR\alpha^-\beta^+$ T cells producing predominantly IL-4 and non-T cells producing IFN-γ [80]. However, these elevated IFN-γ levels are not critical for development of colitis because TCR-α/IFN-γ double-knockout mice display similar pathology as TCR-$\alpha^{-/-}$ mice. In contrast, both anti-IL-4 neutralizing antibody treated TCR-$\alpha^{-/-}$mice and TCR-α/IL-4 double-knockout mice exhibited no or much milder clinical or histological signs of inflammation, indicating the predominance of a pathological T_H2 type immune response in the gastrointestinal tract of these mice [81]. Double-mutant mice (TCR-$\alpha^{-/-}$/Ig-$\mu^{-/-}$) lacking B cells show more severe colitis and starting earlier in life than in TCR-$\alpha^{-/-}$ mice. These findings suggest that B cells are not required for the initiation of colitis, but B cells can probably suppress colitis at later stages of the disease. TCR-α deficient mice maintained germ free or colonized with a limited number of defined intestinal bacteria do not develop intestinal inflammation [82].

Trefoil factor deficient mice

Intestinal trefoil factors (ITFs) are peptides secreted by mucus cells of the gastrointestinal tract after inflammatory damage [83]. Mice with targeted disruption of ITF show severely impaired mucosal healing and decreased epithelial regeneration and die after induction of colitis by addition of dextran sulfate sodium to the drinking water [84]. In acetic acid or TNBS-induced colitis in rats a beneficial role has been reported for ITF in repair processes within the intestinal mucosa. Therefore these models can be useful in studying wound-healing processes in the gut and potentially new therapeutic approaches for intestinal injury.

*Multiple drug resistant (*mdr1*) gene deficient mice*

The multidrug resistance (MDR) gene 1, which is responsible for drug resistance to chemotherapy in certain types of cancer, is expressed in the intestinal epithelium and subsets of hematopoietic cells. Mdr1$\alpha^{-/-}$ mice display spontaneous bowel inflammation [85]. As in many other IBD models, an immune response to the resident bacterial flora triggers mucosal inflammation since oral antibiotics ameliorate inflammation and inhibit initial development of disease. Adoptive transfer of mdr1$\alpha^{-/-}$ bone marrow to irradiated wild-type mice does not induce intestinal pathology, in striking contrast to chimera of mdr1$\alpha^{-/-}$ mice reconstituted with wild-type bone marrow. Thus, mucosal inflammation in these mice is most likely caused by dysfunction of intestinal epithelial cells and not by alterations in lymphocyte function.

Wiskott Aldrich syndrome protein deficient mice

The Wiskott-Aldrich syndrome protein (WASP) is involved in cytoskeletal reorganization processes during activation of lymphocytes. WASP-deficient mice display mucosal inflammation by 4 months of age with crypt hyperplasia and infiltrates of lymphocytic and granulocytes in the lamina propria [86].

STAT-3 knockout mice

STAT-3 is a part of signal transduction pathways of many cytokines and growth factors [87]. Mice with specific disruption of the STAT-3 gene in macrophages and neutrophils produce highly elevated amounts of proinflammatory cytokines such as TNF-α, IFN-γ, IL-1, and IL-6 after systemic challenge with lipopolysaccharides, and this T_H1 type immune response may lead to lethal septic shock [88]. Twenty-week-old mutant mice display chronic enterocolitis associated with increased T_H1 cell activity and the presence of macrophages with a constitutively activated ("IFN-γ primed") phenotype. STAT-3 in macrophages is a critical factor within the signal transduction pathway of IL-10, which for this cell type is a potent inhibitor of immune responses and proinflammatory cytokine synthesis. It is therefore thought that the absence of an IL-10 mediated counterregulatory effect on colonic macrophages, which are continuously subjected to stimulation by luminal bacterial or food antigen, is sufficient for the development of chronic intestinal inflammation.

