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Murine Models of Ulcerative Colitis

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Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology limited to the large intestine. The disease is prevalent in industrial societies and is associated with specific ethnic populations. A number of murine models, each focused on distinct aspects of the disease process, were developed over the past 20 years to further our understanding of the pathogenesis of UC. These models have been and remain our best resource for the study of the disorder as a result of their homology to human UC and the ease in which they can be manipulated and examined. This review examines and distills what has been learned from these models and how this information is related back to human UC.

Key words: Ulcerative colitis, Murine models, Colon, Cancer, Inflammation

INTRODUCTION

Although ulcerative colitis (UC) is still regarded as an idiopathic disorder, considerable progress has been made within the last decade in forming a conceptual framework for this disease and the specific laboratory methodologies that elucidate it. This review will examine a panel of murine models that probe the role of the inflammatory response and factors that favor the deregulation that results in the clinical and pathologic disorder. UC is a disorder that is more prevalent in industrialized societies, those located in northern latitudes, and with higher prevalence within specific ethnic populations (Hiatt and Kaufman, 1988). Although there is less compelling evidence from twin pair and other family pedigree studies for predictable inheritance patterns, as compared to Crohns disease, many studies point to the interplay between genes and the environment. Whatever mix of disordered genes or gene products that will ultimately be identified, local factors, i.e., commensal bacterial or food antigens, appear to induce, in concert, an overly amplified inflammatory response. Recently, several studies have confirmed, though not explained, that smoking and prior appendectomy are protective factors reducing the risk of acquiring the disease. UC is predominantly an inflammation limited to the intestinal mucosa. In rare clinical cases, the inflammation can extend into the deeper layers of the bowel wall, increasing the risks of systemic bacterial infection and colonic perforation. In the typical clinical case, however, the more superficial inflammation is characterized by an increase in bloody bowel motions, a strong sense of fecal urgency, and mild to moderate abdominal pain. The disease almost always involves the rectum and may extend, concentric in each location, to more proximal segments of the colon and even into the ileum in cases of backwash ileitis (Fig. 1). In general, the more extensive the involvement, the more severe the intestinal and constitu-

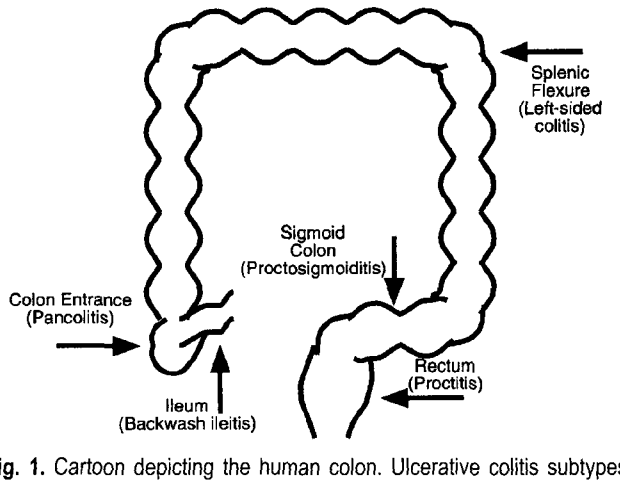

Fig. 1. Cartoon depicting the human colon. Ulcerative colitis subtypes are identified within each identified landmark.

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tional symptoms including anemia, weight loss and growth retardation, as well as alterations in bone density.

The onset of the disease is more common in younger age groups, although it may appear in middle or advanced age (Stowe *et al.*, 1990). As with many chronic intestinal inflammations, chronicity increases the risks for gene mutations and the development of dysplasia. The carcinomas that arise from a background of UC are clinically more aggressive than sporadic cancers and may not be associated with the same altered genetic sequence that occurs in non-colitis related colon cancer. Cancer surveillance usually begins after a decade of disease and the accumulative risks can reach 20-30% after 30 years of disease (Gillen *et al.*, 1994). Given the early age of onset for many patients, understanding the inflammatory mechanisms in UC will add greatly to the prospects for reducing life-long cancer risk.

