The influence of the gut microbiota on susceptibility to colorectal tumors in Smad3$^{-/-}$ mice

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Background

- Smad3 is a transcription factor downstream of TGFβ: loss of response to TGFβ is an indicator of malignancy in human colorectal cancer (CRC)
- Many risk factors for CRC, including diet, smoking, and obesity, modulate the composition of the host gut microbiota
- Smad3$^{-/-}$ mice develop colorectal (CR) tumors in 50% to 66% of individuals when inoculated with *Helicobacter bilis*
- *H. bilis* inoculation results in host immune responses to commensal microbiota
- Differences in GI microbiota could account for variable susceptibility to tumor development in inbred population
- We hypothesized that consistent differences in the gut microbiota (GM) would be found between mice that do and do not develop CR tumors

Methods

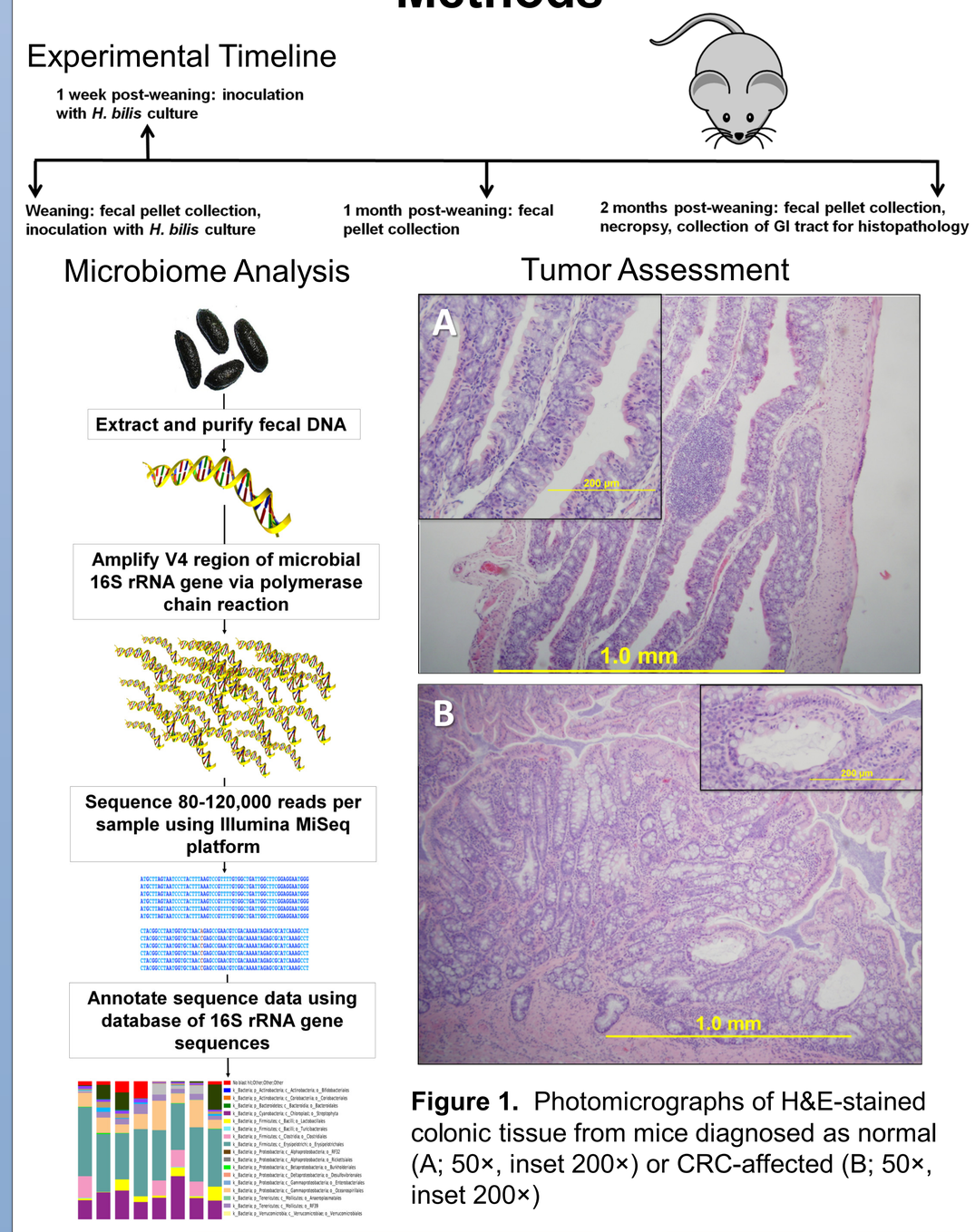
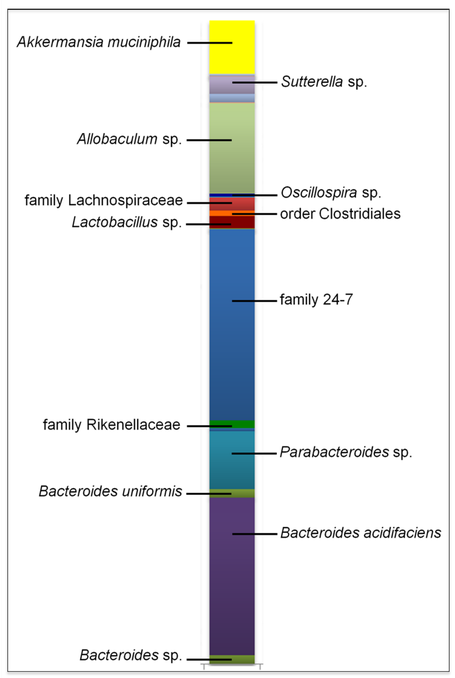


