การเหนี่ยวลำไส้อักเสบในสัตว์ทดลอง

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บทคัดย่อ

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กลุ่มโรคการอักเสบของระบบทางเดินอาหารเป็นโรคที่มีปัจจัยการเกิดโรคที่ซับซ้อนซึ่งเกี่ยวข้องกับระบบทางเดินอาหารทุกส่วน โดยแบ่งเป็น 2 ลักษณะได้แก่ โรคโคโรนกและโรคลำไส้อักเสบแบบมีผลเป็นรูป อย่างไรก็ตามสาเหตุการเกิดโรคเหล่านี้มีไม่แนวขัด ด้วยเหตุนี้สัตว์ทดลองเป็นแบบใช้วิธีการยอมรับว่าเป็นโรคที่มีประโยชน์มากและเป็นเครื่องมือที่ขาดไม่ได้เพื่อที่จะให้มีทางเลือกที่หลากหลายสำหรับการส่งผลต่อและพยาธิวิศวกรรมของโรค ตลอดจนจะต้องทำการออกแบบการศึกษาระบบทองศึกษาเพื่อให้ได้บ้านมาของการวิจัยที่เฉพาะเจาะจง การทบทวนวรรณกรรมเรื่องนี้มีจุดประสงค์เพื่อรวบรวมรูปแบบการเหมือนแนวลำไส้อักเสบในสัตว์ทดลอง โดยแบ่งตามหลักการและสาเหตุของการเหนี่ยวลำไส้อักเสบ ซึ่งสามารถแบ่งได้ 4 ประเภท ได้แก่ รูปแบบการเหมือนแนวลำไส้อักเสบตัวอย่าง ตัวอย่างรูปแบบการเหมือนแนวลำไส้อักเสบตัวอย่าง ตัวอย่างรูปแบบการเหมือนแนวลำไส้อักเสบท่อ และตัวอย่างรูปแบบการเหมือนแนวลำไส้อักเสบโดยการเจาะสูงพื้นฐาน ตัวอย่างรูปแบบการเหมือนแนวลำไส้อักเสบท่อผู้ผลิตการวิจัยข้ามประเทศที่เหมือนกันขยายการพัฒนาการร่วมกันเพื่อให้สอดคล้องกับวัตถุประสงค์ของการศึกษาเพื่อให้ได้ข้อมูลการศึกษาที่สามารถนำไปประยุกต์ใช้จริง

คำสำคัญ : ลำไส้อักเสบ, กลุ่มโรคการอักเสบของระบบทางเดินอาหาร, สัตว์ทดลองตัวแบบ
Induction of Colitis in Experimental Animals : A Review

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Abstract

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Inflammatory bowel disease (IBD) is a complex multifactorial disease that involves all or part of digestive tract consists of two forms; Crohn’s disease (CD) and ulcerative colitis (UC). However, the etiology of the disease remains elusive and unclear. Hence, an experimental animal model becomes to be recognized as a valuable method and indispensable tool to provide a wide range of options for investigating the mechanism and disease pathophysiology and also facilitate the study on preclinical design to target specific components. The objective of this review is to summarize models for induction of colitis in experimental animals. These models are categorized by the principles and causes of colitis induction, in which these are divided into 4 categories, i.e., chemical induced colitis model, bacterial induced colitis model, adoptive cell transferred colitis model, and transgenic or gene-knockout colitis model. Thus, the optimal model is individual consideration depended on the aim of the study to obtain the informative and applicable data.

Keywords: Colitis, Inflammatory bowel disease, Animal model

Introduction

Inflammatory bowel disease (IBD) is an inflammatory disease that involves all or part of digestive tract consists of two forms; Crohn’s disease (CD) and ulcerative colitis (UC). Both involve inflammation of the intestine resulting in epithelial disorders and immune response. Incidence of the disease is increasing steadily in industrial countries while developing countries have a rapidly increasing incidence over the past decades (Kaplan and Ng, 2017; Loftus et al., 2007). Clinical signs consist of abdominal pain or cramping, diarrhea (approximately 4 episodes per day), fatigue, fever, weight loss and anorexia, loss of appetite and nutrients insufficiency. Colitis may be insidious due to the disease progression from mild to more severe. In severe case, blood and mucus in stool, rectal bleeding, fistula, fissures hemorrhoids, and anemia are observed (Head and Jurenka, 2003). However, etiology of the disease remains elusive and unclear with multifactorial factors including environmental factors, i.e., microbial exposure, diet behavior, seasons, non steroidal anti-inflammatory drugs (NSAIDs), and genetic factors (Low et al., 2013).