The study of the process of mucosal inflammation and the luminal or cellular factors that modify it has progressed dramatically in recent years. Although the focus has varied widely, e.g., defects in colonic mucous, surface integrity and permeability, activation of intra-epithelial and lamina propria lymphocytes or neutrophils, professional and non-professional antigen recognition, immunoglobulin production, and adhesion molecule activity, it is reasonably clear that a network of responses, abnormalities and failures of repair or homeostasis create a very complex disease process. The use of murine models, each capable of examining an element of the disease pathophysiology, is of great utility in helping to replicate and study individual aspects of the disease process. The mouse models that will be discussed in this review are summarized in Table I.

MULTIPLE DRUG RESISTANCE 1A KNOCKOUT MODEL

Multiple drug resistance 1a (MDR1a) is a P-glycoprotein that is expressed in the intestines of mice and is homologous to human MDR1 (Croop *et al.*, 1989; Thiebaut *et al.*, 1987). P-glycoproteins secrete small molecules into the intestinal lumen and their loss may facilitate systemic uptake of antigens. Defects in this process may be envisioned to recapitulate the uncontrolled uptake of lumenal antigens that likely occurs during breakdown of the intestinal barrier during the initial stages of UC. To test this possibility in an animal model, an *mdr1a*$^{-/-}$ knockout mouse was developed on a C57BL/6 background (Schinkel *et al.*, 1994). Surprisingly, the absence of MDR1a did not produce a distinguishable phenotype on the C57BL/6 background, and there was no evidence of clinical colitis (Schinkel *et al.*, 1994). However, backcross mice on an FVB background developed UC-like symptoms when maintained under SPF conditions (Panwala *et al.*, 1998). Common symptoms included loose stools with mucous and inflammation covering the entire colon (Panwala *et al.*, 1998). Histologically, the *mdr1a*$^{-/-}$ mice developed an inflammatory infiltrate throughout the mucosa, including crypt abscesses (Panwala *et al.*, 1998).

The pathogenesis of UC in the *mdr1a*$^{-/-}$ knockout mice is markedly affected by bacterial co-infections. For example, UC symptoms were accelerated and intensified upon concurrent infection with *Helicobacter bilis*. In contrast, infection with *Helicobacter hepaticus* actually produced an attenuation of the disease severity (Maggio-Price *et al.*, 2002). These disparate responses observed with *Helico-*

Table I. A summary of mouse ulcerative colitis models

Model	Gross Appearance	Histological Appearance	Cancer Development	Important Attributes
mdr1a$^{-/-}$	Inflammation of complete large intestine, loose stools	Inflammation through the mucosa, crypt abscesses	Not observed	Disease state intensified by *Helicobacter bilis* infection
IL-2	Inflammation of complete large intestine, intestinal bleeding	crypt abscesses, loss of crypt architecture	Not observed	IFN-γ production, MHC II and high MAdCAM-1 expression
β_2m^{null}×IL-2^{null}	Similar to IL-2	Similar to IL-2	32%	No anmeic disease, adenocarinomas have APC and p53 mutations
TCRα	Inflammation limited to the rectum or spread over entire colon	crypt abscesses, loss of crypt architecture	Not observed	Disease state intensified by *Helicobacter bilis* infection
MHC II	Similar to TCRα	Similar to TCRα	Not observed	Impaired oral tolerance to dinitrofluorobenzene
$G\alpha_{i2}$	Inflamed descending colon, low body weight	Neutrophilic inflammatory infiltrate, loss of crypt architecture	31%	IFN-γ and IL-1β production, MHC II expression, IgG2a secretion
C3H/HeJBir	Limited to the cecum and right colon, soft stools with blood	Highly neutrophilic which develops into chronic in later satges	Not observed	IFN-γ production, IgG2a response to bacterial antigen

bacter strains in mice raise the intriguing possibility that bacterial stimulus underlies a significant fraction of UC cases and these effects may be highly species-specific. Furthermore, under certain circumstances and depending on the species involved, bacterial colonization may actually serve a protective role to the colonic epithelium. These possibilities clearly warrant further research that may specifically identify causative bacterial species that are relevant to the human disease.

