DSS-induced Colitis Screen

Background

Chemically-induced intestinal inflammation in mice has been used to model aspects of human inflammatory bowel disease (IBD), and has provided insights into the mechanisms of disease. This screen is designed to detect mutants with increased susceptibility to colitis induced by the chemical dextran sulfate sodium (DSS).

IBD is a chronically recurring inflammatory disorder of the intestine, with causative contributions from genetic, environmental and immunological factors. The clinical appearance of IBD is heterogeneous, and can include diarrhea, abdominal pain, rectal bleeding, fever, weight loss, and signs of malnutrition (1). Crohn’s disease and ulcerative colitis are the two major forms of IBD. Crohn’s disease can affect any part of the gastrointestinal tract, most frequently the terminal ileum and colon. In contrast, ulcerative colitis exclusively affects the mucosal lining of the colon and rectum. Evidence suggests that IBD results from excessive and sustained inflammatory host immune responses against antigens of commensal intestinal microbes (1). This can occur upon breakdown of the integrity of the intestinal epithelium, which provides a physical and immunological barrier between intestinal mucosa and microbes in the lumen. Defects in the mucosal immune system, at both the cellular and molecular levels, can also facilitate the aberrant inflammatory response.
Observations of familial and ethnic clustering of IBDs, as well as a high rate of disease concordance in monozygotic twins, support a genetic contribution to disease development (1). Sequence variations in several genes, including **NOD2/CARD15**, **DLG5**, **SLC22A4**, **SLC22A5**, **ABCB1/MDR1**, **ATG16L1**, and **IL23R**, have recently been associated with susceptibility to Crohn’s disease (2).

In mice, chemically-induced intestinal inflammation is acute, relatively easy to perform, and highly reproducible, making it a good basis for mutation screening. DSS induces colitis characterized by weight loss, bloody diarrhea, intestinal ulcerations and infiltrations with granulocytes (3;4). DSS is thought to be directly toxic to gut epithelial cells of the basal crypts, resulting in compromise of intestinal epithelial integrity. T and B cells are not required for development of DSS-induced intestinal inflammation, and thus the model is particularly useful for investigating innate immune contributions to colitis (5). A sharp DSS dose-response curve (for weight loss) enables sensitive screening for susceptible or resistant mutants (Figure 1). In this protocol, ENU-mutagenized C57BL/6J G3 mice are fed for several days with 1% DSS (w/v) in the drinking water, a dosage that is insufficient to cause weight loss in wild type C57BL/6J mice.

**Reagents and Solutions**

**DSS-water**

1 % (w/v) Dextran sulfate sodium salt (MW: 36,000-50,000 Da; MP Biomedicals) in autoclaved drinking water. Store at 4°C until use.

**Method**
There are three groups of mice: C57BL/6J mice on regular water, C57BL/6J mice on DSS-water, and G3 mice on DSS-water.

1. On day 1, weigh each mouse two times.
2. After initial weight measurement, replace the drinking water in appropriate mouse cages with DSS-water. Estimate 10 ml of DSS-water per mouse per day. Control mice receive the same water without DSS.
3. Weigh all mice on each subsequent day at the same time of day for a total of seven days. Refresh DSS-water every 7 days.
4. Calculate the percentage of initial body weight for each day of the experiment based on the weight measured on day 1 (Figure 2).

**Critical Parameters and Troubleshooting**

Mice should be at least 7 weeks of age in this screen. Younger mice are generally still growing and gaining weight, which can mask the colitis-induced weight loss.

Mutants which exhibit severe weight loss relatively early (by 4-5 days after DSS-water is initiated), can at that point be returned to regular water. This may rescue these mice from death and allow them to be bred, which helps to more rapidly generate a homozygous stock. Progeny can then be retested to confirm transmissibility.

Siblings of susceptible mutants that die can be retested using a lower dose of DSS (0.5%) to confirm susceptibility but avoid mortality.

**Alleles Identified**
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References