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Review

Animal models of inflammatory bowel disease

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Introduction

The gastrointestinal tract functions not only as a place for nutrient uptake but also as a barrier to pathogens. A direct consequence of this physiological function is a very complex network of immunological interactions, leading to a tightly controlled mucosal immune balance. Foreign antigens, such as dietary antigens and enteric bacteria, are subject to immunological tolerance, so that these antigens never lead to excess immune reactions. Dysfunction of such immunological tolerance mechanisms is presumed to be a cause of ulcerative colitis (UC) and Crohn's disease (CD) (Figs. 1 and 2), but the pathologic mechanisms of these diseases remain unclear.[1] The lack of appropriate experimental models of intestinal inflammation has been one of the reasons for the lack of understanding of these mechanisms. However, 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.[2] Animal models of intestinal inflammation can be divided into four categories: spontaneous colitis models, inducible colitis models in mice with a normal immune system, adoptive transfer models in immunocompromised hosts, and genetically engineered models (knockout [KO] mice and transgenic mice), as shown in Table 1. These models have led to a rapid progression in our understanding of mucosal immunopathology, with nearly 20 novel animal models of intestinal inflammation having been developed since 1993. Most of these models are adoptive transfer models and genetically engineered models of chronic intestinal inflammation, with many of these models resulting from the availability of gene targeting/transgenic technologies in mice, and a better understanding of the pathogenic role of certain cell populations with a pathogenic function. It became clear that, by inducing systemic immune disorders in these models, inflammation would occur in the intestine and this provided new insights into the pathogenic mechanisms and development of new therapies for inflammatory bowel disease (IBD). Some of these models, including those reported recently, are discussed in this review.

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Genetically engineered models

Gene knockout (KO) models

Interleukin-2 (IL-2) KO/IL-2 receptor (R)α KO mice

IL-2 is an indispensable regulatory cytokine of the immune system that has multiple functions, including the activation of T cells, macrophages, lymphokine-activated killer (LAK) cells, and natural killer (NK) cells; the differentiation of B cells; and activation-induced cell death (AICD). In 1993, Sadlack[3] reported that, in mice with a disrupted *IL-2* gene, approximately 50% would die at between 4 and 9 weeks of age with splenomegaly, lymphadenopathy, and autoimmune hemolytic anemia and that chronic colitis would occur in the rest at between 6 and 15 weeks. The small intestine of this model is intact, whereas the colon (from rectum to cecum) is severely affected with ulcers and wall thickening. Pathologically, crypt abscesses, mucin depletion, and dysplasia of the epithelial cells (which are the features of human IBD) were observed. Infiltration of activated T cells and B cells; increases in IgG1, IgE, and anticolon antibodies; and increased expression of MHC class II were also observed. Studies of