TNFΔ AU-rich-element mice

Patients with CD have increased mucosal concentrations of TNF-α. A chimeric monoclonal antibody that inhibits

TNF (cA2, Infliximab) reduces symptoms of active CD and is used in patients who respond insufficiently to conventional therapy [89]. Gene targeting of AU-rich elements (ARE) in the untranslated region of the TNF-α mRNA in mice is associated with increased constitutive and inducible levels of TNF [90]. Overproduction of TNF leads to polyarthritis and chronic intestinal inflammation with infiltrating inflammatory cells and transmural inflammation, which is dependent on the presence of T and B cells. This recent animal model emphasizes the known pathogenic role of TNF production in IBD, and TNF-α gene mutations or polymorphisms could potentially add to genetic susceptibility to IBD in a subset of patients.

General mechanisms of chronic mucosal inflammation

A steadily increasing number of experimental animal models with some clinical manifestations similar to those observed in human inflammatory bowel disease has recently been developed and have contributed largely to important advances in our current understanding of the immunological, pathological, and physiological features of chronic intestinal inflammation (Table 1). Despite the varying nature of these models the aspects which they have in common greatly support the concept that environmental factors affecting genetically susceptible hosts are responsible for induction of mucosal inflammation.

$CD4^+$ T cell mediated effector mechanisms

It is now generally accepted that T lymphocytes infiltrating the lamina propria, in particular the $CD4^+$ T helper subset, play a key role in both normal and pathophysiological immune regulatory processes in the gastrointestinal tract [91] (Fig. 1). $CD4^+$ T cell involvement for induction of pathogenesis in the gut has been shown in several knockout (IL-2, IL-10, TCR, $G_{i\alpha}2$), transgenic (HLA-B27/β2m, STAT-4), hapten-based (TNBS, oxazolone), and perhaps most strikingly adoptive transfer models ($CD45RB^{HIGH}$, CD3εtg26). Altered balances between T_H1 and T_H2 effector pathways are associated with various pathological manifestations [92]. Several studies have demonstrated elevated levels of IFN-γ, IL-2, and TNF in the gut of CD patients consistent with a T_H1 type response [93]. The dominance of a polarized T_H1 pathway in CD is further confirmed by increased expression of IL-12 [94, 95], which is the key T cell differentiation factor towards cellular immune responses. The majority of animal models display T_H1 cytokine secretion patterns and some histological findings (transmural, granulomatous inflammation) consistent with CD. In these mice genetic and environmental factors, particularly the luminal bacterial flora, are responsible for early activation of the IL-12/STAT-4 signal transduction cascade in $CD4^+$ T cells [62], which subsequently differentiate into IFN-γ producing T_H1 effector cells. IFN-γ primed tissue macrophages produce large amounts of TNF and other proinflammatory molecules and induce chronic mucosal damage via matrix metalloproteinases. Interestingly, a pivotal role of IL-12 is consistently observed in most models, whereas the presence of IFN-γ in some models is not required for onset of bowel inflammation. IL-12 dependent TNF production by T_H1 cells and subsequent activation of proinflammatory processes by TNF itself are likely to compensate for the absence of IFN- γ [48]. A critical role for TNF in intestinal pathology is further underlined by a recent study showing that deregulated expression of TNF in gene-targeted mice is associated with inflammation of the small intestine [90].

It is know clear that T_H1 immune responses in the normal gut are tightly controlled by anti-inflammatory mechanisms. The absence of an appropriate counterregulatory response is sufficient for development of intestinal pathology, as shown in IL-$10^{-/-}$, CRFB-$4^{-/-}$, and TGF-$\beta^{-/-}$ mice. Two different $CD4^+$ T cell subsets, Tr1 and T_H3 cell, have been proposed as central suppressors of inappropriate intestinal immune responses. Antigen-specific Tr1 cells probably downregulate immune responses in the gut by secretion of IL-10 and prevent upon cotransfer colitis in the $CD45RB^{HIGH}$ model [96]. Such cells have also been identified in the human intestine, where they were shown to be responsible for T cell unresponsiveness to antigens of enteric bacteria [97]. T_H3 cells, which produce mainly TGF-β and to a lesser extent IL-4 and IL-10, are discussed in the context of antigen-specific oral tolerance [98]. Primed TNF-producing macrophages are a predominant target for the anti-inflammatory effect of IL-10. This has been elegantly shown in mice, which in a macrophage/neutrophil specific manner are deficient for STAT-3, a protein associated with IL-10 signal transduction processes [88]. Although a pathophysiological role of T_H2 effector mechanisms remains unclear in IBD patients, a predominance of IL-5 has been shown in human UC [99]. Histopathological similarities to UC, polarized T_H2 responses, and disease amelioration by anti-IL-4 strategies have been observed in the inflamed colon of TCR-$\alpha^{-/-}$ mice [80] and the oxazolone colitis model [41].