INTERLEUKIN-2 KNOCKOUT MODEL

A mouse model of UC that has been extensively studied is the interleukin-2 (IL-2) knockout. IL-2 is an important component of the immune system and plays an essential role in T cell replication and cytokine production. The loss of this important immune modulator results in an uncontrolled immune response following initial insult to the colonic mucosa. The immune response recurs episodically during the course of the disease. This model was initially developed on a C57BL/6 genetic background (Schrole *et al.*, 1991). Four weeks after birth, 50% of the mice became anemic and were dead within 9 weeks (Sadlack *et al.*, 1993). Those animals that survive develop UC-like symptoms between 6 and 15 weeks, including diarrhea, intestinal bleeding, rectal prolapse, and inflammation of the entire large intestine (Sadlack *et al.*, 1993). Histologically, the colons of the IL-2 knockout mice resemble a UC-like disease, with an abundance of crypt abscesses, loss of crypt architecture, and an inflammatory infiltrate that is consistent with what is found in UC patients with chronic disease (Sadlack *et al.*, 1993). Interestingly, knockout mice raised in a germ free (GF) environment were initially found to be disease-free. Furthermore, mice raised in a specific pathogen free environment (SPF) had no clinical symptoms, although inflammation was observed during weeks 17 to 20 (Sadlack *et al.*, 1993). More recently, it has been found that if IL-2 knockout mice are followed for longer periods of time, the SPF mice develop a lethal form of UC whereas the GF mice develop mild UC (Schultz *et al.*, 1999).

Upon further analysis of the IL-2 knockout mice, it was found that prior to disease onset, T cell receptor (TCR)$\alpha\beta$-positive T cells expressed cytotoxic activity in the colons (Simpson *et al.*, 1995). This finding was unexpected since TCR$\gamma\delta$-positive T cells are most commonly associated with immune function in the colon, but did not exhibit this cytotoxic action in the knockout mice. Other immune-related indices are altered in the IL-2 knockout mice, including high levels of T and B cells within the colonic mucosa (Sadlack *et al.*, 1993). Several recent studies have examined cytokine production by T cells isolated from IL-2 knockout mice using *in vitro* systems. Isolated lamina propria lymphocytes (LPLs) grown in culture with IL-2 supplementation showed a decreased secretion of the anti-inflammatory IL-4, and an increased secretion of IL-10 (Erhardt *et al.*, 1997; Waidmann *et al.*, 2002). Although IL-2 introduced into the media may complicate a direct *in vivo* association, it is possible that IL-12, an IL-2 homologue, may serve a compensatory role and repress the production of IL-4 as well as promote the production of pro-inflammatory cytokines in the knockout mice. In a related study, the mRNA expression level of a panel of cytokines, including IFN-γ, TNF-α, IL-1α, IL-1β, IL-6, and IL-10, was increased in the colons of UC-affected IL-2 knockout mice (Autenrieth *et al.*, 1997; Waidmann *et al.*, 2002). Thus the marked perturbations in the levels of pro-inflammatory cytokines within the colons observed in the IL-2 null mice supports the idea that there is a related cytokine, possibly IL-12, that may substitute for IL-2, and drive the progression of disease.

While disruption of IL-2 expression is clearly associated with alterations in cytokine production, other abnormalities have been observed. For example, major histocompatability complex class II (MHC II), normally absent in the colonic epithelium, was readily observed in IL-2 knockout mice during active inflammation (Sadlack *et al.*, 1993). Aberrant expression of cell surface proteins, such as MHC II, may trigger an immune response towards host cells, thus providing an alternate pathway for the absence of IL-2. In addition, mucosal addressin cell adhesion molecule-1 (MAdCAM-1), a protein involved in lymphocyte homing during immune responses, expression was elevated and MAdCAM-1 dependent colonic invasion by transplanted T cells was enhanced in the absence of IL-2 expression (Waidmann *et al.*, 2002). Thus, it is conceivable that abnormal expression of cell surface proteins that occurs in the absence of IL-2 may stimulate an immune response that is ultimately damaging to the epithelial barrier, an effect that may initiate UC and/or propagate an active disease state.