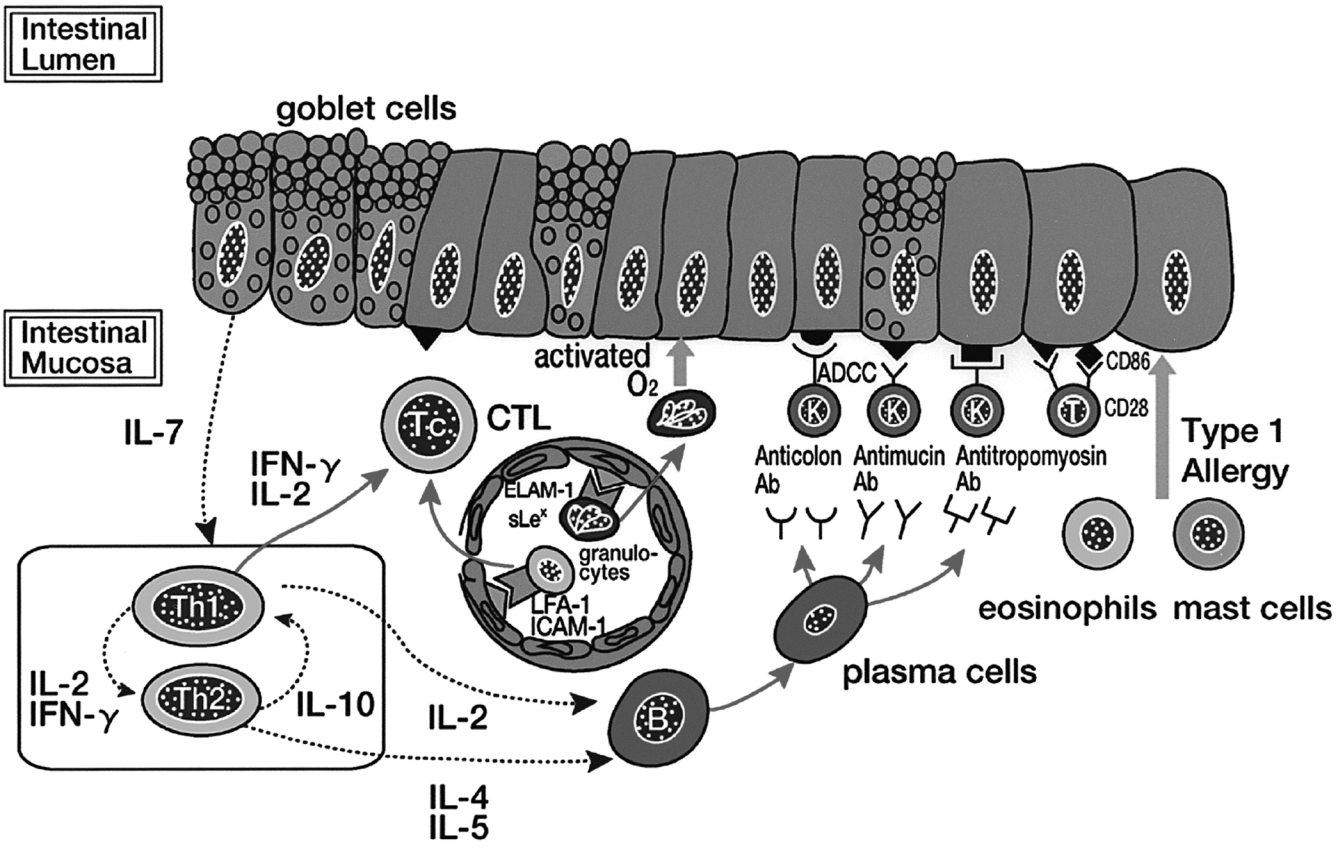

Fig. 1. Pathophysiology of ulcerative colitis

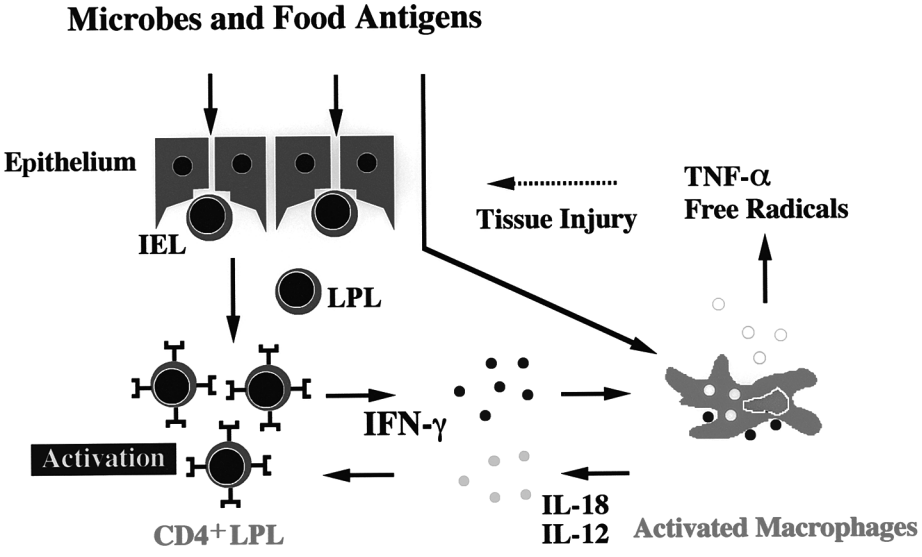

Fig. 2. Pathophysiology of Crohn's disease

double KO mice, that is, mice with the deletion of *IL-2* and other genes such as *RAG-2-/-*, *JH-/-*, and *β2m-/-*, revealed that $CD4^+$ T cells, but not B cells or $CD8^+$ T cells, were essential for the activation of colitis. In this model, elevated IL-12 levels and increased interferon-γ (IFNγ) were reported, and this suggests that the infiltrated CD4+ T cells are part of the T-helper type-1 response.

