



An Investigation in the Role Exercise has During Tumoreogenesis in APC-Min Mice

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INTRODUCTION

- Obesity has become an epidemic in both the human and animal population affecting 36% of adults in American and 25-40% of dogs and cats.
- This increase in obesity is a of a growing concern because of the associated health risk including but not limited to type 2 diabetes mellitus, metabolic disorders, coronary heart disease, stroke, respiratory problems, high blood pressure and some cancers, including colon cancer.
- With a 5% chance, colorectal cancer is the third most common cancer diagnosed in both men and women in the United States.
- As white adipose tissue grows in size, it will eventually become hypoxic due to lack of perfusion. This causes the up regulation of the HIF-1 transcription factor, leading to he transcription of genes such as GLUT1, LEP and VEGF to try and rescue the cell, but will eventually lead of expression of genes that cause inflammation and apoptosis.
- The death of the cell will cause recruitment of macrophages and CD8+ T cells causing an inflammatory response and the release of cytokines into circulation leading to systemic inflammation and causing metabolic dysfunction.
- An increase in adipokines such as *leptin*, as well as a decrease in some such as *adiponectin* have been shown to potential risk factors in the development of cancer.
- Previous experiments have shown that exercise reduces *leptin* levels as well as the inflammatory factors present in both the tissues and systemically.
- We will test the hypothesis that exercise slows the growth of tumor development and lowers tumor load by measuring the load of tumors in active and sedentary APC-Min mice and by measuring inflammatory factors in the adipose tissue, blood, and tumors.
- The microbiome has also been shown to be a risk factor for the development of colorectal cancer. Exercise may alter the environment of the lower GI tract, changing the mircroflora into a more protective flora.

Purpose and Hypothesis

Purpose: This experiment explores the role of exercise in tumor size and growth of colorectal cancer. If exercise can be shown to slow tumor growth through the reduction of inflammatory factors, exercise can be shown to be a useful adjunctive therapy in the treatment of colorectal cancer in both humans and animals.

Hypothesis: Exercise will decrease cancer size and tumor load through an increase in anti-inflammatory cytokines, and a decrease in inflammatory mediators and hormones originating from adipose tissue.

Hypothesis 2: We will determine if exercise will make the colon a more acidic environment, allowing the normal flora to contain more lactic acid bacteria such as *Lactobacilus sp.* and other microbes that are protective

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Methods

- 48 mice will be used, 24 wildtype and 24 APC-Min mice
- Both the wildtype and the APC-Min mice will be randomly divided into two groups, an exercised group and a non-exercised group.
- The exercised group will have access to a running wheel from age of weaning to 90 days of age. Distance traveled and amount of time on the running wheel will be monitored daily to assure that mice are in fact exercising.
- At 90 days of age all 4 groups are sacrificed, adipose tissue, blood, and tumor tissue samples are collected and the colon examined with tumor size and number recorded.
- A bioassay is then run on both the tissue and blood samples for both *leptin* and IL-10, an anti-inflammatory cytokine, to determine if there was a change in concentration of adipokines that correlate with a change in both tumor load and size in the colon.
- Feces will also be collected at both the onset of exercise and at 90 days.
- Sequencing will be preformed on the feces to ascertain the microbiome



Model Justification

- The APC-Min mouse is a model that has a mutation in the 850 codon of the APC gene, this causes the development of colon tumors. The APC gene, a gatekeeper gene, down regulates the Wnt pathway which causes proliferation. When a mutation occurs there occurs an over proliferation of tumor cells. This has been shown to be an effective model for human familial adenomatous polyposis, which left untreated will develop into colorectal cancer. Therefore, this becomes an acceptable model to test the affects of exercise on tumorogenesis and tumor size.

SUMMARY & CONCLUSIONS

- Obesity and the systemic inflammatory response that accompanies it is associated with many health risks including a predisposition for colorectal cancer. Previous experiments have shown that exercise reduces these inflammatory factors. Therefore this experiment is designed to test if there is a negative correlation between tumorogenesis and tumor size with exercise through the reduction of these inflammatory mediators.