INTERLEUKIN-2 DOUBLE KNOCKOUT MODELS

To further elaborate a role for T and B cells in UC pathogenesis, the following studies have combined the IL-2 knockout mice with a panel of mouse lines that are absent for genes involved in T and B cell maturation, including recombination activating gene 2 (RAG-2), JH and β_2-microglobulin. RAG-2 is a subunit of a protein recombinase and is found in T and B cells. It is required for T and B cell maturation. The JH gene, which is located within the HLA locus, encodes a region of the heavy chain protein, and is required for B cell maturation. Ma et al. (1995) found that a RAG-2 defect actually reversed the UC phenotype found in IL-2 knockout mice. On the other hand, IL-2×JH compound mutant mice were found to

suffer from UC, but were protected against anemia (Ma *et al.*, 1995). The absence of UC-like disease in the absence of both T cells and B cells (RAG-2-null), but not B cells alone (JH-null), has led to the conclusion that T cells are essential to the pathogenesis of the UC disease (Ma *et al.*, 1995).

β_2m is a component of the MHC I complex and in its absence, MHC I molecules cannot be transported to the surface of cells where they normally activate $CD8^+$ T cells. The β_2m^{null}×IL-2^{null} double knockout mice develop UC-like symptoms reminiscent of IL-2 knockout mice, but do not develop anemia, a significant advantage of this model (Simpson *et al.*, 1995). Importantly, between 6 and 12 months after birth, approximately 32% of β_2m^{null}×IL-2^{null} double knockout mice develop colonic adenocarcinomas (Shah *et al.*, 2001). Further examination of these tumors revealed high rates (up to 100%) of mutation in the APC tumor suppressor gene. In addition, approximately 50% of the tumors had p53 mutations, while more than 80% showed evidence of microsatellite instability (Sohn *et al.*, 2001). The development of adenocarcinomas with associated mutational alterations in key tumor suppressor genes highlights the importance of the in β_2m^{null}×IL-2^{null} double knockout model as an excellent experimental system for studying UC.

T CELL RECEPTOR KNOCKOUT MODELS

The TCR is intimately involved in development and cellular equilibrium of the T cell population. Deletion of proteins that comprise the TCR will ultimately affect T cell function and homeostatic balance, resulting in dysregulation of the immune system (Mombaerts *et al.*, 1991; Mombaerts *et al.*, 1992). To further evaluate the role of T cells in the pathogenesis of UC, Mombaerts *et al.* (1992) generated a knockout model of TCRα on a 129/Svx C57BL/6 genetic background. Anorectal prolapse and diarrhea were commonly observed in the knockout mice, with inflammation confined to the rectum, while in some cases there was spreading over the entire colon (Mombaerts *et al.*, 1993). Histologically, the TCRα knockout model was similar to human UC, with a mixed inflammatory infiltrate, presence of crypt abscesses, and loss of crypt architecture. The disease course was worsened if the knockout mice were co-infected with *H. bilis* (Burich *et al.*, 2001).

TCRα knockout mice provide an important experimental system for evaluating the balance of pro- and anti-inflammatory cytokines as a contributing factor in UC pathogenesis. In general, T cells are closely involved in the production and transcriptional regulation of cytokines. Specifically in this disease model, subpopulations of immune cells have abnormal cytokine production in UC-affected mice. For example, TCRα knockout mice that suffer from UC-like disease (~60%) develop a subpopulation of T cells referred to as $CD4^+$ TCR β^{dim} T cells (Takahashi *et al.*, 1997). $CD4^+$ TCR β^{dim} T cells produce high levels of IL-4 in the absence of IFN-γ, IL-2, IL-6, and IL-10 (Takahashi *et al.*, 1997). On the other hand, mesenteric lymph node (MLN) cells, which are more common in UC-affected TCRα knockout mice, produce higher levels of IL-4 and IFN-γ mRNA compared to their non-affected littermates (Mizoguchi *et al.*, 1996). IL-2 regulation is similarly complicated by the observation that IL-2 mRNA levels are markedly reduced in MLNs from UC-affected mice (Mizoguchi *et al.*, 1996). Thus, alterations in the levels of cytokines associated with UC disease in the TCRα knockout mice highlight the importance of maintaining a physiological balance of pro- and anti-inflammatory signals within the colonic mucosa.