Colitis in the *IL-2* KO mouse is considered to be due to the lack of AICD and thymic agenesis. Besides

Table 1. Animal models of chronic intestinal inflammation: an overview

Genetically engineered models
Gene knockout mouse models
IL-2 knockout/IL-2 Rα knockout mice
IL-10 knockout mice
STAT3 knockout mice
T-cell receptor mutant mice
TNF-3′ UTR knockout mice
Trefoil factor-deficient mice
Transgenic mouse and rat models
IL-7 transgenic mice
STAT-4 transgenic mice
HLA B27 transgenic rats
Models of spontaneous colitis
C3H/HeJBir mice
SAMP/Yit mice
Inducible colitis models
Trinitrobenzene sulfonic acid-induced colitis
Oxazolone colitis
Dextran sulfate sodium colitis
Carrageenan colitis
Peptidoglycan-polysaccharide colitis
Adoptive transfer models
CD4+/CD45RB^{high} T-cell transfer colitis
Colitis induced by transfer of hsp60-specific CD8 T cells

IL, Interleukin; IL-2R, IL-2 receptor; TNF, tumor necrosis factor; UTR, untranslated region; hsp, heat-shock protein

antigen stimulation by antigen-presenting cells, co-stimulatory signals, such as B7-1/B7-2-CD28, are essential for T-cell activation. Antigen stimulation lacking co-stimulatory signals induces apoptosis of T cells, in other words, AICD. Prolonged inflammation in *IL-2* KO mice is presumed to be due to the impairment of AICD, which means incomplete depletion of activated T cells.[4] The administration of IL-2 within a week of birth would prevent colitis in these mice, and the transfer of bone marrow cells from *IL-2* KO mice into *RAG-2* KO mice induces colitis, but the concurrent transfer of wild-type (WT) bone marrow cells does not. These findings would lead us to the idea that IL-2-dependent T cells are generated in the thymus at an early stage after birth. A deficit of these regulatory T cells induces a T-helper type-1 response in this model. Because colitis occurs in the the germ-rich colon and because it occurs under specific pathogen-free (SPF) conditions, but not under germ-free conditions, the role of intestinal bacteria in its pathogenesis was emphasized. Recently, it has been reported that mild colitis occurs under germ-free conditions, but its pathophysiology still remains unclear, and further investigation is needed. At least, its inflammatory mechanisms are thought to be the dysregulation of induction of tolerance to intestinal antigens, due to the impairment of regulatory immunity. Anti-CD 40L antibody and anti-IL-12 antibody prevent colitis in this model, which is of great interest from the viewpoint of treatment of IBD.

IL-10 KO mice

IL-10 is produced by T cells, B cells, macrophages, thymic cells, and keratinocytes, and it downregulates the function of T helper (h)-1 cells, NK cells, and macrophages. In 1993, Kuhn et al.[5] reported that, in *IL-10-/-* mice, inflammation occurred in the whole intestine. The lesions were mainly observed in the duodenum, proximal jejunum, and ascending colon. Pathological thickening of the intestinal walls, due to hyperplastic change, was observed in the duodenum and jejunum. In the colon, goblet cell depletion, degeneration of the epithelium, infiltration of IgA-producing plasma cells, and an increase in MHC class II expression were detected. As in the *IL-2-/-* mice, the activation of CD4+ Th1 cells and the depletion of the regulatory T cells, their inhibitor, is presumed to be the cause of the inflammation. Recently, it has been demonstrated that distinct inflammatory mechanisms mediated early versus late colitis in this colitis model.[6] Colitis that developed in the *IL-10-/-* mice evolved into two distinct phases: IL-12 played a pivotal role in early colitis, whereas its absence and the synthesis of IL-4 and IL-13 in late disease indicated that other immune mechanisms sustained chronic inflammation.