In the past decades, different animal models of colitis have been developed as valuable methods and indispensable tools to provide wide range of options for investigating the mechanism and disease pathophysiology and also facilitate for studying preclinical therapy design to
target specific components (Kiesler et al., 2015; Low et al., 2013). Therefore, the objective of this review aims to describe various methods to induce colitis in animals, which can be divided into 4 categories including chemical induced colitis model, bacterial induced colitis model, adoptive cell transferred colitis model, and transgenic/ gene knockout colitis model.

**Chemical induced colitis model**

Chemically induced colitis animal model is one of the most commonly used models because it is simple to induce and, the onset, duration, and severity of inflammation are immediate and controllable. This review compiles 4 methods depending on types of exogenous chemical causing agents.

1. **Acetic acid**

Acetic acid was used as a chemical injury agent to mucosal epithelium by intrarectal administration. This induction causes a transient phenotype mimicking ulcerative colitis. Acetic acid was diluted to 10-50% in distilled water. Acetic acid solution (0.5 mL) was instilled into the rectum of Sprague-Dawley rat for 10 sec, then the lumen was flushed by saline (0.5 mL) for three times (MacPherson and Pfeiffer, 1978). In 1991, Yamada and his co-workers employed the same agent with some modifications. The rat was anesthetized and acetic acid was diluted to 4% (pH 2.3). Acetic acid solution (1 mL) was slowly infused into rectal lumen of the rat for 30 sec, and the excess solution was withdrawn. The colon was flushed by phosphate buffer saline (PBS) (Yamada et al., 1991). Subsequent studies were further demonstrated and focused on different concentrations and time exposed of acetic acid. The depth of injury depended on the concentration of acetic acid, volume of the solution, and contact time. Histomorphology of the mucosa after 24 hr of induction showed that the mucosa was extensively destroyed and ulcerated (Figure 1) (Elson et al., 1995). This model initially injured the mucosa with destruction extend to the lamina propria layer, submucosa, and muscle layers. The advantages of acetic acid-induced colitis model are inexpensive and easy to induce. Nevertheless, the induction is lack of chronicity due to the injured epithelium was observed within first 24 hr after the induction. Thus, this model is suggested to be useful for primary evaluating and screening of a new drug.

![Figure 1 Histomorphology of colon at 24 hours by acetic acid solution postenema.](image)

(Elson et al., 1995)

2. **Dextran sulfate sodium (DSS)**

The DSS-induced colitis model was well established and has been used over 2 decades in the study of IBD for investigating pathogenesis and preclinical studies. DSS was dissolved in drinking water and administrated orally to the animals. The dosage of DSS was usually about 1-5% and the duration of induction was in the range of days to months depend on the purpose of the study (acute or chronic). Moreover, cycle-induction was performed in the same studies to mimic relapsing process of the disease (Perše and Cerar, 2012). DSS is a polysaccharide with a highly variable molecular weight (MW), ranging from 5-1400 kDa. Some study indicated the MW of DSS was an essential factor for colitis induction. The high MW of DSS, e.g., 40kDa, exhibited the most severe colitis in BALB/c mice whereas the mice induced with the low MW, e.g., 5 kDa, developed mild colitis. However, the higher MW, e.g., 500 kDa, failed to induce colitis due to preventing the molecule through the mucosal membrane (Kitajima et al., 2000).