Environmental factors

Studies in germ-free environments clearly demonstrate that bowel inflammation in almost all experimental models described above depends on the presence of the enteric microflora. In addition, the basis for inflammation in several models is a disturbance of the mucosal

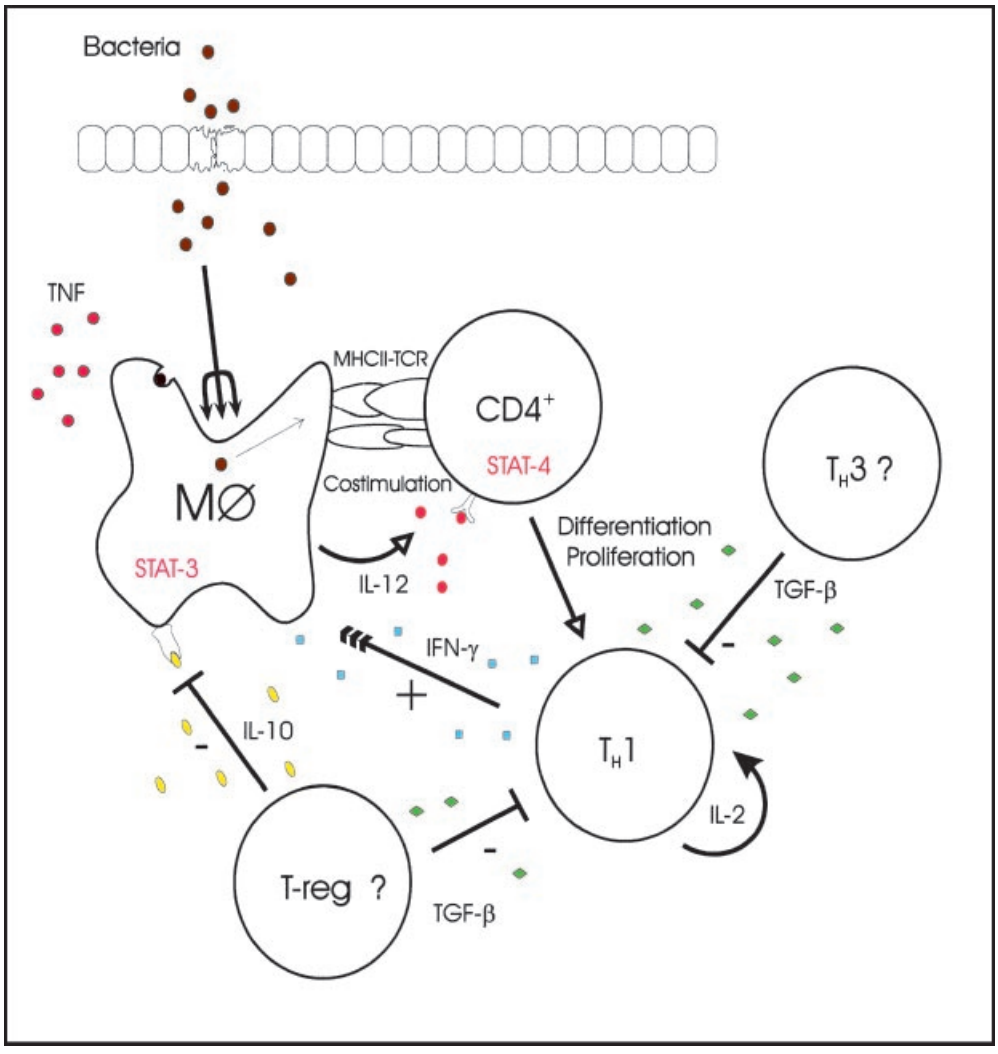

Fig. 1 Proposed model of the immunopathogenesis of T_H1-mediated colitis. Macrophages are activated by penetrating bacterial antigens after mucosal damage and secrete IL-12 and other proinflammatory molecules. Subsequently, antigen-specific activated $CD4^+$ T cells differentiate into IFN-γ and TNF producing T_H1 type effector cells. In the normal gut, however, inappropriate immune responses are tightly controlled by regulatory T cells (Tr1, T_H3) producing anti-inflammatory cytokines (IL-10, TGF-β). In some models IL-4 producing T_H2 cells appear to have pathogenic function rather than IFN-γ producing T_H1 effector cells