STAT3 KO mice

Recently, it was reported that, in a model mouse with the specific knockout of *STAT3* (which is in the downstream of the IL-10 signal transmission pathway) in macrophages and neutrophils, colitis occurred similarly to that in *IL-10-/-* mice.[7] However, colitis was not observed in a model with *STAT3-/-* specifically in the T cells. Thus, it is suggested that impairment of the regulation of macrophages, but not of T cells, was of much significance in the *IL-10-/-* mouse.

T-cell receptor (TCR) mutant mice

In 1993 it was reported that colitis occurred in TCR mutant mice.[8] Because colitis was not observed in *RAG-/-* and *TCRδ-/-* mice, and because it disappeared in the *TCRβ* mouse by crossbreeding with C57BL/6 mice, it is presumed that only in the *TCRα-/-* mice is colitis permanent.[9] At 16 weeks after birth, soft stools, consistent inflammation, and hypertrophy of the entire colon (from rectum to cecum) was observed in this model, but the small intestine remained intact. Histopathologically, hyperplasia of the colonic epithelium, decreases in the number of crypt abscesses and goblet cells, and infiltration of lymphocytes, plasma cells, and neutrophils were observed. B cells were polyclonally activated, and a number of autoantibodies were produced as a result of the immunological disorder. Among

these autoantibodies was one to tropomyosin, which has been detected in human UC patients. As colitis was more severe in double-KO mice, which are deficient in both TCRα and B cells (*Igμ-/-*), these autoantibodies are presumed to work against, rather than to promote the inflammation. These autoantibodies have the ability to clear the apoptotic cells that expose autoantigens, and this clearance is considered to heal the autoimmune inflammation.

The TCRs of TCRα-deficient mice express α-β+. Recently, it was reported that the β-chain of T cells from the spleen adhered to the preTCRα isoform, while it formed a TCRββ+ homodimer in the colon. The depletion of preTCRα influences the maturation of peripheral T cells, and impairment of thymic education and an increase in extrathymic differentiation is found in TCRα-deficient mice. While most of the other animal models have T-helper type-1 immune responses (IFNγ, tumor necrosis factor [TNF]α-predominant), this model is suggested to have a T-helper type-2 immune response (IL-4, IL-5-predominant).[10] It has not yet been made clear what induces a T-helper type-1 or type-2 immune response, but the amount of antigen, the binding affinity between TCR and MHC, and the presence of co-stimulatory molecules and cytokines are presumed to be the causes.[11] A decrease in the binding affinity between TCR and MHC, due to the depletion of the α chain, and the secretion of IL-4, a T-helper type-2 cytokine, by TCRα-ββ+ cells, might induce T-helper type-2 colitis in this model. This mouse is regarded as an UC-like model, due to the distribution of the lesions, the pathological findings, and the possibility that it has T-helper type-2 colitis. Recently, it has been reported that anti-IL-4 antibody inhibits the activation of colitis in *TCR-/-* mice, and a therapeutic effect of this antibody in human UC patients is expected.

Tumor necrosis factor (TNF)-3′ untranslated region (UTR) KO mice

Recently, it has been said that TNFα, an inflammatory cytokine, is important in the pathogenesis of CD. Some large-scale controlled studies have proven the efficacy of anti-TNFα antibody (CA2) and it is already used as a therapeutic drug in the United States and Europe. In 1999, a transgenic mouse with overexpression of human TNFα was introduced as an arthritis model, but no colitis was observed in this model.[12] It was reported that colitis would occur by the overexpression of TNFα in a different way.[13] In the 3′-UTR area of TNF, there is an AU-rich element (ARE) consisting of AUUUA repeats. An ARE also exists in the 3′-UTR area of IL-2, c-fos, and granulocyte macrophage-colony-stimulating factor (GM-CSF), and it destabilizes the mRNA of the cytokines in the upstream region. Mice deficient in the ARE of TNFα show high levels of serum TNFα and have arthritis and colitis. Mice deficient in both the TNFR-1 (TNF receptor, p55) and ARE of TNFα will have neither arthritis nor colitis, whereas mice deficient in both the TNFR-2 (p75) and ARE of TNFα will have severe arthritis and mild colitis. Moreover, colitis was totally suppressed, but arthritis was not, in mice deficient in both the RAG-1 and ARE of TNFα. These findings suggest that, in TNF-3′ UTR KO mice, TNFR-2 was inhibitory for arthritis and that lymphocytes were essential for colitis but not for arthritis.

