Title: Kras Gene Exacerbates Microbial Dysbiosis and Tumor Aggressiveness in Murine Model of Colon Cancer

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The intestinal microbiota plays a causative role in colorectal cancer (CRC). In this study, we hypothesized that driver oncogenic mutations in Apc and Kras, independently and synergistically, induce changes in the intestinal microbiota, resulting in the development of more aggressive colorectal adenomas. To test this hypothesis, we employed a murine model of CRC involving mutations in the Apc gene, inducing small bowel polyposis, as well as mutations in the Kras gene, promoting more aggressive colonic tumor growth and inflammation. Histological analysis revealed increased tumor load and inflammation in mice carrying both Apc and Kras mutations compared to those with the single Apc mutation. Fecal and adherent microbial communities, characterized by Illumina amplicon sequencing, from the small bowel and colon of mice harboring the Apc mutation were significantly different from wildtype communities (ANOSIM $R = 0.093\text{-}0.297$, $P \leq 0.037$). Notably, the accumulation of both Apc and Kras mutations significantly altered fecal bacterial community composition (post-hoc $P < 0.001$). Correlation analysis revealed significant associations between inflammatory markers linked to the Kras mutation and the genera Prevotella and Bacteroides (Spearman $P < 0.05$). These findings suggest that the Kras mutation amplifies the effects of the Apc mutation on the intestinal microbiota while driving tumor inflammation, potentially promoting the development of aggressive CRC in these models.