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ENTERIC PARASITE INFECTION-INDUCED ALTERATION OF THE GUT MICROBIOTA REGULATES INTESTINAL GOBLET CELL BIOLOGY AND MUCIN PRODUCTION VIA TLR2 SIGNALING

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Background: Goblet cells (GCs) are the major source of mucin which are the main components of the mucus layer that represents the front line of innate defense in the gastrointestinal (GI) tract. Hyperplasia of GCs and increased mucin production are observed in many enteric nematode infections such as *Trichuris muris* infection. Increased mucin production contributes to parasite clearance by trapping in mucus and inhibiting motility. The GI tract contains trillions of commensal microbes, and these microbes control mucin production from GCs by activating different signaling cascades. During nematode parasite infection due to the coexistence of parasites and microbiota in close proximity of GCs in gut, it is likely that this nematode-microbiota interaction plays an important role in mucin production. Toll-like receptors (TLRs), components of the innate immune system, sense gut microbiota stimuli. The human GC-like cell line, LS174T, expresses TLR2 mRNA which was enhanced by stimulation with synthetic TLR2 ligands. We hypothesize *T. muris*-induced altered microbiota modulates GC response and mucin production via TLR2 signaling.
Aims: To elucidate the role of *T. muris*-induced altered gut microbiota in the regulation of intestinal GC response and mucin production via host TLR2 signaling.
Methods: C57BL/6 mice were infected by gavage with ~300 *T. muris* eggs and infectivity was confirmed by worm burden. Microbiota was analyzed by 16s rRNA sequencing. Colonic GCs response, mucins and TLR2 expression and cytokines production were assessed in germ-free (GF) mice receiving non-infected and *T. muris*-infected microbiota (collected on day 36 post-infection to exclude worms). Muc2 and Muc5ac expression were assessed in wild-type (WT) and TLR2 deficient ($TLR2^{-/-}$) mice transplanted with *T. muris*-infected microbiota following antibiotic treatment.
Results: We observed a difference in microbial composition between non-infected and *T. muris* infected mice. Transfer of *T. muris*-infected microbiota into GF mice significantly increased GC numbers and TLR2 expression as well as up-regulated Muc2 and Muc5ac expression and IL-4, IL-13 production compared to GF mice with

non-infected microbiota. Antibiotic-treated *TLR2*$^{-/-}$ mice after receiving microbiota from *T. muris*-infected mice showed significantly decreased expression of Muc2 and Muc5ac compared to antibiotic-treated WT mice receiving the same microbiota. **Conclusions:** *T.* muris-induced altered microbiota influences intestinal GC response and mucin production via TLR2. In addition to enhancing our understanding on the interaction of parasite with resident microbiota in host defense, this study provides new information on TLR2 based innate signaling in the regulation of GC biology and mucin production.

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