Trefoil factor-deficient mice

Intestinal trefoil factors (ITFs) are peptides secreted by mucus cells of the gastrointestinal tract after inflammatory damage.[14] Mice with targeted disruption of ITF show severely impaired mucosal healing and decreased epithelial regeneration, and they die after the induction of colitis by the addition of dextran sulfate sodium to the drinking water.[15] In acetic acid or trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats, a beneficial role has been reported for ITF in repair processes within the intestinal mucosa. Therefore, these models could be useful in studying wound-healing processes in the gut, and could, potentially, lead to new therapeutic approaches for intestinal injury.

Transgenic mouse and rat models

IL-7 transgenic mice

It has been demonstrated that IL-7 was the substance within the serum of UC patients that influenced the differentiation and proliferation of the T cells in the thymus.[16] Furthermore, the colonic epithelial cells in humans were shown to produce IL-7, which was formerly believed to be made only by thymic stromal cells and bone marrow cells.[17] The epithelial cell-derived IL-7 was shown to be an essential cytokine for the proliferation and the functional regulatory mechanism of epithelial cells, intraepithelial lymphocytes, and intramucosal lymphocytes. This investigation contributed much towards the elucidation of the mechanism of mucosal immunology.

Further investigation of IL-7 transgenic mice (Fig. 3), which overexpress IL-7 mRNA, revealed that acute colitis occurred in them at 1 to 3 weeks of age and that there was infiltration of neutrophils, CD4+ T cells, and γδT cells in the intestine.[17] High levels of IL-7 protein expression were found in the inflamed regions of the intestine in these mice. At 8–12 weeks of age, proctoptosis with anal bleeding occurred, and, pathologically, serial and diffuse infiltration of monocytes, decreases in goblet cells, and increases in crypt ab-

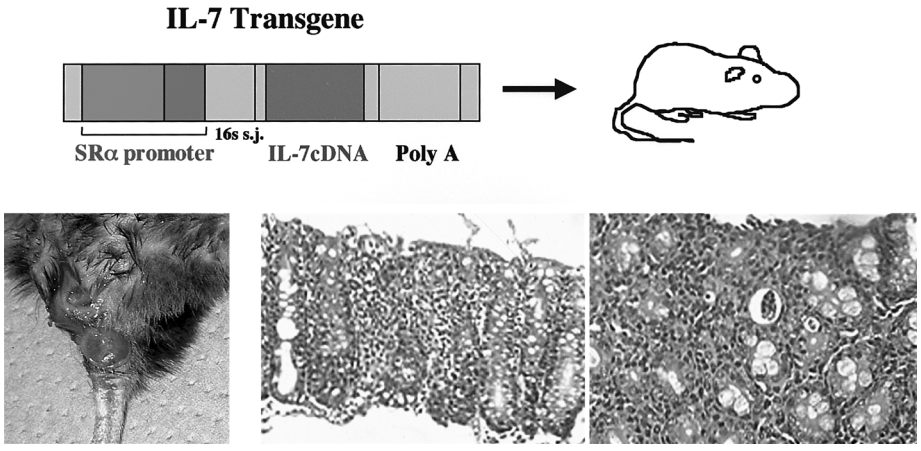

Fig. 3. IL-7 transgenic mice develop chronic colitis

scesses were observed in the lamina propria of the intestine. This was a chronic colitis that closely resembled human UC. In contrast to the acute colitis, IL-7 protein was decreased in this chronic colitis model. This is presumed to be due to the decrease in goblet cells that are rich in IL-7. It is suggested that, in the acute phase, the excessive secretion of IL-7 induces activation of the mucosal lymphocytes, which causes colitis, while, in the chronic phase, apoptosis of the activated lymphocytes, which results from the lack of IL-7, is presumed to be the cause of colitis. This model is regarded as a model of UC, but the increases in IL-2 and IFNγ, and decrease in IL-4 within the mucosal lymphocytes showed a pattern of colitis of type-1 helper T cells.