The TCRα knockout mice may also provide insight into the B cell response to recurrent antigen exposure. Total serum IgG levels are elevated during active UC disease, with higher levels of IgG1 and IgG2 compared to the non-affected knockouts and heterozygotes (Mizoguchi *et al.*, 1996; Takahashi *et al.*, 1997). Furthermore, LPLs and MLN cells harvested from the small intestine, are enriched with non-specific IgG, as well as IgG1- and IgG2a-specific secreting cells, in affected mice (Mizoguchi *et al.*, 1996; Takahashi *et al.*, 1997). The increased levels of IgG-secreting cells and serum IgG suggest an active immune response against a previously recognized antigen (s).

MHC CLASS II KNOCKOUT MODEL

MHC II is expressed on all antigen presenting cells (APC), and when bound to peptide, is the ligand for TCR on $CD4^+$ T cells, a crucial step in the activation and propagation of an immune response. The absence of MHC II may provide insight into the role of immune dysfunction in UC. Thus, an MHC class II knockout mouse was produced by Grusby *et al.* (1991). These mice suffered from moderate to severe UC disease (Mombaerts *et al.*, 1993). In addition, MHC II knockout mice lacked the ability to develop oral tolerance to chemical antigen challenge, providing a possible mechanism for the subsequent development of UC-like disease (Desvignes *et al.*, 1996). Further studies have demonstrated low levels of $CD4^+$ T cells in MHC II knockout mice, whereas IgA antibodies produced by B cells are maintained at normal levels, suggesting that the UC phenotype may require both $CD8^+$ T cells and B cells for the development and maintenance of the disease state (Snider, *et al.*, 1999). Thus, the MHC II gene knockout provides an experimental system that underscores the importance of diminishing oral tolerance as a causative mechanism of UC-related disease.

$G\alpha_{i2}$ KNOCKOUT MODEL

$G\alpha_{i2}$ proteins are involved in a variety of cellular signaling mechanisms, most notably activation of the MAP kinase pathway (Gupta *et al.*, 1992). Recently, MAP kinase has been associated with a pro-inflammatory response (Jaffee *et al.*, 2000). Thus the involvement of $G\alpha_{i2}$ proteins within the MAP kinase pathway, and their association with inflammation, underscore the importance of the $G\alpha_{i2}$ knockout model as a promising tool for investigating the role of the immune system during chronic UC. The $G\alpha_{i2}$ knockout model was generated on both a C57BL/6J and 129Sv genetic background (Rudolph *et al.*, 1995a). Heterozygote mutants were crossed to produce wildtype, heterozygote and $G\alpha_{i2}$ knockout mice (Rudolph *et al.*, 1995a). The nullizygous $G\alpha_{i2}$ mice were characterized by a reduced growth rate and lower adult body weight, as well as a reduced lifespan compared to their heterozygote and wildtype littermates (Rudolph *et al.*, 1995a). Mutant mice had loose occult-positive stools, and the descending colons were covered by an inflammation commonly associated with UC (Rudolph *et al.*, 1995a). Histologically, the affected mice resembled human UC, with active inflammation, predominantly comprised of neutrophils that appeared early in the disease process, with an accompanying loss of crypt architecture at later stages (Rudolph et al., 1995a). In addition, 31% (8 of 26) of the $G\alpha_{i2}$ mutant mice displayed evidence of adenocarcinomas that were non-uniformly distributed throughout the colon (Rudolph *et al.*, 1995a).

Further analysis of the $G\alpha_{i2}$ knockout phenotype has provided additional insight into potential mechanisms by which altered cytokine balance underlies this UC-like disease. Prior to disease onset, unaffected $G\alpha_{i2}$ knockout mice have more memory $CD4^+$ cells within the mucosa of the intestine compared to wild-type controls (Ohman *et al.*, 2000). In addition, thymocytes isolated from $G\alpha_{i2}$ knockout mice are enriched with $CD4^+$ and $CD8^+$ cells and produce high concentrations of IFN-γ, TNF, and IL-2, but not L-4, compared to wildtype littermates (Rudolph *et al.*, 1995b). The large intestine of unaffected $G\alpha_{i2}$ knockouts produce more IFN-γ and IL-1β compared to the wildtype animals (Ohman *et al.*, 2000). The production of pro-inflammatory cytokines prior to the onset of clinical disease supports the idea that the immune system may be involved in the earliest stages of the disease process. Furthermore, colons of $G\alpha_{i2}$ knockout mice with active inflammation produced higher levels of IFN-γ, IL-1β, TNF, and IL-6, as well as IL-12 mRNA, compared to wildtype controls and non-affected knockout animals (Hornquist *et al.*, 1997; Ohman *et al.*, 2000).

