Hormonal effects on adenoma development in a rat model of human familial colon cancer

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RRRC Rat Resource & Research Center www.rrrc.us

ASLAP The American Society of Laboratory Animal Practitioners

BACKGROUND

- **Colon cancer affects men at an earlier age and higher rate compared to women**
- **The Pirc (polyposis in the rat colon) rat model recapitulates this sex disparity**
- **Orchidectomy significantly protected male Pirc rats from tumor development while replacement of testosterone through supplementation reversed the effect**
- **Complex gut microbiota modulates disease susceptibility of familial colon cancer**
- **When male Pirc rats were co-housed, some had higher tumor burdens while others had lower tumor burdens**

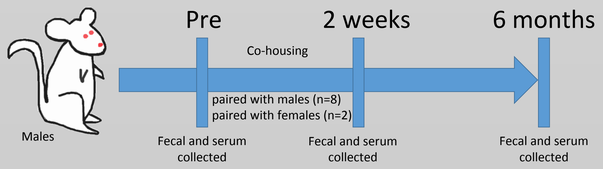
HYPOTHESIS / OBJECTIVES

The increased tumor burden in co-housed male rats is due to changes in the microbiome that is affected by differential levels of the stress hormone corticosterone

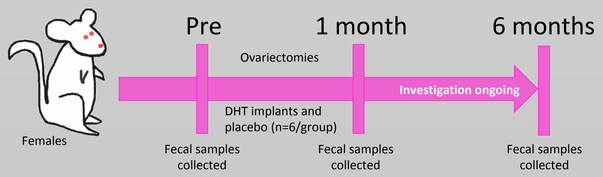
Female rats supplemented with DHT (dihydrotesterone) would have a higher tumor burden mediated through changes in the microbiome

METHODS

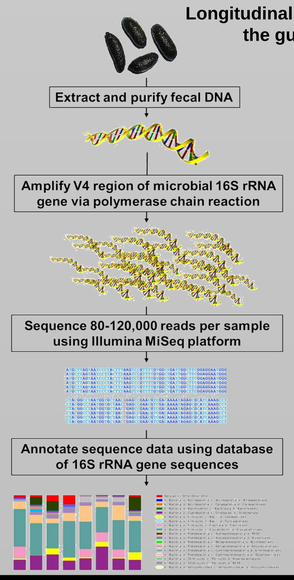
Co-housing Study



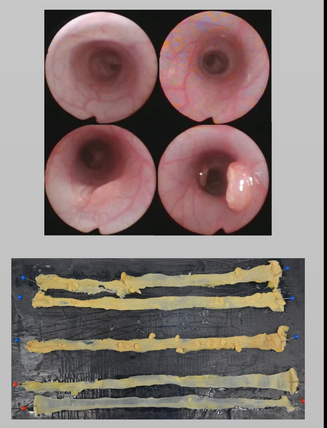
Ovariectomy Study



Longitudinal characterization of the gut microbiota



Colonoscopy and Tumor Counts



CO-HOUSING RESULTS

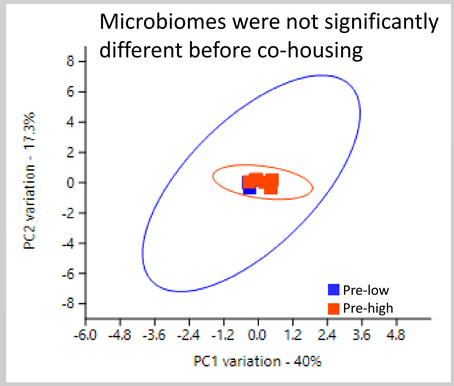


Figure 1. Principal component analysis (PCA) showing the microbiome composition before co-housing. Each square represents an individual rat's microbiome with blue indicating the low tumor burden rats and red the high tumor burden rats. 95% Ellipses show the minimal difference between individual microbiome diversities within and between groups.

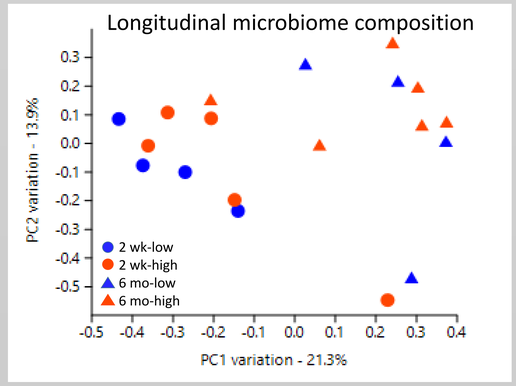
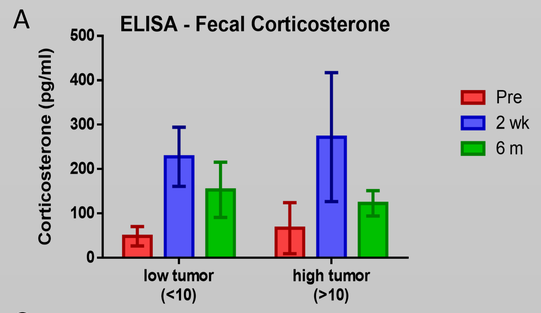
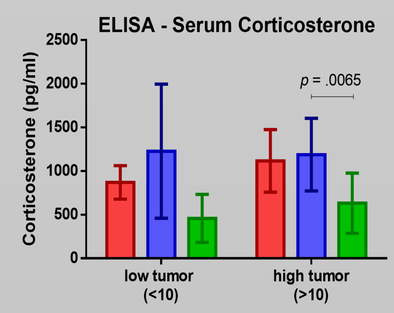