Signal transducer and activating transcription (STAT)-4 transgenic mice

Recently, STAT molecules, which are essential in the signal transduction of many cytokines, have been discovered, and seven STAT families have been reported so far.[18] Each member of a STAT family works for several cytokines, and this may be a reason for the redundancy of cytokines. STAT-4 is peculiar to the signal transduction of IL-12, and *STAT-4-/-* mice are a representative KO model of T-helper type-1 colitis.[19] STAT-4 transgenic mice with overexpression of STAT-4 were reported as a colitis model.[20] As expected from its mechanism, this mouse exhibits a T-helper type 1-colitis, a transmural inflammation of the intestine, resembling CD.

HLA B27 transgenic rats

Rats transgenic for human HLA-B27 (a molecule involved in human spondyloarthropathies) and β2-microglobulin develop a spontaneous IBD that affects the stomach, ileum, and, of particular note, the entire colon.[21] Crypt hyperplasia and mucosal infiltration of, mostly, mononuclear inflammatory cells characterize the disease. A functional role of activated type-1 helper T-lymphocytes (presumably from aberrant antigen presentation via B27) in the pathogenesis has been suggested.[22] This model has been used extensively to study the effect of resident intestinal bacteria in the 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 potential.[23] In addition, these studies have demonstrated that various bacterial species can induce diverse types of pathology, for example, colitis and gastritis, in these rats.[24]

Models of spontaneous colitis

C3H/HeJBir mice

Perianal ulcers and colitis are occasionally seen in the C3H/Hej strain of mice, and C3H/HejBir is a derivative of selective breeding of C3h/Hej mice with colitis.[25] In this model, colitis, limited to ileocecal lesions and the right side of the colon, occurs spontaneously in the third to fourth week of life and disappears after 10 to 12 weeks. Ulcers, crypt abscesses, and regeneration of epithelium were seen, but thickening of the intestinal wall and granulomas were not observed. Increased levels of IFNγ and IL-2 were observed in the lamina propria lymphocytes, which suggests that colitis in this model is a T-helper type-1 response. This model has also been used in combination with inducible colitis models,[26] and, together with the parent strain, may be valuable for studying and identifying genetic susceptibility factors.

SAMP/Yit mice

SAMP/Yit mice are a substrain obtained by selective breeding of AKR mice with spontaneous colitis.[27] Colitis develops in all of these mice by 30 weeks of age. Inflammation is focal in the terminal ileum, with all-layer lesions, skip lesions, and crypt abscesses. Lamina propria lymphocytes in these mice, when stimulated, will generate higher levels of IFNγ and TNFα than those in AKR mice. This model closely resembles CD. A recent report revealed that antibody blockade of intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 ameliorated inflammation in the SAMP/Yit adoptive transfer model of CD in mice.[28] The blocking of either ICAM-1, VCAM-1, or alpha integrins had no significant beneficial effect. However, the blocking of ICAM-1 and alpha integrins, or the blocking of ICAM-1 and VCAM-1, showed a 70% resolution of the active inflammation, but no resolution of the chronic inflammation. Thus, the blocking of ICAM-1 and VCAM-1 may have a therapeutic benefit for the acute inflammatory component of CD.

Inducible colitis models

Trinitrobenzene sulfonic acid (TNBS)-induced colitis

In 1989, it was reported that colitis would occur by treatment with a TNBS enema after destruction of the mucosal barrier with an ethanol enema. Susceptibility to TNBS varies in each mouse, but some will develop hapten-induced delayed-type hypersensitivity and will proceed to develop chronic colitis. Granulomas with infiltration of inflammatory cells in all layers are seen in the intestine of this model. The isolated macrophages produce large amounts of IL-12, and lymphocytes produce large amounts of IFNγ and IL-2.[29] This evidence suggests that the colitis seen in this model is induced by a T-helper type-1 response, as a major CD model.