Serum-derived auto-antibodies are commonly associated with active UC in human patients. In unaffected $G\alpha_{i2}$ knockout mice, serum auto-antibodies are elevated and are accompanied by antibodies to dietary epitopes during active inflammation (Uhlig *et al.*, 2001). In addition, antibody secretion, specifically IgG and IgA, is higher in the large intestine of healthy knockouts compared to wildtype animals (Ohman *et al.*, 2000). Finally, intestinal secretion of IgG2a and colonic expression of MHC II were both elevated in $G\alpha_{i2}$ knockout mice that displayed UC-like disease (Hornquist *et al.*, 1997). These observations further support a lack of oral tolerance and provide evidence for an autoimmune reaction in UC disease.

C3H/HeJBir MODEL

A model of UC was discovered as a result of a natural predisposition in C3H/HeJ mice (Sundberg *et al.*, 1994). The spontaneous nature of this murine model distinguishes it from the preceding models that have been discussed and perhaps provides a novel mechanism for studying the idiopathic nature of UC. Brother-sister mating of C3H/HeJ, which suffer from IBD-like symptoms, produced a mouse subline, C3H/HeJBir, characterized by frequent blood in the stool and occasional peri-anal ulcerations and soft yellow feces beginning at weaning. Symptoms, however, were generally resolved by 10 weeks of age (Sundberg *et al.*, 1994). The disease process is limiting to the cecum and right colon, with chronic inflammation and ulceration most apparent at the peak of disease (Sundberg *et al.*, 1994). Histologically, the disease most closely resembles UC. The inflammation is highly neutrophilic in the acute stage and becomes more varied as the disease enters a chronic phase (Sundberg *et al.*, 1994). A greater frequency of $CD4^+$ T cells was observed in the C3H/HeJBir strain compared to the C3H/HeJ mice. The affected mice secrete IFN-γ and IL-2 (Cong *et al.*, 1998). Examination of the serum of the C3H/HeJBir strain indicates no response to epithelial and food antigens, but a strong IgG2a response to certain bacterial antigens is evident (Brandwein *et al.*, 1997; Cong *et al.*, 1998). The antigens are likely to be proteins and MHC II-restricted, but not a superantigen (Cong *et al.*, 1998). In a subsequent study from the same laboratory, C3H/HeJBir mice failed to develop clinical symptoms of IBD unless dextran sulfate sodium (DSS) was administered in the drinking water (Mahler *et al.*, 1998). These most recent findings raise the possibility that an unidentified pathogen may contribute to pathogenesis of the disorder (Mahler *et al.*, 1998). Other possibilities that must be considered include differences in housing conditions, an impurity or contamination in the original diet, or a genetic polymorphism in the C3H/HeJ inbred line that was lost in subsequent generations (Elson *et al.*, 2000).

CONCLUSION

UC is a disease of unknown etiology with a typically variable and often unpredictable associated pathology. Murine models have provided a powerful research tool for investigating the disease pathogenesis and for evaluating potential therapies for this highly debilitating disease. The wide range of experimental murine systems that have been developed to model UC have each revealed novel mechanisms that may play a role in the disease process. Importantly, these often-disparate models have revealed a common disease pathogenesis. For example, colonic cytokine production in several of the models clearly show that IFN-γ, TNF, IL-1β, IL-6, and IL-12 are increased during the course of the disease, whereas IL-2 and IL-4 are often decreased. This cytokine profile provides strong evidence that the inflammatory response within the large intestine is mediated by T_H1 T cells. T_H1-based immune reactions produce elevated levels of IFNγ, promote B cells to switch to the IgG2a isotype, and assist in the clearance of microbial pathogens from the body. The role of T_H1 cells in eliminating infections strongly implicates their potential role in the UC disease process. In addition, increased levels of IgA and IgG, especially IgG2a in the serum, together with secretions from the large intestine, also indicate a role for recurrent mucosal infection in the development and progression of the disease. Abnormal expression of MHC II and MAdCAM-1, as well as the effect of the *mdr1a* gene deletion in mice, raise the possibility of a generalized inflammatory response underlying UC, an outcome that may result in damage to the intestinal barrier. Experimental support for this latter possibility has been established by Gordon and co-workers (1995) in an elegant experiment in which embryonic stem (ES) cells were transfected with a dominant negative N-cadherin mutant under the control of an intestinal promoter. The genetically engineered ES cells were introduced into a C57BL/6J blastocyst to produce a chimeric intestinal epithelium. A disorder that is similar to Crohns disease, an inflammatory bowel disease that shares several key pathologies with UC, was observed when impaired N-cadherin function resulted in a disruption of the intestinal epithelial barrier (Hermiston and Gordon, 1995).