barrier function and subsequent immune responses to penetrated luminal antigens. The exposure of the mucosal immune system to antigens of the intestinal microflora is associated with a permanent danger of inadequate hyperresponsiveness. In healthy conditions a permanent immunological activation state is tightly controlled, whereas tolerance is probably broken in the inflamed gut [100]. In addition, it has been shown that such loss of tolerance can be adoptively transferred to immunodeficient mice [7, 62], which lack appropriate counterregulatory mechanisms. Interestingly, selective colonialization of healthy germ-free animals with certain microbes has shown that not all components of the flora have an equal potential to induce mucosal inflammation. *Bacteroides vulgatus* [101] and *Heliobacter hepaticus* [102, 103] have a colitis-inducing capacity in some colitis models, whereas in contrast "probiotic" *Lactobacillus* species can prevent colitis in IL-$10^{-/-}$ mice [104] and are discussed as a potential new therapeutic strategy [105].

Animal models of IBD: from basics to therapy

Studies in animal models of chronic intestinal inflammation have provided many new insights into the complex immune system of the gut and identified many key pathological and protective immunoregulatory mechanisms. These findings provide the basis for many novel potential therapeutic strategies, in which pathophysiological/protective ways of the inflammatory process are specifically inhibited/supported and evaluated for therapy (Table 3). Until now a humanized and a mouse/human chimeric neutralizing antibody to TNF-α [106] and recombinant IL-10 and IL-11 [107, 108] have successfully been used in patients with CD, although the responses to anti-TNF therapy are more dramatic than by treatment with recombinant IL-10. Antibodies or antagonists to important cellular adhesion molecules [109, 110, 111] and some proinflammatory molecules including IL-1, IL-4, IL-6, and TNF or their receptors have beneficial effects in animal models of IBD. Since IL-12 seems

Table 3 Novel potential therapeutic strategies for the treatment of IBD (*CD* Crohn's disease, *UC* ulcerative colitis, *P* preparation phase)

Therapy	Animal model	Clinical trial	References
Cytokines			
IL-10	CD45 transfer, TNBS, DSS, PG-PS	CD	25, 46, 100, 107, 119
IL-11	HLA-B27, TNBS	CD	108, 120, 121
IFN-α		UC, CD	122, 123
NIF	Immune complex		124
rhG-CSF	Immune complex		125
Antibodies			
Cytokines/antagonists			
Anti-IFN-γ	CD45 transfer, TNBS		46, 126
Anti-TNF-α	TNBS, CD45 transfer	CD	46, 89, 106, 127
Anti-IL-12	TNBS, IL-10$^{-/-}$, IL-2$^{-/-}$	CD-P	32, 71, 75, 100
Anti-IL-6R	TNBS, IL-10$^{-/-}$, CD45 transfer		52
Anti-IL-4	TCR$^{-/-}$, oxazolone		41, 128
IL-1R antagonist	TCR$^{-/-}$, immune complex, PG-PS, TNBS		14, 15, 24, 129, 130
Adhesion molecules			
Anti-ICAM	DSS		131, 132
Anti-a4/Madcam	Cotton-top tamarin, CD45 transfer, IL-2$^{-/-}$		110, 111, 133, 134
Anti-CD44 V7	TNBS		109
Anti-CD11b/CD18	TNBS		135
Antisense DNA			
NF-κB p65	TNBS, IL-10$^{-/-}$, DSS	CD, UC	112
ICAM-1 (ISIS 2302)	DSS	CD	113, 114, 136
Gene transfer			
IL-4	TNBS		118
Other			
Ox40 Ig fusion protein	IL-2$^{-/-}$, TNBS		137
IL-2 Ig fusion protein	TNBS		38
PPR-g ligands	DSS		138
Anti-EN-RAGE/RAGE	IL-10$^{-/-}$, TNBS		139

to play a central role in T_H1-mediated responses to enteric bacteria in CD, and anti-IL-12 treatment ameliorates disease in TNBS colitis, it will be interesting to obtain the results of anti-IL-12 therapy in patients with CD. Antisense phosphorothioate oligonucleotides have been shown to penetrate efficiently into many different cell types and potentially to provide a new specific therapeutic option in IBD.

