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Ulcerative colitis-associated Escherichia coli colonize the intestinal mucosa of susceptible host and promote colitis via haemolysin production

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Background: Ulcerative colitis (UC) is a chronic inflammatory condition of the gastrointestinal tract that has been linked to intestinal microbial dysbiosis. Recent studies have identified *E. coli* of phylogroup B2, (such as strain p19A) harbouring extra-intestinal pathogenic *E. coli* virulence factors including *alpha-hemolysin genes* (*hly*), as linked to intestinal inflammation among UC patients. However, its role in intestinal immunopathology is unclear because of the lack of a suitable animal model. Here we establish a mouse model of chronic intestinal infection by the UC derived *E. coli* pathobiont p19A.

Material/methods: Mice lacking single immunoglobulin and toll-interleukin one receptor (TIR) domain ((SIGIRR) (Sigirr $^{-/-}$)) were chosen, because they exhibit a heightened intestinal inflammatory tone, and show increased susceptibility to enteric bacterial pathogens. Fourteen Sigirr$^{-/-}$ mice six to ten weeks old were pre-treated with vancomycin ((5 mg in 100 µl PBS)/mouse) for 6 hours before infection with

bacteria. Next day, 3 % DSS was added into drinking water for 4 days to induce colitis. UC associated *E. coli* p19A WT expressing luminescence (lux) on chromosome, alpha-hemolysin knock out (Δ*hlyI, II*) p19A mutant and non-pathogenic lab *E. coli* DH10B were cultured in LB broth at 37°C, 200 rpm overnight, followed by 1:100 subculture until OD_{600} reaches to 2.5 x 10^8. 100 µl of subculture was used for oral gavage into mice. Mice were monitored every day and euthanized on 5^{th} day post-infection. Colonization with p19A WT was visualized by in-vivo imaging system (before and after washing the luminal contents).

Results: First day post infection with UC-associated *E. coli* p19A WT, mice shows signs of illness, with modest levels of weight loss and displaying a hunched appearance. Luciferase imaging and fecal shedding data (10^8-10^9 CFU/gram stool) shows that vancomycin pretreatment led to persistent p19A WT colonization of the cecal,colonic lumen and intestinal mucosal surface of the Sigirr $^{-/-}$mouse. While p19A WT infection caused only minimal pathology on its own, it dramatically worsened the course of DSS colitis, in concert with deep penetration of the damaged colonic mucosa. Notably, intestinal tissue histology shows that p19A mutant (Δ*hlyI, II*) was severely attenuated in its ability to promote DSS colitis in *Sigirr* $^{-/-}$ mice.

Conclusions: Our findings provide evidence that UC associated phylogroup B2 *E. coli* strains p19A WT can readily and persistently colonize the intestines of susceptible hosts, and significantly worsen the course of colitis. The intestinal tissue damages in DSS colitis *Sigirr* $^{-/-}$ mice colonized with p19A mutant (Δ*hlyI, II*) were severely attenuated, which indicates that p19A *E. coli* harbouring two alpha-hemolysin gene, might be responsible for barrier dysfunction and intestinal tissue damages in susceptible hosts. This model thus facilitates research into the role played by UC associated *E. coli* pathobionts in colitis pathogenesis.