Histological changes in the DSS-induced colitis presented in 2 forms consist of acute (early stage) and chronic form (advanced stage). Acute form showed the histological changes in depletion of mucin, epithelial degeneration, and epithelial cell necrosis, leading to disappearance of epithelial cells. The histomorphology of female C57BL/6JOlaHsd colon exposed to 3% DSS (MW 45 kDa) for 5 days followed by drinking water for 7 days showed losing crypt appearance with mucosa and submucosa erosion, and phlegmanous inflammation (Figure 2). Neutrophils migrated to the mucosal epithelium was termed as cryptitis and the numerous neutrophils migrated through mucosal epithelium into crypt lumen was termed as crypt abscess (Perše et al., 2012).
The chronic form of DSS-induced colitis presented in few weeks after DSS administration. Female C57BL/6JOlaHsd mice exposed to 3% DSS (MW 45 kDa) solution for 9 days followed by drinking water for 28 days showed histomorphology of the widening gap between muscularis mucosa and crypt base. Many features in chronic DSS-induced colitis were presented including chronic erosion, transmural inflammation, and lymphoid follicle in subserosa were observed (Perše et al., 2012). To induce the relapsing model, DSS was added into drinking water 3% (w/v) for 5 days and then mice were transferred to drinking water 11 days. The cycle was repeated to mimic relapsing disease in human (Ghia et al., 2007).

This model showed the advantages such as simple to induce, acute and chronic or relapsing model can be produced depend on the DSS concentration. It was applicable for studying of colitis-associated carcinogenesis, and similar to IBD in human. (Kanneganti et al., 2011; Perše and Cerar, 2012; Wirtz et al., 2007). The DSS-induction-factors depended on DSS properties such as MW and duration of induction, including manufacturer and batch of DSS. The host factors, strain, gender, and genetic susceptibility were emphasized for animal responses.

3. Oxazolone

The oxazolone-induced colitis was firstly performed in 1998 by dilution of oxazolone in ethanol and instilled to the mouse rectum (Boirivant et al., 1998). Oxazolone is a haptenating agent that rapidly develops colitis. Oxazolone (4-ethoxymethylene-2-phenyl-2-oxazolin-5-one) 6 mg was diluted in 50% ethanol and subjected to a syringe equipped with 3.5 F catheter. The catheter was inserted to a mouse anus for 4 cm and the oxazolone solution (150 µL) was purged. After that, the mouse was adjusted into a vertical position to ensure distribution of oxazolone to entire colon and cecum (Boirivant et al., 1998). After administration of the enema for 2 days, diarrhea was observed and the symptom was diminished at day 10. Macroscopic changes of colons in the oxazolone-induced colitis in mouse presented a hemorrhagic edematous colon limited to the distal half of the colon after the rectal administration for 2 days (Figure 3B).

Histological studies indicated that the ulcers were localized in the distal colon. Photomicrograph of hematoxylin and eosin (H&E) of oxazolone-treated mouse on the day 2 displayed significant edema and inflammatory cells accumulation localized in the superficial mucosal layer. The presence of superficial hemorrhage, distortion of crypts, loss of goblet cells, mucin depletion, and ulceration were observed. Histological changes showed infiltration of lymphocytes and luminal exudate (Figure 4). This model rapidly developed colitis within a few days after the enema administration but the colitis displayed limitedly only the distal half of the colon. Thus, the oxazolone-induced colitis was suitable for a study with a specific lesion and target.
5. Trinitrobenzene sulfonic acid (TNBS)

Intrarectal administration of trinitrobenzene sulfuric acid (TNBS) induced colitis was susceptible in mouse and rat (Neurath et al., 2000). TNBS as a haptenating agent was dissolved in distilled water to the concentration of 5% (w/v). Then, TNBS solution was mixed with one volume of absolute ethanol. Ethanol plays a role for breaking mucosal barrier, and then allows TNBS to penetrate into epithelium (Elson et al., 1995). A 3.5-F catheter was attached to a 1 mL-syringe and filled with TNBS solution. After the mouse was anesthetized, the catheter was inserted to the mouse colon for 4 cm and slowly instilled 100 µL of TNBS solution into the lumen of colon. The catheter was removed gently and the mouse was hold in head-down-position for 60 sec to prevent the TNBS leakage and ensured that the TNBS solution remained in the lumen (Wirtz et al., 2007). The model of TNBS-induced colitis was applicable in rabbit by injected TNBS directly to ileum, and resulted in ileitis. The optimal concentration of TNBS and ethanol were varied (Scheiffele and Fuss, 2002). TNBS affected the macroscopic changes of colon by shortening and pancolitis with hemorrhage edematous after 7 days of intrarectal administration. The appearance of TNBS-treated mouse colon displayed an inflammation for entire colon (Figure 3C) (Boirivant et al., 1998).