In this model, colitis is suppressed when haptens are given orally,[30,31] The CD4+ T cells in the inflamed lesions produce markedly high levels of TGFβ, IL-4, and IL-10, but not IFNγ. Because the administration of anti-transforming growth factor-beta (TGFβ) antibody does not suppress the colitis, the development of colitis is suppressed by the production of TGFβ from regulatory T cells via oral tolerance.[30] Drugs administered by way of an enema will directly reach the intestine and will not go through Peyer's patches, which are important in the induction of oral tolerance. Thus, induction of regulatory T cells does not occur, and colitis is provoked by the locally activated lymphocytes.

Anti IL-12 antibody,[27] anti-CD40 antibody,[32] antisense nuclear factor kappa (NFκ)B,[33] and IL-2R fusion toxin[34] have therapeutic effects on this model as well, and their application to the therapy of IBD is expected in the near future. A single enema of TNBS will result in different levels of colitis in each mouse, so we established a more reliable model by using a hypodermic injection of TNBS, followed by confirmation of sufficient anti-TNBS antibody in blood, in advance of the TNBS enema. We reported that CD4 analogues were effective in this model,[35] and its application to patients with CD is under investigation.

Oxazolone colitis

A number of animal models of colitis have been reported, but all are T-helper type-1 colitis, except for *TCRα-/-* mice. In 1998 it was reported that an enema of oxazolone with ethanol would induce colitis.[36] In comparison with TNBS, this agent causes colitis earlier. The peak of body weight loss and diarrhea is seen on the second day after the enema, and symptoms diminish after 10–12 days. Colitis, accompanied by ulcers, is localized in the distal colon. Histopathological studies show that the numbers of epithelial cells, goblet cells, and glands have decreased compared with controls. In contrast to TNBS colitis, these findings closely resemble those of UC. The stimulated lamina propria lymphocytes produce increased amounts of IL-4 and IL-5, but not IFNγ, which suggests that the colitis in this model is induced by a T-helper type-2 response. The finding that anti-IL-4 antibody ameliorates the colitis and anti-IL-12 antibody worsens it in this model further shows that this is a T-helper type-2 response.

The concentration of TGFβ in this model was higher than that in the control in the inflamed lesions (distal colon), and even higher in the non-inflamed lesions (proximal colon). To the contrary, in patients with UC, it was reported that a higher concentration of TGFβ was found in the inflamed lesions than in the non-inflamed lesions. Because the administration of anti-TGFβ antibody worsened the colitis, it is certain that TGFβ works as an anti-inflammatory cytokine. The differences in its distribution need further investigation.

Dextran sulfate sodium (DSS) colitis

The administration of DSS dissolved in water to mice and rats caused hematochezia, body weight loss, shortening of the intestine, mucosal ulcers, and infiltration of neutrophils.[37] Acute colitis, which occurs during the administration of DSS, and chronic colitis, which occurs a little time after the administration of DSS, are seen in this model. Acute colitis is considered to be induced by innate immunity, but not acquired immunity, because it also occurs in severe combined immunodeficiency (SCID) mice. However, chronic colitis is considered to

be caused by lymphocytes that are activated by the cytokines secreted from the activated macrophages.

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.[38,39] Removal of 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 spp.) is important for the development of mucosal lesions and ulcerations,[40] although the exact pathophysiolgical mechanisms remain unclear.

Peptidoglycan-polysaccharide (PG-PS) colitis

The intramural injection of the bacterial cell-wall component PG-PS into the distal colon of rats induces transmural enterocolitis.[41] In genetically susceptible Lewis rats, chronic granulomatous colitis, with thickening of the colon wall and infiltrating lymphocytes, macrophages, and neutrophils, develops 3–4 weeks after they have been injected with streptococcal PG-PS. PG-PS increases mucosal permeability and myeloperoxdase activity, and enhances NO production and collagen synthesis. Treatment with a recombinant IL-1 receptor antagonist[42] or IL-10[43] attenuates the disease, with IL-10 treatment being particularly effective in the chronic stages of inflammation. Data obtained from this model clearly show that the cell-wall components of nonpathogenic resident enteric bacteria are sufficient to induce acute and chronic colitis in a susceptible host when they penetrate the colon wall.

