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REVIEW

# Experimental Models of Inflammatory Bowel Diseases

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**SUMMARY**

Experimental models of inflammatory bowel diseases have provided valuable insights into the complex mechanisms operative in the development and pathogenesis of these diseases. This review describes widely used models and how they help us understand the immunology of intestinal inflammation.

**The understanding of the intestinal inflammation occurring in the inflammatory bowel diseases (IBD) has been immeasurably advanced by the development of the now numerous murine models of intestinal inflammation. The usefulness of this research tool in IBD studies has been enabled by our improved knowledge of mucosal immunity and thus our improved ability to interpret the complex responses of mice with various causes of colitis; in addition, it has been powered by the availability of models in which the mice have specific genetic and/or immunologic defects that can be related to the origin of the inflammation. Finally, and more recently, it has been enhanced by our newly acquired ability to define the intestinal microbiome under various conditions and thus to understand how intestinal microorganisms impact on inflammation. In this brief review of murine models of intestinal inflammation, we focus mainly on the most often used models that are, not incidentally, also the models that have yielded major insights into IBD pathogenesis. *(Cell Mol Gastroenterol Hepatol 2015;1:154–170; http://dx.doi.org/10.1016/j.jcmgh.2015.01.006)***

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For more than two decades, animal models of intestinal inflammation have provided a wealth of information about mucosal immunology, particularly as the latter relates to the maintenance of intestinal homeostasis or the disruption of such homeostasis and the intestinal inflammation encountered in the inflammatory bowel diseases (IBD). No single model captures the complexity of human IBD, but each model provides valuable insights into one or another major aspect of disease, and together they have led to the establishment of now a generally accepted set of principles of human IBD pathogenesis. Chief among these are that (1) different causes of induced or genetically based inflammation give rise to a finite number of common pathways of immunopathogenesis; (2) normal resident gut microbiota can drive intestinal inflammation; (3) loss of oral tolerance and disruption of the epithelial barrier contribute to the development of intestinal inflammation; and (4) polarized T helper ($T_H$) cell responses as well as defects in innate immunity mediate disease. In this review, we focus on selected experimental models of intestinal inflammation that amply verify these principles and in doing so provide important contributions to our understanding of the immune dysregulation that characterizes IBD. In addition, we provide a brief summary (Table 1) of less common mouse models that are based on genetic defects that lead to increased susceptibility to gut inflammation.

## DSS Colitis

Disruption of the intestinal epithelial barrier and thereby the entry of luminal bacteria or bacterial antigens into the mucosa has been clearly established as a disease mechanism in enterocolitis by the fact that intestinal inflammation can be more easily induced or may occur spontaneously in numerous murine models characterized by molecular abnormalities that cause massive barrier loss. The importance of an intact epithelium in the prevention of mucosal inflammation was initially demonstrated by Hermiston and Gordon[1] in an influential study published in the 1990s. In this study, a chimeric mouse was created in which small intestinal epithelial cell adhesion mediated by E-cadherin was undermined by the introduction of an epithelial cell transgene expressing dominant negative N-cadherin. The small intestines of these mice contained patches of villi with poorly adherent and incompletely differentiated transgenic enterocytes adjacent to patches of normal enterocytes with normal adherence. The striking finding was that inflammation occurred in the lamina propria of these mice but only in areas subjacent to the defective epithelium, strongly suggesting that entry of commensal microorganisms into an otherwise normal lamina propria can induce an inflammatory response.