The TNBS-induced colitis model was driven by a Th1-mediated immune response, resulted in CD4⁺ T cells, macrophages, and neutrophils infiltration to the lamina propria. The microscopic changes in colon at 7 days after the enema administration displayed a bowel wall thickening and severe transmural colitis (Figure 5). TNBS-induced colitis model has been widely applied in experimental animals due to closely mimic CD and the model was inexpensive and simple. This model was suitable for the study of immunologic aspects such as a pattern of cytokines secretion and the study on the delayed type of hypersensitivity reaction in the intestinal tract.

Bacterial induced colitis model

Salmonella-induced colitis model

*Salmonella enterica* serovar Typhimurium is a gram negative enterobacteria which is a cause of food-borne disease. *S. enterica* serovar Typhimurium infection in a mouse leads to salmonellosis similarly to human. An increase of *S. enterica* serovar Typhimurium colonies causes strong inflammatory response and results in colitis (Barthel et al., 2003).

*S. enterica* serovar Typhimurium was suspended in cold phosphate buffer saline (PBS) at the concentration of 10⁸ CFU/µL. Adult specific-pathogen-free (SPF) female C57BL/6 mouse was treated with 20 mg/kg streptomycin. After the streptomycin treatment for 16 hr, the mouse was withdrawn food and water for 4 hr, and then fed with the suspension of serovar Typhimurium. The cecum section exhibited inflammation at 2 days after the induction. Edematous changes were presented in submucosa and lamina propria. Moreover, crypt disruption and elongation were observed with decreasing numbers of goblet cells. The epithelial layer was erosion with the infiltration of polymorphonuclear cells in the lamina propria and submucosa. Polymorphonuclear cells additionally transmigrated to the intestinal lumen.
The mouse colon section of Salmonella-induced colitis mice showed inflammation with the presence of polymorphonuclear cells infiltration to the laminar propia and edema. The epithelial erosion and ulceration were noted (Figure 6). Enterocolitis was regularly related with an increase of smooth muscle motility, resulted in folded segmented of intestinal tube forward into an adjacent segment called intussusception. On the other hand, this colitis induction model pretreated with streptomycin did not showed signs of inflammation in ileum.

Figure 6 Sectioned cecum stained with H&E of Salmonella-induced colitis in mouse.

ce, crypt elongation; e, edema; er, erosion of the epithelial layer;
L, intestinal lumen; p, polymorphonuclear cells; lp, lamina propria; sa, submucosa.

(Barthel et al., 2003)

In conclusion, pretreatment of streptomycin was susceptible to induce colitis by S. enterica serovar Typhimurium that was closely similar to inflammatory response in human colitis and animal models for intestinal salmonellosis. Of note, this model usually resulted in systemic infection within 5-7 days. Thus, it was recognized that S. enterica serovar Typhimurium infection was a valuable model to investigate and study an acute phase of colitis (Barthel et al., 2003).

Adoptive cell transfer colitis model

A major step forward in development of murine model of intestinal inflammation came with the discovery of cell transfer that was specific to immune response in colitis. The first report of adoptive transfer induced colitis was published in 1993 by Morrissey and coworkers. Adult female normal C.B-17 and congenic C.B-17 severe combined immunodeficient (SCID) mice which virtually lack of both T and B lymphocytes and accept xenogeneic cells were maintained in SPF condition. The mouse was fed with sterile drinking water and food. To prepare CD4+/CD45RB+ cell, the normal mouse was collected axillary inguinal and mesenteric lymph nodes and treated into a cell suspension. The cells were washed and incubated at 4°C for 30 min in a mixture cultured supernatant from the following hybridomas (anti-Lyt-2.2 and anti-I-Ad). The cells were washed again and the viable cells were purified and moved to stain with anti-CD4 and anti-CD45RB monoclonal antibody. Immunofluorescent analysis was determined on CD4+CD45RBlo and CD4+CD45RBhi cells. After the purification, the cells were washed and resuspended in cold PBS. After the C.B-17 SCID mouse was anesthetized, the cells suspension (2×10^6) was injected intravenously into the retro-orbital sinus carefully.