Figure 2. PCA showing the microbiome composition at the 2 week and 6 month post co-housing time points. Each symbol represents an individual rat's microbiome with blue indicating low tumor burden rats and red high tumor burden rats. Dots mark the 2 week time point while triangles mark the 6 month time point. Separation along PC1 represents age differences in the microbiomes. Significant differences were found between the groups (PERMANOVA, $p<.05$).





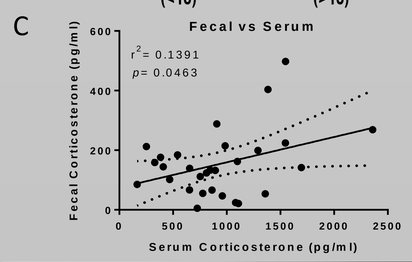


Figure 3. ELISA Corticosterone levels. A) and B) Bar charts of Corticosterone levels collected through fecal and serum samples. The fecal and serum corticosterone levels peak at 2 weeks after co-housing for both low and high tumor burden animals then regress by 6 months. C) Pearson's correlation graph between the fecal and serum corticosterone levels. Based on trends observed in A) and B) and positive correlation in C), fecal samples can be potentially used as surrogates to measure serum corticosterone levels.

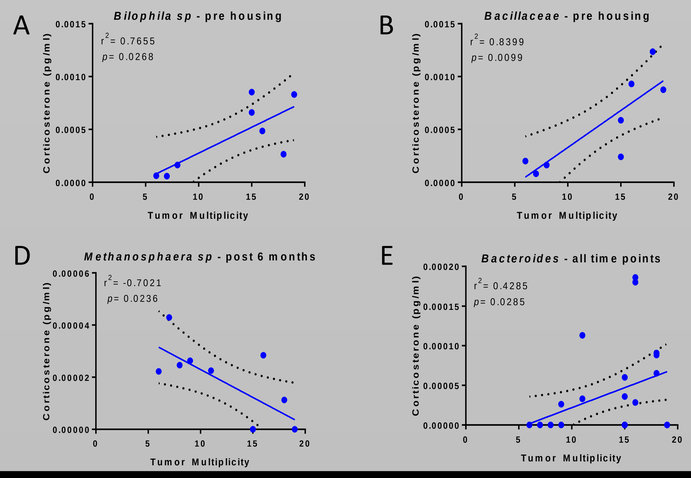


Figure 4. Correlations of Operational Taxonomic Units (OTUs). Several OTUs at different time points show positive or negative correlation with tumor multiplicity (Pearson's $p<.05$). Each dot represents OTU abundance at a certain time point in relation to the rat's terminal tumor multiplicity. A) and B) positively correlate with tumor burden at 6m and are potential biomarkers. C) and D) demonstrate a positive and negative correlation respectively, post co-housing. Relative abundance of order *Bacteroides* in E) positively correlates with tumor multiplicity irrespective of co-housing time points.

OVARIECTOMY RESULTS

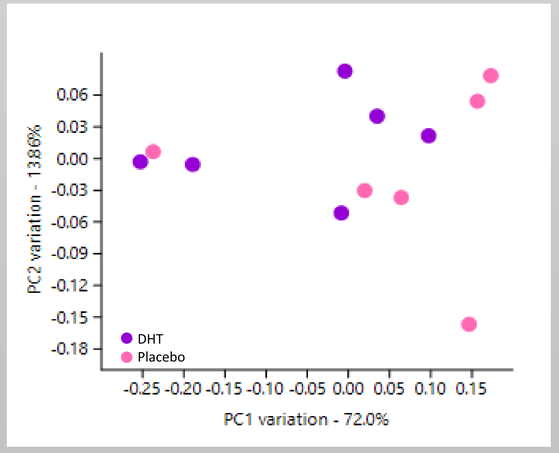


Figure 5. PCA showing the microbiome composition at 1 month post ovariectomy. Dots represent each rat's microbiome with purple and pink indicating rats implanted with DHT and placebo respectively. There are no significant differences in the microbiome at this time point observed by PERMANOVA analysis.

CONCLUSIONS

Co-housing Study

- **Fecal corticosterone shows similar trends to serum samples**
- **Corticosterone levels did not correlate with tumor burdens in co-housed male Pirc rats**
- **The microbiome did significantly change over the 6 month investigation**
- **Certain bacteria positively or negatively correlate at early time points indicating their potential role in tumor development**

Ovariectomy Study

- **There are no significant microbiome changes at one month post ovariectomy**
- **The ovariectomy investigation is ongoing**

ACKNOWLEDGEMENTS

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