

**Short-chain fatty acids regulate regulatory T cells and intestinal pathology during oral mucosal infection.**

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Complex interactions between the microbial flora and the host exert sophisticated means of immune tolerance and regulation mechanisms. One mechanism is by inducing the accumulation of regulatory T (Treg) cells. Here we show that the depletion of resident bacteria using antibiotics (Abx) causes oral and gut immunopathology during Oropharyngeal Candidiasis (OPC) infection. Abx treatment causes decrease in the frequency of Foxp3+ regulatory cells (T<sub>regs</sub>) and IL-17A producing T cells, with a concomitant increase in oral tissue pathology. Although oral *C. albicans* (CA) is commonly controlled in the oral cavity, Abx treatment led to CA dependent oral and gut inflammation. The combination of short chain fatty acids (SCFA) partially controlled the pathology in Abx treated mice, correlating to an increase in the frequency of Foxp3+, IL-17A+, and Foxp3+IL-17A+ double positive (T<sub>reg</sub>17) cells in tongue and oral draining lymph nodes. SCFA enabled the restoration of Th17 cells and Treg cells and oral infection clearance but did not reverse weight loss. Because SCFA treatment did not fully reverse the gut inflammation, it is evident that resident microbiota have SCFA independent homeostatic mechanisms in gut mucosa. We also found that SCFA potently induce Foxp3 and IL-17A expression in CD4+ T cells, depending on the cytokine milieu *in vitro*. Taken together, our data reveal that SCFA derived from resident bacteria play a critical role in controlling gut immunopathology by regulating T cell cytokines during oral mucosal infections.