

Toll like receptor 2 controls neutrophil driven immunopathology by inhibiting CXCL5 production during *Mycobacterium tuberculosis* HN878 infection

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BACKGROUND

W-Beijing strains of *Mycobacterium tuberculosis* (Mtb.) have been associated with multidrug resistance disease and are present globally. Toll like receptor 2 (TLR2) is one of the key innate immune receptors that recognizes various Mtb ligands. Polymorphisms in TLR2 gene have been associated with the increased risk of TB disease in humans.

Previously, we investigated the significance of TLR2 during HN878 (clinical isolate of W.Beijing strain) infection. We reported that TLR2 controls bacterial burden and neutrophil driven inflammation in lungs during HN878 infection. In this study, we tested the hypothesis that TLR2 controls neutrophil infiltration into lungs by inhibiting CXCL5 from epithelial cells during HN878 infection.

MATERIALS AND METHODS

Wild type (WT) and TLR2KO mice were infected with low dose (20-25 CFU) of HN878 via aerosol. At day 10 post infection (pi.), WT and TLR2KO mice were treated intra-peritoneally with either anti-CXCL5 neutralizing antibody or isotype control three times a week starting from day 10 to 24 pi. At day 25 pi., mice were sacrificed and lungs were harvested. EPCAM⁺ epithelial cells, neutrophils CD11b^{high} Ly6G⁺, alveolar macs CD11b⁺CD11c⁺, tissue resident macrophages CD11b⁺CD11c⁻ and dendritic cells CD11b⁺ CD11c⁺ were sorted from lungs of infected mice and CXCL5 gene expression was determined by real time-PCR.

RESULTS

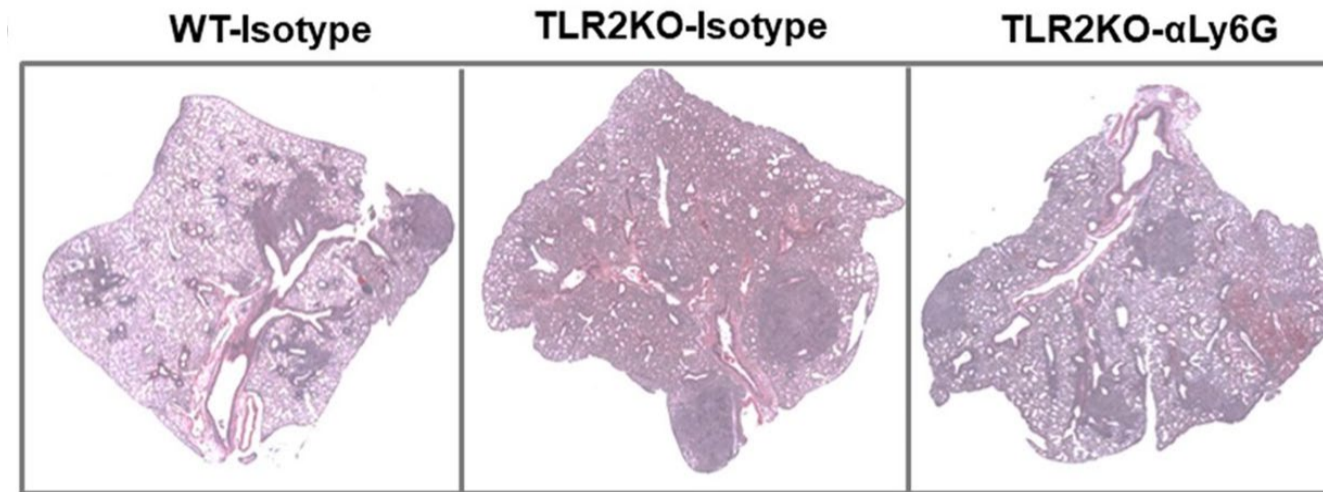
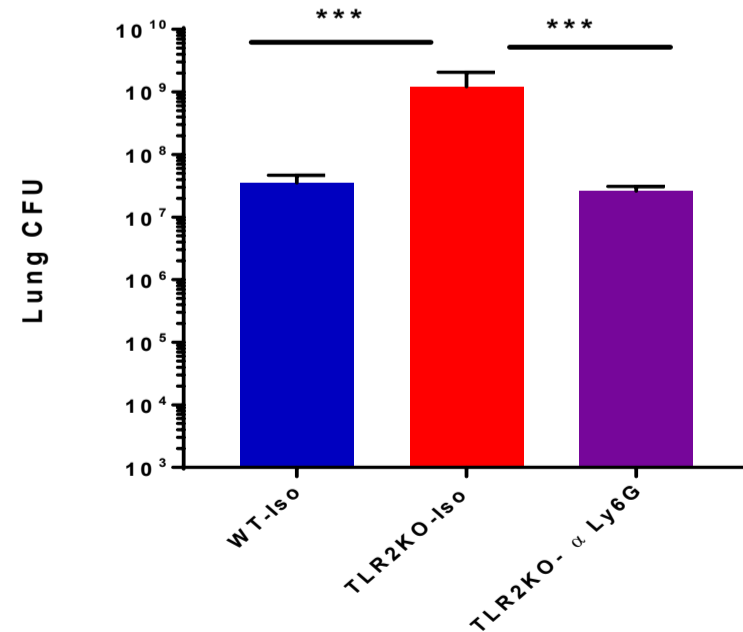