A novel promising therapeutic approach is the use of specific antisense phosphorothioate oligonucleotides directed against the translation start sites of proteins involved in proinflammatory processes. These small molecules can efficiently penetrate the cell membrane and neutralize the synthesis of target proteins at the translational/transcriptional level. These drugs have been used to downregulate the transcription factor nuclear factor (NF) κB, which is involved in promoter regulation of many proinflammatory cytokines and is critical for inflammatory processes in IBD. It has been shown that local therapy with antisense phosphorothioate oligonucleotides against the p65 subunit of NF-κB reduces levels of proinflammatory cytokines in isolated macrophages of CD patients and is clinically effective in TNBS colitis [112] and DSS colitis (S. Pettersson, personal communication). Antisense strategies against intercellular adhesion molecule 1 have recently been used in a therapeutic trial in patients with CD [113, 114], and an antisense trial against NF-κB p65 is currently in progress (S. Pettersson, unpublished data). Gene therapy could provide another means for specific inhibition or modulation of immune responses in the gut [115].

As the practical use of somatic gene therapy is highly dependent on safe and efficient transfer methods, several different gene delivery systems have been recently developed. Of the various types of viral and nonviral vector systems, recombinant replication defective human adenoviruses of serotype 5 (Ad5) have shown promising results. Many studies have shown that the replication-

defective Ad5 vector has a highly efficient mode of entry into a broad spectrum of eukaryotic cells of many different species and can, unlike retroviruses, infect both dividing and nondividing cells. Recombinant adenoviruses can efficiently transduce intestinal epithelial cells in vitro and in vivo and subepithelial areas in the inflamed colon in mice [116]. A recombinant adenoviruses encoding a mutated, nondegradable IκB has been used to block NF-κB in intestinal epithelial cells in vitro [117]. Another study has demonstrated that an adenovirus containing the cDNA for IL-4 ameliorates TNBS colitis in rats [118], and similar data have recently been presented for IL-10 expressing adenoviruses. Since there is steady progress in the development of new adenoviral and other viral and nonviral gene transfer vehicles, further progress in the field of intestinal gene therapy can be expected in the near future. Targeted therapy either by antisense oligonucleotides, gene therapy, or other specific inhibitors of protein functions, for example, peptides or drugs designed on the basis of their three-dimensional structures has a promising potential and is certainly a possible future direction for the treatment of inflammatory bowel disease.

Conclusion and future directions

Studies with animal models have improved our understanding of the complex field of human IBD and allowed the molecular dissection of pathophysiological mechanisms responsible for development of chronic intestinal inflammation. There is now convincing evidence that both genetic predisposition to sustained inflammatory responses and loss of tolerance to environmental factors are major contributing factors to mucosal inflammation. Most of the models highlight the promotion of an IL-12 dependent mucosal T_H1 response against unknown components of the bacterial microflora as a critical pathological event. The development of novel therapeutic strategies on the basis of such better understanding of the mucosal immune system is an exciting challenge for the future.

It will be important for future approaches to mucosal immunopathogenesis to develop further animal models that more closely mimic human IBD, for example, models with truly chronic relapsing course and acute flares by using inducible transgenic mouse systems. In our opinion, it will also be important to understand more precisely the mechanisms of apoptosis resistance of lamina propria T cells, since many effective new treatment modalities (e.g., anti-TNF, anti-IL-12, anti-IL-6R) appear to exert their effects at least in part by blocking apoptosis resistance with consecutive T cell apoptosis. In addition, it will be important to understand the molecular mechanisms of oral tolerance in the gut and mechanisms responsible for the generation of T_H3 and Tr1 cells that could have therapeutic potential for human IBD. Finally, the development of novel therapeutic approaches (e.g., by recombinant molecules, designer molecules/low molecular weight inhibitors, antibodies, antisense DNA, gene transfer) will be an important field that could be very relevant for the development of novel immunomodulatory strategies to treat patients with IBD with added specificity and fewer side effects than conventional immunosuppressive strategies.

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