Increased susceptibility to oral Trichuris muris infection in the specific absence of CXCR5-expressing dendritic cells

Increased susceptibility to oral *Trichuris muris* infection in the specific absence of CXCR5-expressing dendritic cells

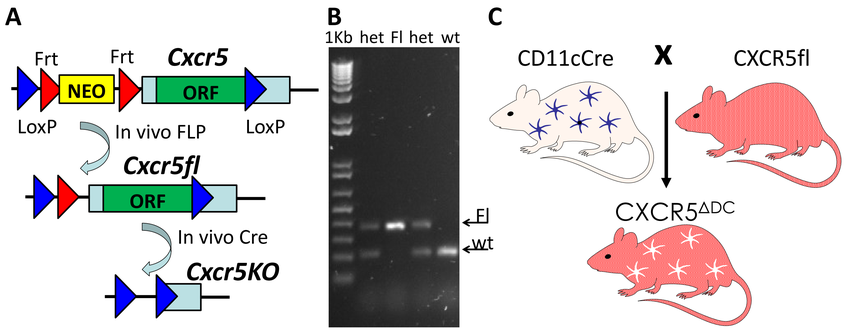
Barry Bradford[1], David Donaldson[1], Ruth Forman[2], Kathryn Else[2] & Neil Mabbott[1]

1.The Roslin Institute and R(D)SVS the University of Edinburgh, UK
2. Faculty of Biology, Medicine and Health, University of Manchester, UK

Introduction

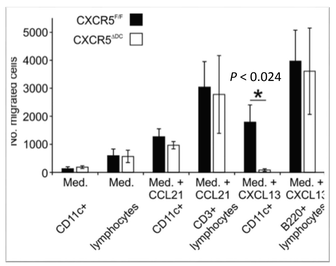
Trichuris muris is a natural mouse helminth pathogen which establishes infection specifically in the caecum. The rapid expulsion of *T. muris* before the adult worms reach fecundity in resistant mouse strains is associated with the induction of a protective T helper cell type 2 (Th2)-polarised immune response. In contrast, susceptible mice mount an inappropriate Th1 response to *T. muris* which results in persistent infection. Expression of the chemokine CXCL13 by stromal follicular dendritic cells mediates the attraction of CXCR5-expressing cells towards and into the B cell follicles. Previous studies have suggested that CXCR5-expressing conventional dendritic cells (cDC) help regulate the induction of Th2-polarized responses. In this study we generated C57BL/6 CD11c-specific CXCR5 knockout mice (CXCR5$^{\Delta DC}$) and infected them with high dose *T. muris* in order to assess their ability to generate protective Th2 responses.

Generation and characterization of CXCR5$^{\Delta DC}$ mice.



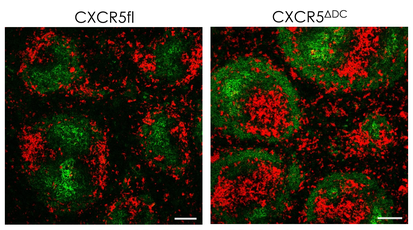
(A) *Cxcr5* gene-targeted construct, showing recombination post FLP or Cre.
(B) Genotyping of CXCR5fl allele via primers specific to the regions surrounding the 5' *LoxP* site.
(C) Generation of CD11c-restricted CXCR5 knockout, CXCR5fl alleles were bred to homozygosity whilst incorporating the CD11cCre transgene. Resultant offspring express possess a CD11c-specific knockout of CXCR5 (CXCR5$^{\Delta DC}$).

Impaired chemotaxis of CD11c+ cells to CXCL13



Ex-vivo chemotaxis assay reveals impaired CD11c+ migration to CXCR5 ligand CXCL13 in CXCR5$^{\Delta DC}$ mice.

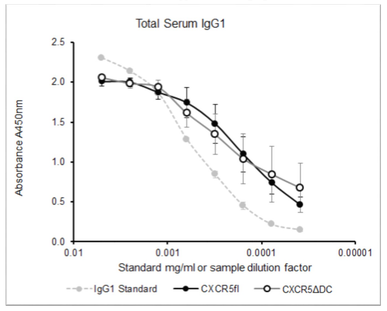
Altered cDC localisation in lymphoid follicles

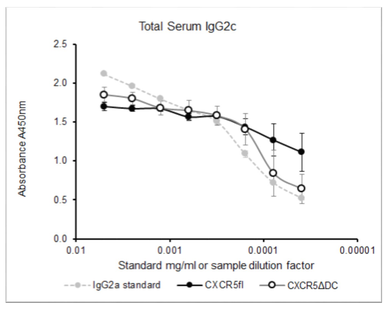


CD21/35 (CR1/2) / CD11c (Itgax)

Immunohistochemical localisation of CD11c+ cells in lymphoid tissues (Spleen shown) reveals altered follicular localisation with retention of CD11c+ cells in T cell areas in CXCR5$^{\Delta DC}$ mice.

Unaltered naïve serum Ig isotypes

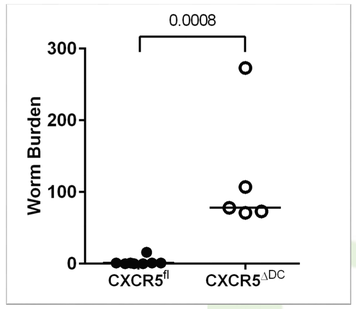




Despite altered CD11c+ cell trafficking in lymphoid tissues of CXCR5$^{\Delta DC}$ mice, no differences in naïve serum antibody isotypes or resting cytokine levels(data not shown) were observed when compared to CXCR5fl mice.