Adoptive transfer models

CD4+/CD45RB^{high} T-cell transfer colitis

This model was established in 1990 with rats and in 1993 with mice by Powrie et al.[44] Body weight loss and colitis occurred in SCID mice and *RAG-2-/-* mice by the administration of CD4+CD45RB^{high} T cells collected from the spleen and the lymph nodes of wild-type mice. The colitis was accompanied by extreme thickening of the intestinal wall, hyperplasia of the epithelium, and infiltration of lymphocytes into the lamina propria, but no ulcers were observed in the colonic lesions, and the inflammation of the small intestine was mild. However, the administration of CD4+CD45RB^{low} T cells suppressed colitis in this model.

CD45 is a general marker of lymphocytes, and its isotype CD45RB is recognized as a marker to distinguish the naive T cell (CD45RB^{high}) from the memory T cell (CD45RB^{low}).[45] However, as this is not an exact marker of the memory T cell, a more precise marker is awaited. There is an opinion that CD45RB^{high} is involved in the T-helper type-1 response and that CD45RB^{low} is involved in the T-helper type-2 response, because there is evidence that CD4+CD45RB^{high} T cells produce T-helper type-1 cytokines (IFNγ, TNFα, IL-2) dominantly, and the latter cells produce T-helper type-2 cytokine (IL-4).[46,47] According to reports on this model, regulatory T cells are regarded as a member of the CD45RB^{low} family, and, thus, are believed to be involved in the regulation of inflammation.[48–52] It appears that models with transferred CD45RB^{high} T cells alone will have impaired T-cell regulation and colitis.

The administration of anti-IL-12 antibody, anti-IFNγ antibody, or anti-TNFα antibody, respectively, attenuated the colitis in this model.[53] On the other hand, using *IFNγ-/-* mice or *STAT-4-/-* mice as the donors resulted in no colitis.[54,55] These data suggest that colitis in this model is a T-helper type-1 response.

The fact that co-transfer of CD45RB^{low} T cells suppressed colitis in this model is of intense interest. Attenuation of colitis was observed with the administration of IL-10 or with the co-transfer of T cells cultured with IL-10.[50] Using the IL-10 transgenic mice as the donor aroused no colitis,[56] while the co-transfer of CD45RB^{low} T cells of *IL-10-/-* mice did not suppress colitis in this model.[57] The fact that administration of anti-IL-10 antibody or anti-TGFβ antibody, respectively, prevented the suppression of colitis suggests that a network of regulatory T cells, including those producing IL-10 as well as those producing TGFβ, has a great influence on this inflammation.

Colitis induced by transfer of heat shock protein (hsp)60-specific CD8 T cells

Severe (generally lethal) intestinal pathology (predominantly in the small intestine) in this recently introduced mouse model is induced by the adoptive transfer of an hsp60-specific CD8+ T-lymphocyte clone, preactivated by bacterial hsp60, into *TCRβ-/-* or SCID mice.[58] The formation of colitis in these mice requires the presentation of hsp60 on MHC class I and depends on a functional role of TNFα, because adoptively transferred cells do not induce colitis in TCRβ/TNF receptor I/tumor necrosis factor receptor II triple-KO 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 the initial analysis of this model

indicate that autoimmune hsp60 CD8+ T cells that are reactive to cellular hsp60 mediate the pathogenesis.

Conclusion

A steadily increasing number of experimental animal models with some clinical manifestations similar to those observed in human inflammatory bowel disease have recently been developed and have contributed greatly to important advances in our current understanding of the immunological, pathological, and physiolgical features of chronic intestinal inflammation. 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 the induction of mucosal inflammation. Impairment of the regulatory T cells and/or macrophages has been stressed as the mechanism of these models. The concept of regulatory T cells is still in chaos, because multiple components, such as T-helper type-1 responses that mainly lead to the sectction of IL-10; T-helper type-3 responses, that mainly lead to the production of TGFβ; and T cells that regulate the immune system by intercellular actions have been reported. A number of transfer experiments have indicated that T cells, including regulatory T cells, have the ability to suppress colitis, and this finding emphasizes their importance in the immune system. Elucidation of the influence of immune cells, including macrophages, dendritic cells, B cells, cytotoxic T cells, helper T cells, and regulatory T cells on human inflammatory bowel disease, based on the evidence obtained from the animal models, may reveal the pathogenesis of the disease, and result in essential therapy.

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