Effect of social interactions on colon tumor load in male *Apc*$^{Pirc/+}$ rats

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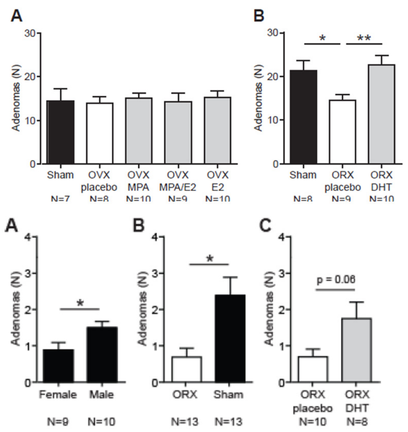
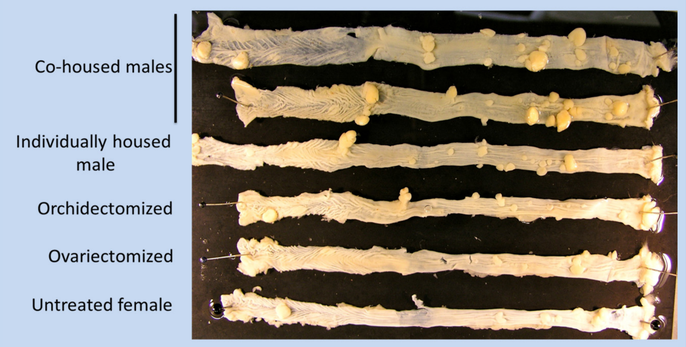
Introduction

Colon cancer is the second leading cause of cancer death in the U.S. Within the human population there is an overall trend that cancer effects more males than females with the exception of sex specific cancers like prostate and ovarian cancers. This sexual dimorphism is seen in colon cancer with women having a reduced incidence and a later onset. The mechanisms for this difference appears to be hormonally driven, however existing mouse models of intestinal cancer do not show an obvious sex differential. Recently a rat genetic model of human colon cancer was developed that shows a similar gender difference. Compared to the murine colon cancer model (*Apc*$^{Min/+}$) the *Apc*$^{Pirc/+}$ rat more closely models human disease and allows disease monitoring over time through colonoscopy and longitudinal serum analysis.[1]

Background

- Pirc (Polyposis in Rat Colon) rats carry a mutation in the *Apc* tumor suppressor gene which is also the most common mutation observed in human colon cancer.[1]
- Tumor load observations in the *Apc*$^{Pirc/+}$ rat:
  - •Pirc males develop twice as many adenomas as Pirc females
  - •Ovariectomy and female hormone replacement have shown no effect on adenoma formation
  - •Orchidectomy (castration) decreases adenoma development, while supplementation with 5α-dihydrotestosterone (DHT) restores adenoma formation



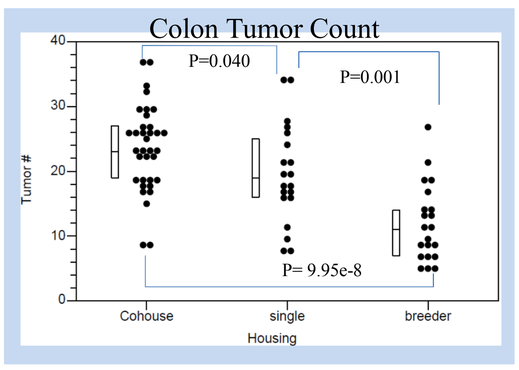


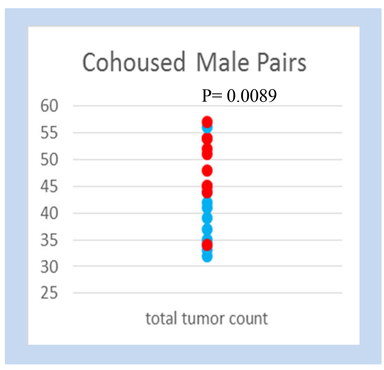
These experiments were carried out at the University of Wisconsin–Madison

Rationale

Male Pirc rats tumor load correlates with housing status

Cohoused males have the greatest tumor load while breeder males have the least. Within the cohoused Pirc male cohort a significant tumor load difference has also been observed. Speculation for this observation is that cohoused males create a long term dominance-subordination hierarchy characterized by an asymmetry of agonistic behaviors. This hierarchy is established within the first few days of interaction and has been observed to last through the life of the animal. This relationship between cohoused males has been correlated with both physiologic and behavioral changes. Dominant rats display increased testosterone levels and increased motor activity compared to subordinates, while submissive animals have increase corticosterone levels and a decrease locomotor activity.[2]