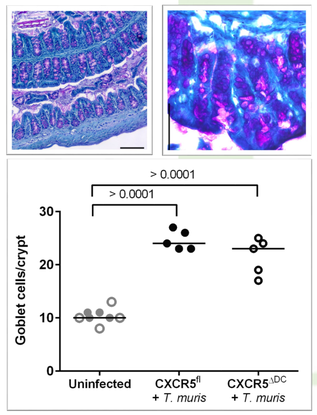
Results

CXCR5$^{\Delta DC}$ mice display increased susceptibility to *T. muris* infection.



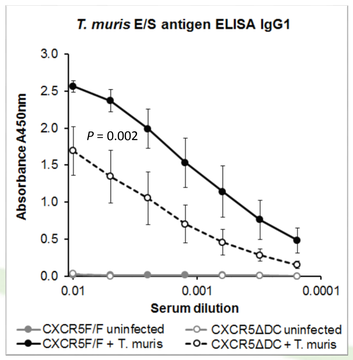
Analysis of worm burden at 30 d.p.i. Unlike CXCR5^{fl} mice, CXCR5$^{\Delta DC}$ mice are unable to clear *T. muris*.

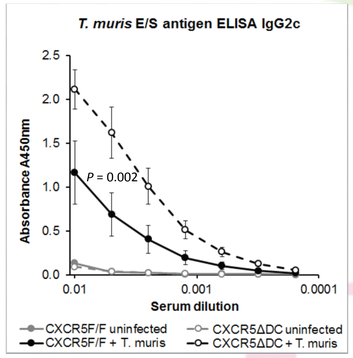
Goblet cell hyperplasia unaltered



Assessment of PAS stained proximal large intestine revealed no deficit in goblet cell hyperplasia following *T. muris* infection of CXCR5^{fl} or CXCR5$^{\Delta DC}$ mice.

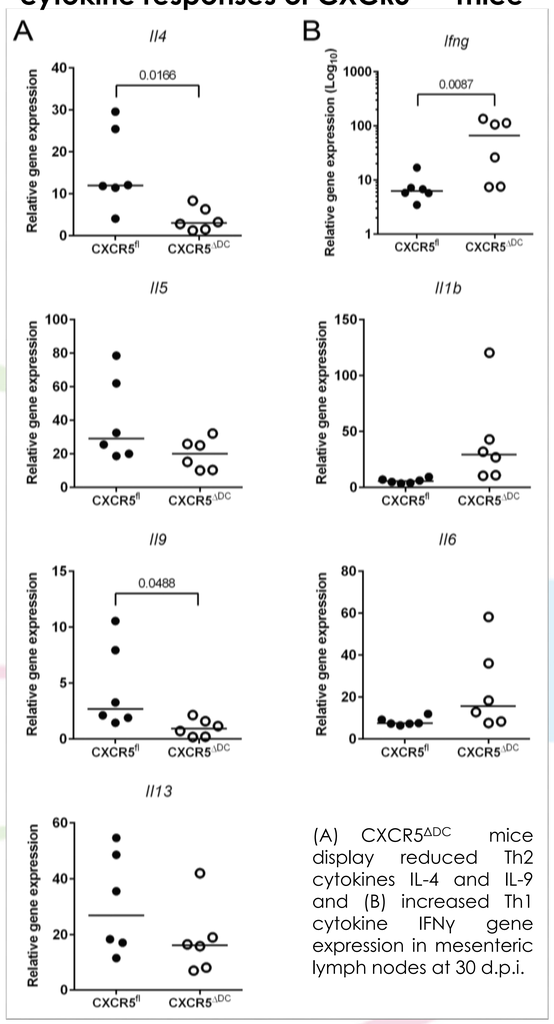
Altered Ig class switching in response to infection





T.muris excretory./secretory [E/S] antigen specific responses measured in serum at 30 d.p.i. reveal CXCR5fl mice produce high levels of protective IgG1 and low IgG2c consistent with the induction of a protective Th2 response. CXCR5$^{\Delta DC}$ mice produce low levels of IgG1 and high levels of IgG2c similar to susceptible mouse strains which develop a Th1 biased response

Altered Th1/TH2 bias observed in MLN cytokine responses of CXCR5$^{\Delta DC}$ mice



(A) CXCR5$^{\Delta DC}$ mice display reduced Th2 cytokines IL-4 and IL-9 and (B) increased Th1 cytokine IFNγ gene expression in mesenteric lymph nodes at 30 d.p.i.

Conclusions

Removal of CXCR5 expression from CD11c+ cells renders C57Bl/6 mice susceptible to high dose *T. muris* infection by suppressing Th2 and enhancing Th1 responses. These data suggest that CXCR5 expression and B cell follicle homing of antigen-presenting cDC is required for the efficient induction of a protective Th2 response to infection with *T. muris*.

Parasite Immunology (2018) DOI/10.1111/pim.12566

Supported by grants BB/F019726/1, BBS/E/D/20231762, BBS/E/D/10002071 and BBS/E/D/20002174 from the Biotechnology and Biological Sciences Research Council (BBSRC).