Influence of Gut Microbiota in the *Smad3*$^{-/-}$ Mouse Model of Colitis-associated Colorectal Cancer

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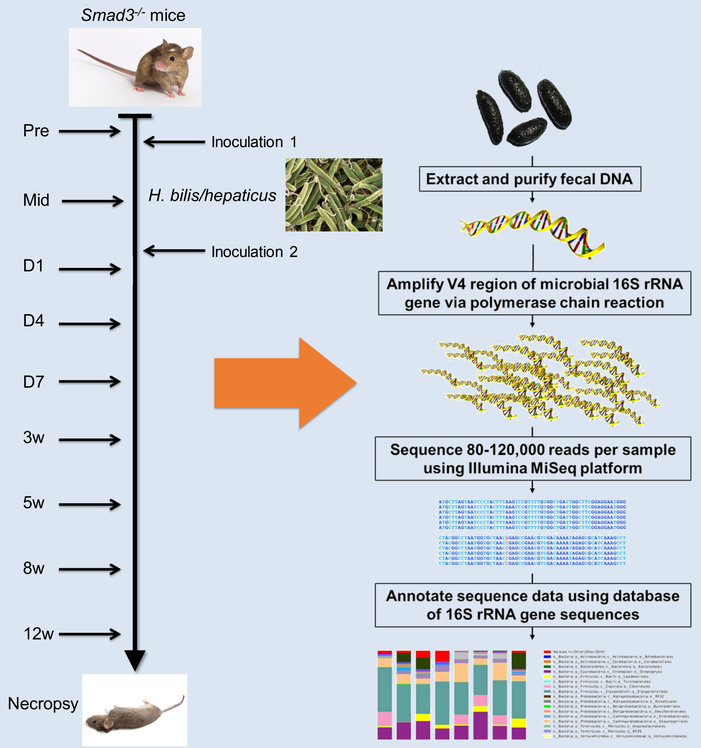
Background

- Colorectal Cancer (CRC) is the second leading cause of cancer-related mortality in the United States.
- *Smad3*$^{-/-}$ mice faithfully model the mechanisms and phenotype of CRC.
- Fecal biomarkers are predictive of CRC very early in the disease model.
- Disease is initiated via inoculation with *Helicobacter* spp., provocateurs of immune responses against commensals.
- We hypothesized that differences in biomarker expression and subsequent CRC development can be explained by differences in the gut microbiota of *Smad3*$^{-/-}$ mice at the time of inoculation with *Helicobacter* spp.

Methods and Experimental Design



Results

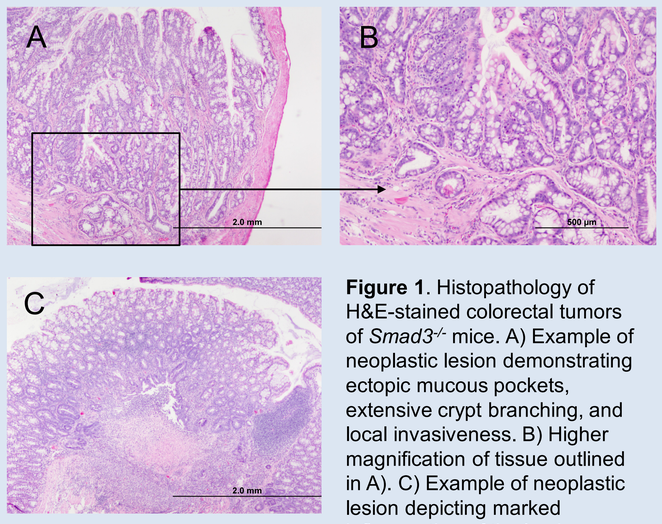


Figure 1. Histopathology of H&E-stained colorectal tumors of *Smad3*$^{-/-}$ mice. A) Example of neoplastic lesion demonstrating ectopic mucous pockets, extensive crypt branching, and local invasiveness. B) Higher magnification of tissue outlined in A). C) Example of neoplastic lesion depicting marked inflammation of the lamina propria.

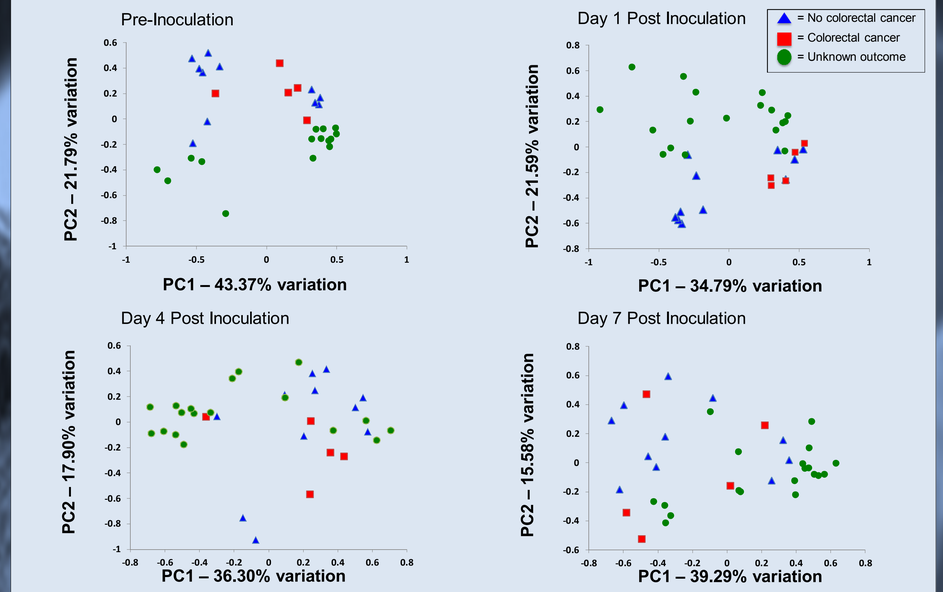


Figure 2. Principal Component Analysis (PCA) of fecal DNA of *Smad3*$^{-/-}$ mice at different time points following *H. bilis/hepaticus* inoculation. Red data points indicate mice which developed colorectal cancer (CRC) by twelve weeks post-inoculation. Blue and green data points represent mice that did not develop CRC or had an unknown outcome respectively. Samples cluster according to disease outcome at early time points, but not at day 7 and beyond.