One may thus envision a model of UC whereby a generalized inflammatory response, initiated by abnormal epithelial cell protein expression, accelerates damage to the intestinal barrier function. This damage, in turn, promotes the development of a specific and recurrent T_H1-mediated inflammatory response to commensal bacteria that are resident within the lumen of the colon (Fig. 2). Such a recurrent T_H1 inflammatory response may, in principal, induce an oxidative stress-dependent damage to DNA, ultimately contributing to the development of colorectal cancer. Additional research efforts that may exploit the wide range of murine models described in this review will undoubtedly enhance our understanding of the pathogenesis of UC disease and possibly provide impetus for the development of new experimental therapies.

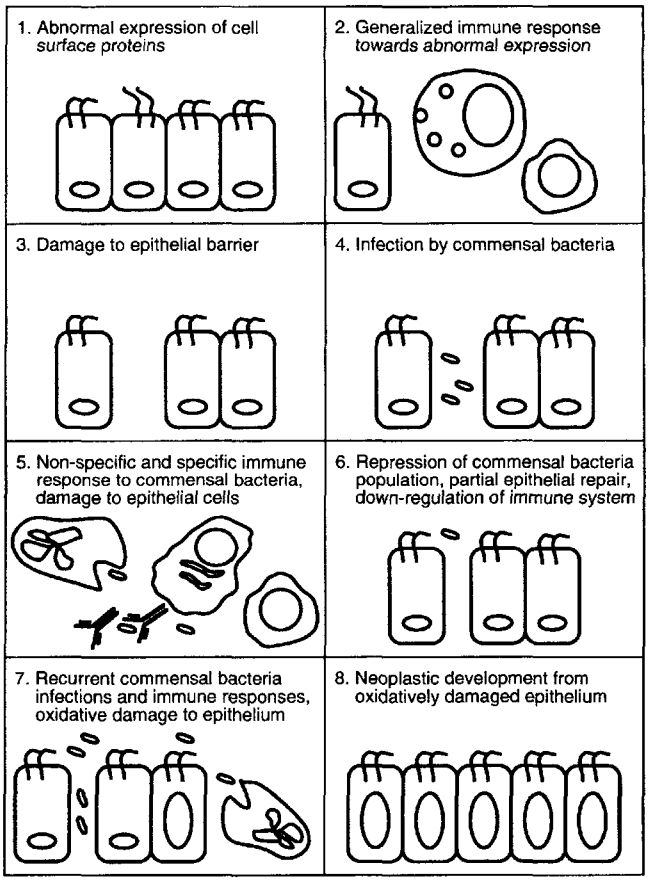

Fig. 2. Model depicting ulcerative colitis development and progression to cancer in the large intestine. 1) Abnormal expression of cell surface proteins occur in the colonic epithelium. 2) A generalized immune response is induced against abnormally expressed proteins. 3) Immune activity leading to epithelial cell death and disruption of the barrier. 4) Opportunistic infection by commensal bacteria with subsequent exposure to the immune system. 5) Specific and non-specific immune response towards commensal bacteria infection. Further epithelial injury due to inadvertent damage to host cells induced by immune cells and their products. 6) Attenuation of commensal bacterial infection followed by initiation of epithelial repair and down regulation of immune response. 7) Cycle of recurrent commensal bacterial infection and immune response. Associated oxidative stress damage in surrounding normal epithelium followed by periods of quiescence and epithelial growth and repair. 8) Neoplastic growth of epithelial cells related to repeated rounds of DNA damage from oxidative stress caused by cycles of immune response.

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