Figure 1: Blocking neutrophil infiltration using anti-Ly6G antibody reduces lung bacterial burden and inflammation in TLR2KO mice to WT level (Gopalakrishnan et al., INI, 2019)

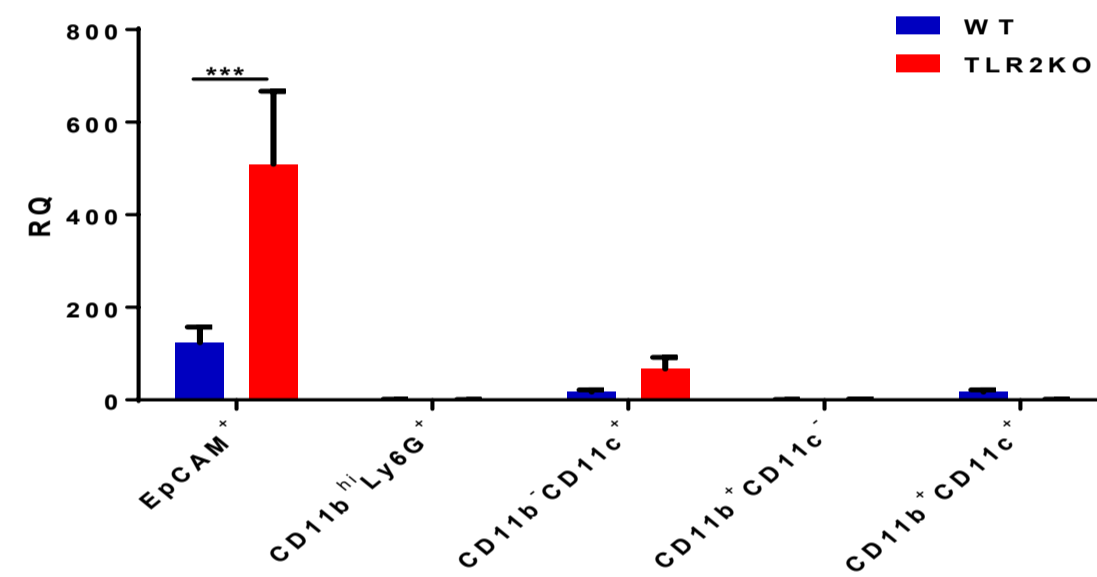


Figure 2: Epithelial cells from TLR2KO mice have significantly higher expression of CXCL5 compared to WT during HN878 Mtb infection.

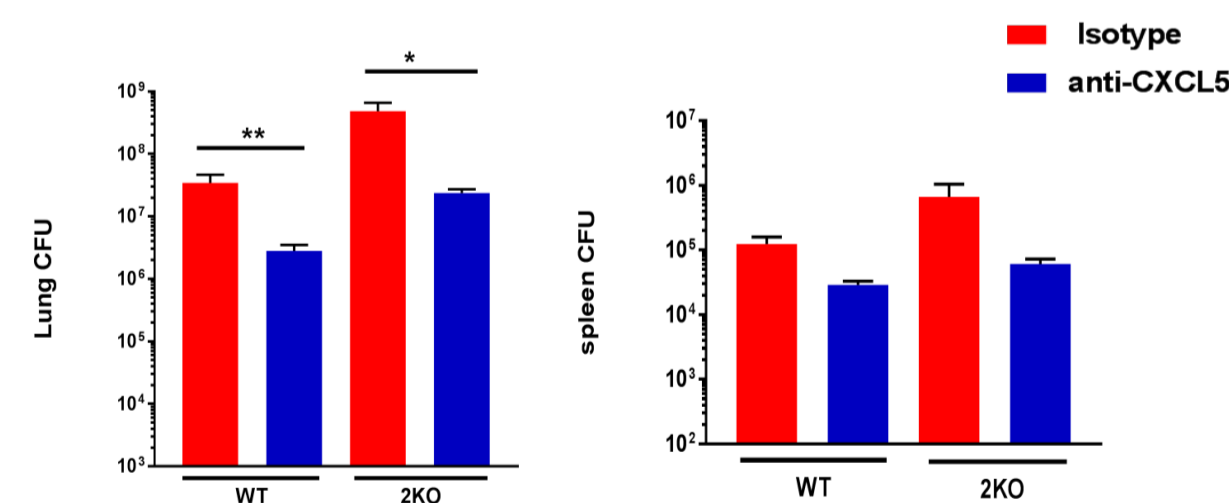


Figure 3: Decrease in lung and spleen bacterial burden in WT and TLR2KO mice treated with anti-CXCL5 antibody