***Abbreviations used in this paper:*** **bp, binding-protein; DSS, dextran sulfate sodium; Foxp3, forkhead box P3; IBD, inflammatory bowel disease; IFN-γ, interferon-γ; IL, interleukin; LAP, latency-associated protein; NKT, natural killer T; PSA, polysaccharide A; PTEN, phosphatase and tensin homolog on chromosome 10; TGF-β, transforming growth factor-β; $T_H$, T helper cell; TLR, Toll-like receptor; TNBS, 2,4,6-trinitrobenzene sulfonic acid; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell.**



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**Table 1.** Experimental Models of Inflammatory Bowel Disease Due to Specific Genetic Defects

| Model | Underlying Defect | Major Consequences | Significance |
|---|---|---|---|
| Muc2 | | | |
| Colitis[147,148] | Deficiency of Muc2, the main gastrointestinal mucin. | Spontaneous colitis (severe in the distal colon) that is enhanced by DSS administration and develops into colorectal cancer. Inflammation is associated with increases in intestinal lymphocytes, TNF-$\alpha$, and IL-1$\beta$. | Loss of epithelial barrier function resulting from Muc2 deficiency causes inflammation. |
| Related models[149,150] | Lack of C3GnT ($\beta$1,3-*N*-acetylglucosaminyltransferase), an enzyme involved in the synthesis of core 3-derived *O*-glycans that are components of colonic mucins.[149] | Increased susceptibility to DSS colitis and DSS/AOM-induced tumorigenesis; $T_H1$ and $T_H7$ proinflammatory cytokine production is elevated. | Enhanced intestinal permeability due to deficiency in core 3-derived *O*-glycans and reduced Muc2 levels increases susceptibility to colitis and colorectal cancer. |
| | Targeted deletion of core 1-derived *O*-glycans, also components of mucins.[150] | Spontaneous colitis (severe in the distal colon and rectum) driven by TNF-$\alpha$-producing macrophages and granulocytes rather than lymphocytes. Inflammation is independent of TLR signaling. | Core 1-derived *O*-glycans deficiency leading to a reduced inner mucus layer and decreased Muc2 enhances intestinal permeability to both proteins and bacteria and causes inflammation, that is associated with epithelial cell expression of the Tn antigen, observed in some UC patients. |
| MDR1a colitis[151] | Lack of P-gp, the product of the *MDR1a* gene alters epithelial barrier function. | Spontaneous colitis driven by $T_H1$ cytokines. | A barrier defect arising from P-gp deficiency causes increased intestinal permeability and translocation of bacteria into the lamina propria, and the development of colitis.[152,153] |
| TRUC model[122] | Disruption of the transcriptional regulator T-bet in the innate immune system of *RAG2*$^{-/-}$ mice. | Spontaneous colitis driven by intestinal flora and increased production of TNF-$\alpha$ and IL-23. Cohousing of TRUC mice with wild-type mice demonstrate transmission of colitis to a normal host and thus reveal the existence of a "colitogenic" microflora (such as *Proteus mirabilis* and *Klebsiella pneumonia* or *Helicobacter typhlonius*).[154] | First and only demonstration of the existence of a colitogenic intestinal microflora. However, treatment of TRUC mice with anti-TNF-$\alpha$ therapy prevents inflammation and bacterial populations from becoming "colitogenic," indicating that the development of the latter requires an abnormal mucosal immune system. |
| NEMO | | | |
| Colitis[155] | Intestinal epithelial cell-specific disruption of NF-$\kappa$B function via targeted deletion of NEMO, an essential regulatory subunit of NF-$\kappa$B also known as IKK-$\gamma$. | Spontaneous and severe chronic intestinal inflammation. | Lack of NF-$\kappa$B signaling results in heightened TNF-$\alpha$ sensitivity and apoptosis of colonic epithelial cells followed by inflammation caused by translocation of bacteria into the mucosa. Highlights role of TNF-$\alpha$ in maintenance of epithelial cell barrier function. |
| Related model[156] | Specific deletion of the catalytic subunit of IKK-$\beta$ in intestinal epithelial cells. | Severe intestinal inflammation after infection with the gut-dwelling parasite *Trichuris muris* and reduced expression of TSLP. | IKK-$\beta$ in intestinal epithelial cells promotes $T_H2$-cell dependent immunity and limits chronic inflammation. |