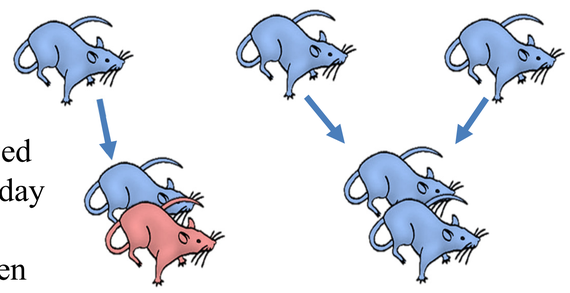


Hypothesis: Because social interactions can effect stress, food access, activity and endocrine systems we hypothesize the dominant rat in cohouse male pair will exhibit higher tumor load, breeder males will have lowest tumor load

Objective: Evaluate social interactions in males and their relationship to the disease phenotype

Methods

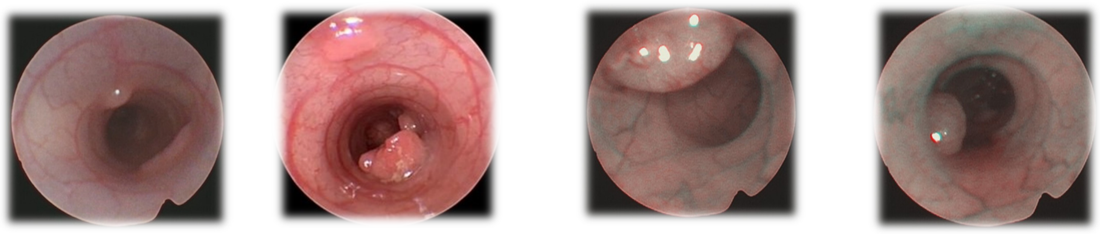
- Male rats were singly housed at weaning until 60 days of age
- Assigned to either cohoused male pairs or cohoused with female
- Social hierarchy was observed between cohoused male pairs by video observation on day 1 and day 15 of housing
  - Dominance was established between cohoused male pairs
- Phenotype monitoring included: physical exam, colonoscopy, and eventual microbiome and serum corticosterone analysis



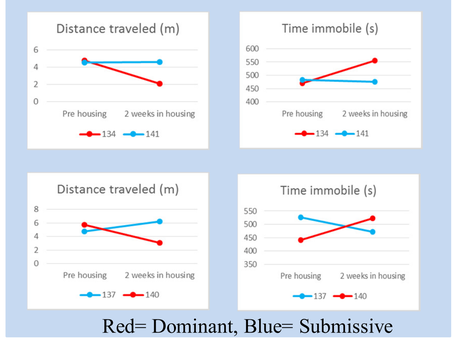
Results

- Dominance Score= Pins + 2 (Holds)

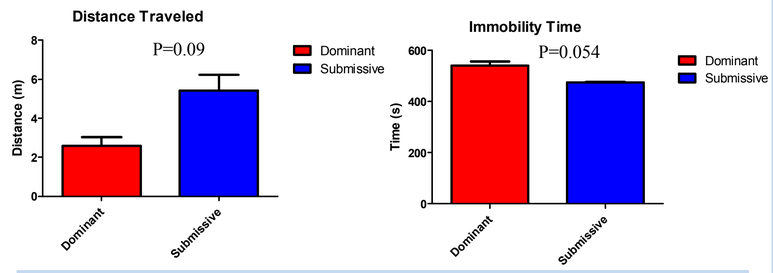
- Colonoscopy (60 days, 90 days)



- Locomotor Test



Red= Dominant, Blue= Submissive



Two male Pirc cohoused pairs were evaluated. Dominance was designated by video scoring. Locomotor tests were performed at two time points: prehousing and 2 week in housing. Animals were placed in cage similar to home cage and monitored by video for 10 minutes.
Note: These results are not statistically significant using Student T-test and underpowered (Power=0.58)

Conclusion

- Data has supported an increasing role of male sex hormone in adenoma formation
- This experiment is ongoing and no final conclusion will be made until quantification of tumor load at necropsy

Future Directions

- CORT ELISA assay on serum samples prehousing and 1 week in housing
- Quantify tumors throughout the gastrointestinal tract and weigh testes at necropsy,
- Explore hierarchy preweaning and select males with high aggression
- Measuring serum testosterone and 5-HIAA (serotonin metabolite) in neural tissue
- Further investigate the effects of androgens on cancer, specifically tumor load in the rat colon

References
- [1] Amos-Landgraf, J.M. *et al* (2007) A target-selected *Apc*-mutant rat kindred enhances the modeling of familial human colon cancer. *Proc. Natl. Acad. Sci. U.S.A.* 104, 4036-4041
- [2] Blanchard, D.C *et al* (1993) Subordination stress: behavioral, brain, neuroendocrine correlates. *Behav. Brain Res.* 58, 113-121

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