Figure 1. Photomicrographs of H&E-stained colonic tissue from mice diagnosed as normal (A; 50×, inset 200×) or CRC-affected (B; 50×, inset 200×)

Results



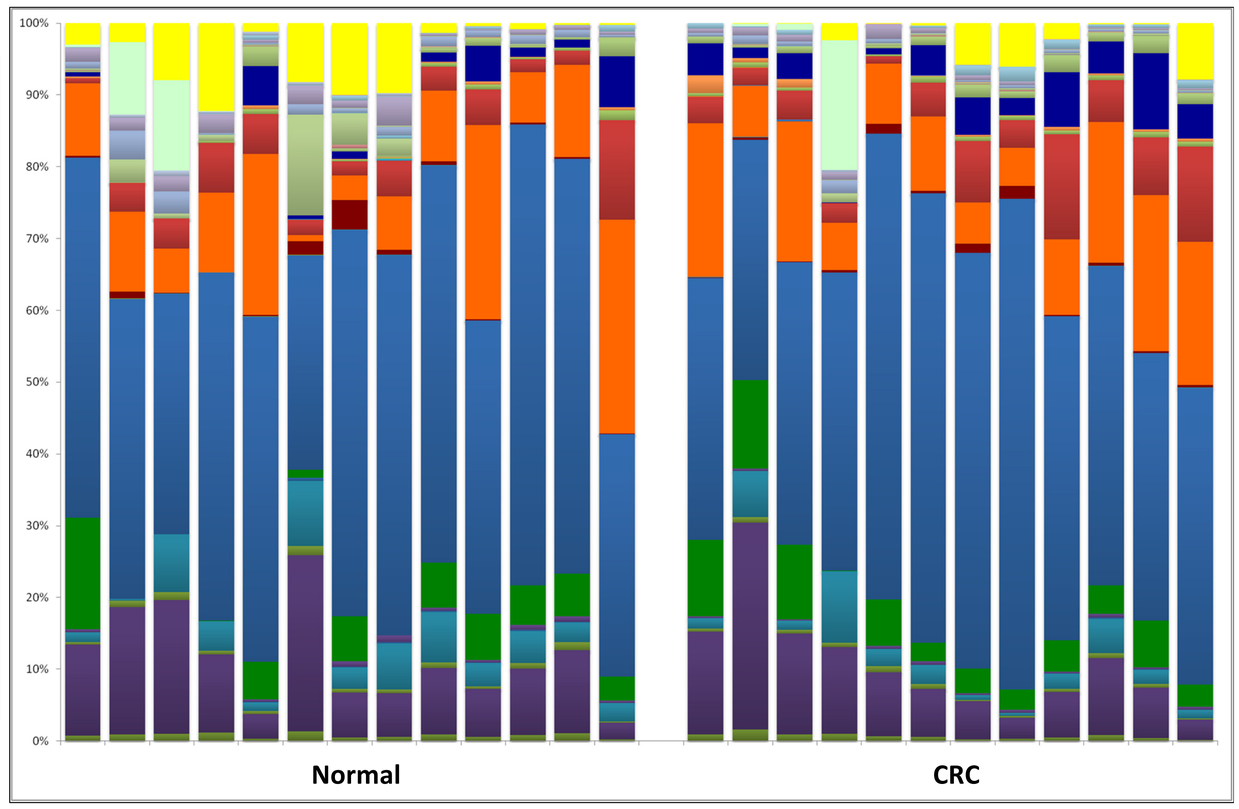


Figure 2. Bar chart showing variable gut microbiota in mice prior to inoculation with *H. bilis*. Each OTU is defined by 99.5% nucleotide identity. Legend of selected OTUs at left.

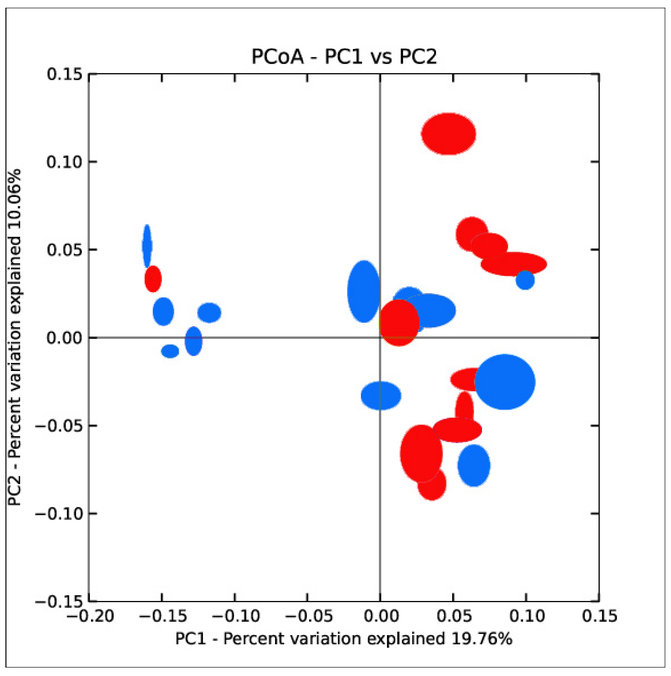


Figure 3. Principal component analysis of GM prior to inoculation. PC1 and PC2 explain 19.76% and 10.06%, respectively, of the total variance observed, but do not consistently discriminate mice that developed CRC (red) from those that did not develop CRC (blue)

Results summary

- 48% of mice inoculated with *H. bilis* showed evidence of CR tumor development 2 months post-inoculation
- No difference in the number of operational taxonomic units (OTUs) identified was found between mice with and without CR tumors
- Several OTUs differed in proportion between mice with and without tumor development were identified, including:
  - ***Akkermansia muciniphila*** (p = 0.032 *; increased in mice without CR tumors)
  - ***Oscillospira*** sp. (p = 0.053 *; increased in mice with CR tumors)
  - A member of ***Ruminococcaceae*** (p = 0.068 *; increased in mice with CR tumors)

* Mann-Whitney rank sum test

Conclusions

- Increased abundance of *Akkermansia muciniphila*, a mucin-degrading bacteria, correlates with protection from *H. bilis*-induced CRC, typically classified as mucinous adenocarcinoma
- Other OTUs, including *Oscillospira* sp. and the family *Ruminococcaceae*, show a trend toward increased abundance in with CRC

Future Studies

- Investigate changes in microbiome composition between time points and compare to tumor occurrence
- Investigate potential mechanism of action of OTUs of significance, including *Akkermansia muciniphila*, *Oscillospira* sp., and microbe from family *Ruminococcaceae*

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