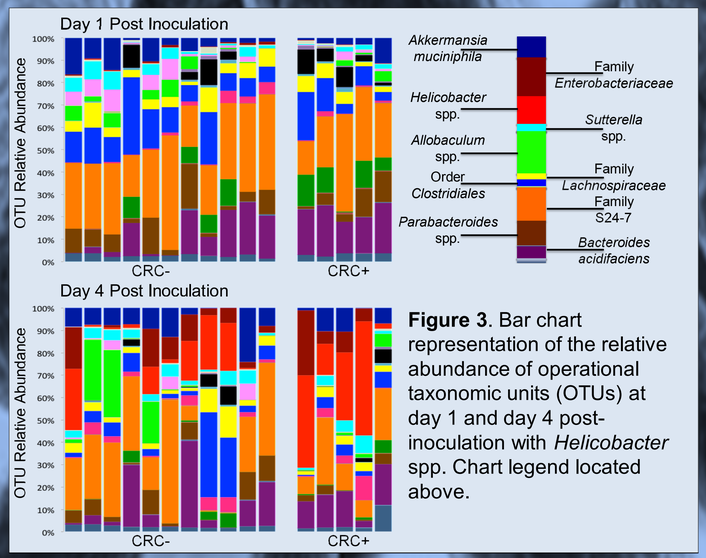


Figure 3. Bar chart representation of the relative abundance of operational taxonomic units (OTUs) at day 1 and day 4 post-inoculation with *Helicobacter* spp. Chart legend located above.

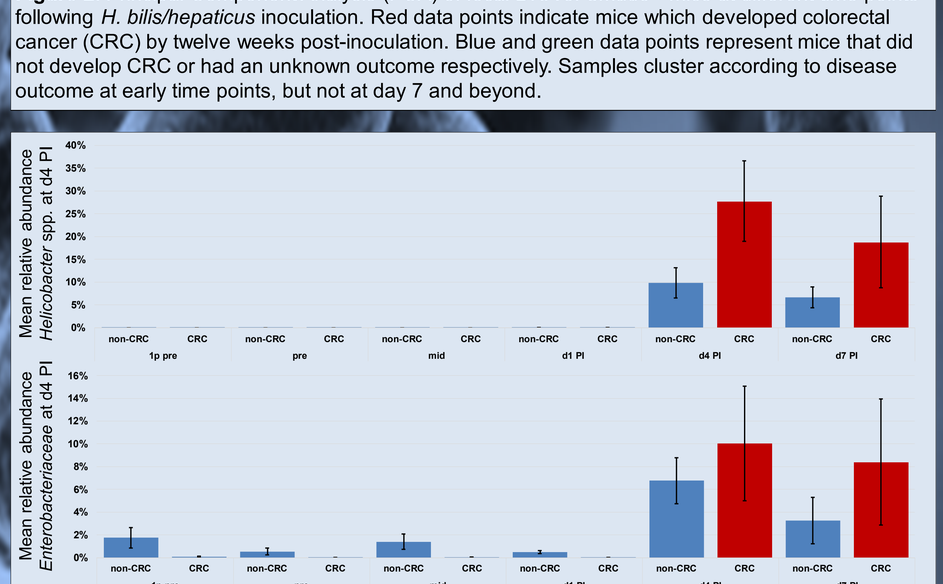


Figure 4. Bar chart showing mean +/- SEM relative abundance of *Helicobacter* spp., and *Enterobacteriaceae* in feces of mice as determined by 16S rRNA sequencing.

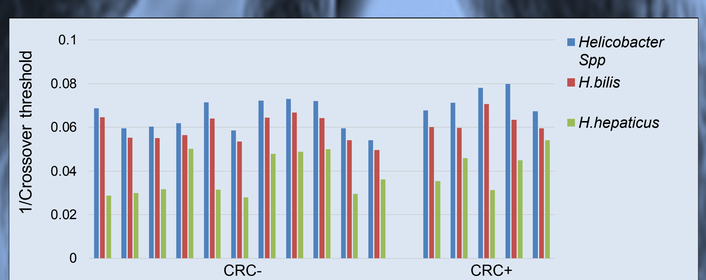


Figure 5. Bar chart showing relative proportions of *H. bilis* and *H. hepaticus* in feces at day 4 post inoculation as determined via Real-Time qPCR..

Conclusions and Future Studies

- *Smad3*$^{-/-}$ mice that developed colorectal cancer (CRC) had a greater relative abundance of members of *Helicobacter* spp., with a trend toward greater abundance of *Enterobacteriaceae*.
- Clustering of samples at early time points suggests compositional similarity of feces in mice which progress to CRC, correlating with the timing of predictive inflammatory biomarkers.
- Further investigation is required to enumerate the effects of variable microbiota compositions and their impact on cancer susceptibility.

Acknowledgements

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