Citrobacter rodentium Infection of DBA/2 Mice as a Model to Elucidate Risk Factors for Severe Colonic Inflammation

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Background: Oral gavage with Citrobacter rodentium is a long-standing model for intestinal inflammatory disorders such as ulcerative colitis. Some inbred mice (e.g., C57BL/6 (B6)) resolve the infection whereas others (e.g., C3H) succumb. One locus has been linked to fatal outcome in C3H mice, but is not implicated in pathogen burden or colonic inflammation. Most host susceptibility factors have been validated in B6 mice, but colonic inflammation is limited in this strain. Identification of host susceptibility factors would benefit from the use of a strain that survives C. rodentium infection but displays frank pathology. Four decades ago, Barthold et al. reported that crypt elongation in DBA/2 (D2) mice is as intense as in C3H mice, but that survival is much greater in the former. To date, no study has uncovered or validated host susceptibility factors in the D2 strain. Given that phenotypic differences between D2 and B6 mice are easily amenable to forward genetic analysis, we characterized C. rodentium infection in these two strains.

Methods: Two- to three-month-old mice were gavaged with 5-6 x 10⁸ CFUs. Fecal bacterial shedding was monitored at 2-3 day intervals, and the integral over time derived. On day 21, colons were fixed and stained in H&E. Edema, epithelial cell hyperplasia and neutrophil infiltration were scored in a blind and semi-quantitative fashion.

Results: Fecal bacterial shedding, epithelial cell hyperplasia and neutrophil infiltration were greater in D2 than in B6 mice. Edema did not differ between these strains. In B6 mice that carried a congenic D2 interval from mid-chromosome 9, fecal bacterial shedding was as low as in B6 mice, epithelial cell hyperplasia was as high as in D2 mice, and neutrophil infiltration was intermediate.

Conclusions: Pathogen burden, epithelial cell hyperplasia and neutrophil infiltration are genetically determined. For the latter two phenotypes, one or several determinants reside on mid-chromosome 9 and will be pursued by positional cloning.