Histological analysis showed that the transfer of CD4/CD45RBhi cells into the recipient SCID mouse resulted in intestinal epithelium hyperplasia (four or five times). The histological changes were limited in the intestine with colon mainly. These presences mainly due to combination of an increase in intestinal epithelial cells and an accumulation of macrophages and lymphocytes in laminar propia layers (Figure 7).
As the same procedure, the study of Bregenholt and coworkers (2001) indicated apoptosis in colitis by transplantation of purified CD4\(^{+}\) T cells from the immune-competent donors to the recipient SCID mouse. In summary, the transferring of naïve CD4/CD45RB\(^{hi}\) T cells into a recipient SCID mouse could develop colitis within 6-8 weeks.

**Transgenic/gene-knockout colitis model**

The development of transgenic/ gene-knockout models of colitis by traditional genetic breeding programs relied on time consuming by rDNA. The interested gene allowed to introduce into the animal called transgene or to delete the targeted gene from the animal called knockout. The mutant animals developed colitis in various onset and duration.

1. **Interleukin-2-knockout mouse (IL-2 KO mouse)**

Interleukin 2 (IL-2) is a vital cytokines which produced from CD4\(^{+}\) T cells and plays an important role to promote T cells growth and expansion and B cells differentiation. Moreover, it activated macrophages and natural killer cells. The IL-2-knockout (IL-2\(^{-}\)) developed colitis up to 4-8 weeks of age and the disease progression or death was up to 10-25 weeks. Severe anemia, intermittent bleeding, and rectal prolapsed were observed.

Histological analysis was found the colon wall thickening because of epithelial layer hyperplasia. The mucin depletion due to goblet cells loss and crypt abscesses were also observed (Figure 8). There was inflammatory cells infiltration into the laminar propia layer (Sadlack et al., 1993; Schorle and Hunig, 1991).

2. **Interleukin-7 transgenic mouse (IL-7 Tg mouse)**

IL-7 is a candidate risk cytokine which related to ulcerative colitis and an important cytokine for proliferation and functional regulation mechanism of various cells including epithelial cells, intraepithelial cells, lymphocytes, and intramucosal lymphocytes. Intestinal epithelial cells release IL-7, resulted in development of lymphocytes expressing IL-7 receptor (IL-7R). Upregulation of IL-7R on mucosal lymphocytes is associated with colitis progression. Generation of IL-7 transgenic mouse was developed by Uehira et al. (1993). PCR-amplified murine IL-7 complementary DNA (cDNA) was ligated with SR\(\alpha\) promoter and designated as SR\(\alpha\)/IL-7. SR\(\alpha\)/IL-7 transgenic mouse was established by microinjection method into fertilized eggs of a C57BL/6J mouse. After that, the mouse was bred and housed under the SPF condition. Transgenic line was maintained by crossing a transgenic mouse with a C57BL/6J mouse and screening transgene-positive siblings by Southern blot analysis of their tail DNA (Uehira et al., 1993; Watanabe et al., 1998).

The IL-7 transgenic mouse developed acute colitis with infiltration of neutrophils and lymphocytes at 1-3 weeks of age. Histological features showed goblet cell loss and
occasional crypt abscess (Figure 9). IL-7 protein was significantly expressed in the inflamed colonic mucosa of the IL-7 transgenic mouse. At 8-12 weeks of age, the mouse displayed rectal prolapse and remittent intestinal bleeding. Upregulation of IL-7R on mucosal lymphocytes was associated with the disease progression. Thus, an IL-7 Tg mouse model was useful to understand T-cell-mediated pathogenesis of colitis for therapeutic interventions targeting T-cell functions (Watanabe et al., 1998).

![Figure 9 Transgenic mice carrying murine IL-7 cDNA developed acute colitis (Watanabe et al., 1998).](image)

**Conclusion**

Animal models have become standard methods and indispensable tools for the study of a wide array of colitis induction. The models are different in species and strains of animals, causing of induction, form and site of colitis and, duration of disease. The species of animal usually employed include mouse and rats especially inbred mouse stains.

