Differences in gut microbiota significantly modulate colon cancer susceptibility in the rat genetic model of familial colon cancer

James Amos-Landgraf[1], Alexandra Kliethermes[2], Susheel Bhanu Busi[1]

[1] Mutant Mouse Resource and Research Center, Dept. of Veterinary Pathobiology, University of Missouri-Columbia, MO; [2] Truman State University, Kirksville, MO.

The use of inbred strains and genetic crosses to resolve the genetic factors that contribute to quantitative traits have often not considered the impact of differences in the gut microbiome(GM). We previously determined that differences in the specific pathogen free complex gut microbiota are causative determinants of cancer susceptibility using either fostering newborn pups or by using complex microbiota targeted rederivation (CMTR) in rats. CMTR of isogenic embryos into surrogate dams each harboring distinct gut microbiota created rats with differing complex GMs. Adenomas develop in rats through loss of heterozygosity(LOH) of the tumor suppressor gene *Apc*, however one complex microbiome in rats suppressed the LOH pathway and drove adenoma development while maintaining heterozygosity of *Apc.* To determine the mechanism of the differential susceptibility we used a multi-omic approach, assessing differences in the microbiome, metabolome and host transcriptome to identify unique signatures of susceptibility and resistance. Of note, the fecal metabolite profile from rats at one month of age predicted either high or low tumor burden at 4 months of age. Differences in bile acid biosynthesis gene expression correlated with differences in bile acid metabolites, which also correlated with differences in tumor burden. To resolve if these correlations were causative, we independently fostered rat pups derived via cesarean onto surrogates that harbor a simplified (~10 microbe) Altered Schaedler flora (ASF). Pups were then either transferred back to a complex GM environment or maintained with a limited GM. ASF animals had a significantly increased tumor burden compared to complex GM rats. Expression analysis of normal intestinal epithelium indicated increased expression of the cytochrome P450 gene Cyp27a1 which encodes a sterol hydrolase gene that breaks down cholesterol in bile acids. Taken together, rat adenoma development is significantly altered by differences in the pathogen free GM through modulation of the bile acid pathway.