Germ and gene tag team

Several common genetic polymorphisms have been associated with Crohn's disease, an inflammatory bowel disease (IBD) that typically affects the colon and distal small intestine; however, only a small minority of individuals that carry risk alleles develop overt disease. This suggests that additional environmental factors trigger disease in these individuals, but the aetiology of Crohn's disease has remained unclear and is a controversial topic. Now, Virgin and colleagues show that infection with an enteric virus promotes intestinal pathology in mice carrying a mutation in a Crohn's disease susceptibility gene, suggesting that an infectious agent can serve as a trigger for this disease.

The autophagy gene *ATG16L1* is a Crohn's disease susceptibility gene, and the disease variant is found in approximately half of all individuals of European descent. In both humans and mice with disrupted forms of *ATG16L1*, intestinal crypt Paneth cells show defective packaging and secretion of antimicrobial granules and contain more transcripts for pro-inflammatory cytokines. To address whether an infectious agent might promote these Paneth cell defects, mice with a disrupted form of *Atg16l1* (*Atg16l1^{HM}* mice) were maintained in a high-level barrier animal facility. *Atg16l1^{HM}* mice housed under

the more stringent barrier conditions did not show any Paneth cell defects; however, following infection with a strain of murine norovirus (MNV), Paneth cell abnormalities were observed in *Atg16l1^{HM}* mice but not in infected wild-type controls.

Comparing gene expression patterns between wild-type and *Atg16l1^{HM}* mice, the authors found that many genes with roles in protein packaging and localization were differentially expressed in the two mouse strains as a result of MNV infection. Furthermore, they showed that only persistent viral infection promoted Paneth cell abnormalities, as *Atg16l1^{HM}* mice infected with a strain of MNV that is cleared by immunocompetent mice had normal Paneth cell function.

The authors then explored how the intestinal changes induced by the virus-susceptibility gene interaction affected the development of dextran sulphate sodium (DSS)-induced colitis. In response to treatment with a low dose of DSS, uninfected wild-type and *Atg16l1^{HM}* mice developed mild intestinal inflammation, characterized by superficial ulceration in the colon. DSS induced similar ulceration in MNV-infected wild-type mice. However, in MNV-infected *Atg16l1^{HM}* mice, DSS treatment resulted in an exaggerated intestinal inflammation that had many features consistent with human Crohn's disease,

including small intestinal pathology and villus blunting in the ileum.

Finally, the authors attempted to identify the mediators induced by the virus-susceptibility gene interaction that were responsible for the exaggerated DSS-induced inflammation. Interestingly, they found that antibody-mediated blockade of tumour necrosis factor (TNF) and interferon- γ (IFN γ) or administration of antibiotics could prevent the development of the extreme DSS-induced pathologies seen in *Atg16l1^{HM}* mice, but these treatments had no effect on the superficial ulcers that developed in all of the DSS-treated groups. These findings are notable as these inflammatory cytokines and the commensal flora are associated with Crohn's disease pathogenesis and are common therapeutic targets in patients with this disease.

These data indicate that viral infection in individuals with a single risk allele can markedly alter the inflammatory response triggered by a subsequent environmental 'hit'. The authors speculate that infectious agents might also promote disease in individuals carrying other Crohn's disease susceptibility alleles, and suggest that genome-wide association studies should consider an individual's history of infection when attempting to identify and assess the contribution of disease risk alleles.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Cadwell, K. et al. Virus-plus-susceptibility gene interaction determines Crohn's disease gene *Atg16L1* phenotypes in intestine. *Cell* **141**, 1135–1145 (2010)