The chemically induced colitis model was divided in 4 methods depended on type of causing agents including acetic acid, dextran sulfate sodium (DSS), oxazolone, and trinitrobenzene sulfonic acid (TNBS). Chemically induced colitis models are the most commonly used method due to ease of development and offer reproducibility. Moreover, these models were symptomatically, morphologically, and histopathologically similar to human colitis. To induce the colitis, the chemical agents are usually instilled in enemas form except DSS which is induced to the animals by oral administration.

Bacterial induction was one of the model to mimic colitis. Pretreatment of streptomycin provided susceptible to induce colitis by *S. enterica* serovar Typhimurium that was closely similar to inflammatory response in human colitis and animal models for intestinal salmonellosis, leading to systemic infection. Thus, the streptomycin-pretreated mouse might offer a versatile alternative model for studying the pathogenesis of gastrointestinal serovar Typhimurium infections.

Discovery of cell transfer that specific to immune response in colitis was achieved by adoptive transfer technique. The specific cells induced colitis in the recipient animals resulted in clinical signs and histopathologic changes mimicked human colitis. This might be of certain benefit in the future treatment of IBD. Due to the recombinant DNA technology, the mutant animals were developed to study colitis. The using of transgenic/knockout mice was one of alternative model to induce colitis. There were various immunological pathways mediated colitis that presented in transgenic/gene-knockout animal models. The most evidence seems to involve different subsets of lymphocytes. Thus, adoptive cell transfer colitis model and transgenic/gene-knockout colitis model are beneficial for the study of specific immuno-inflammatory pathway in colitis.

The summarization of induction methods of colitis in experimental animal models is shown in Table 1. The colitis is occurred by multiple methods and various models are available to study the components associated colitis. To select a suitable model is depended on the specific purpose of the study. This review provides informative consideration for an optimal colitis animal model related to the aim of the study.

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Table 1 Animal models of colitis induction.

<table>
<thead>
<tr>
<th>Models</th>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
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<tbody>
<tr>
<td>Chemically induced colitis</td>
<td></td>
<td>Low cost and easy to perform</td>
<td>Lack of chronicity</td>
<td>Elson et al., 1996; McPherson and Pille, 1979;</td>
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<tr>
<td>Acetic acid</td>
<td>Acetic acid, oxazolone, and TNBS were orally</td>
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<td>Yamada et al., 1991</td>
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<td></td>
<td>administered to the intestinal lumen it termi</td>
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<tr>
<td>Cautioned</td>
<td>Rapidly develop colitis within a few days</td>
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<tr>
<td>Trinitrobenezene sulfonic acid</td>
<td>(TNBS)</td>
<td>Simple and inexpensive</td>
<td>Induction depended on TNBS</td>
<td>Boivert et al., 1998</td>
</tr>
<tr>
<td>Dextran sodium sulphate (DSS)</td>
<td>DSS was mixed in drinking water.</td>
<td>Produced various forms (pseudomembrane formation)</td>
<td>Induction depends on DSS properties</td>
<td>Boivert et al., 1998; Elson et al., 1996; Naush</td>
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<td></td>
<td></td>
<td></td>
<td>(MH, batch, and manufacturers).</td>
<td>th et al., 2000; Wite et al., 2007</td>
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<tr>
<td>Bacterial induced colitis</td>
<td></td>
<td>Both innate and adaptive immune responses can be</td>
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<td>S. enteritidis serovar Typhimurium</td>
<td>The animals was pretreated with azathioprine</td>
<td>Investigated pathogenicity and</td>
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<td>administered the bacterial suspension.</td>
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<td>Adoptive cell transferred induced colitis</td>
<td>Lymphocytes were isolated from inguinal and mesenteric lymph nodes</td>
<td>Can investigate specific immune response</td>
<td>Complexity and take long duration to develop colitis</td>
<td>Moroney et al., 1999; Bregenholt et al., 2001</td>
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<td>CD4+ T cell ipilumine</td>
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<td>Transgenic/gene knockout</td>
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<td>Complexity and take long duration to develop colitis</td>
<td>Sabanayag et al., 1999; Yohn and Huring, 1996</td>
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<td>induced colitis</td>
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<td>Complexity and take long duration to develop colitis</td>
<td>Uetani et al., 1999; Watanabe et al., 1998</td>
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References