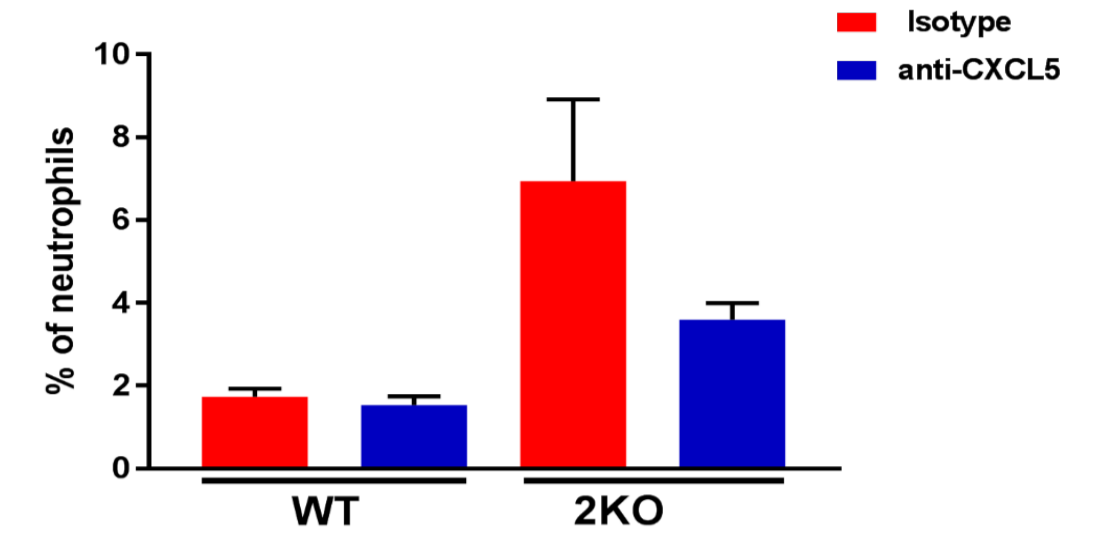
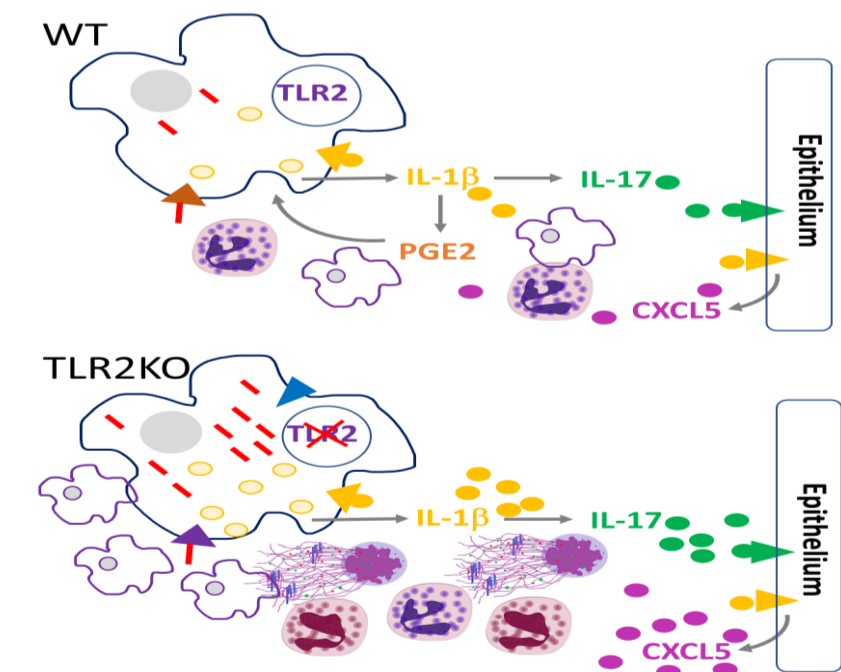


Figure 4: Reduction in percentage of neutrophil recruitment to lungs in WT and TLR2KO mice treated with anti-CXCL5 antibody

CONCLUSION

TLR2 plays an important role in controlling neutrophil driven immunopathology during Mtb infection by inhibiting CXCL5 from epithelial cells.

WORKING MODEL



In ongoing experiments, we are examining whether TLR2 regulates the IL-1β/Type I IFN axis to control CXCL5 production and subsequent neutrophil recruitment.

Contact

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