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**The role of the microbiome in pancreatic adenocarcinoma**

**Abstract:** The gut microbiome has emerged as an important regulator in the balance between health and disease, including oncogenesis. In the pre-morbid state the intestinal microbiome is similar in mice bearing oncogenic mutations and in controls; however, as mice age cancer-bearing hosts develop a unique gut microbiome. We found that gut bacteria access the cancerous tissue which harbors a distinct microbiome in humans and mice. Further, genotypically identical tumor-bearing mice that exhibit divergent disease phenotypes harbor stage-specific microbiomes suggesting that microbial structure is associated with disease aggressiveness. Germ-free or ablative antibiotic treated mice were protected against tumorigenesis whereas transfer of gut bacteria from tumor-bearing mice, but not from control mice, reversed the tumor-protection. Bacterial ablation was associated with innate and adaptive immunogenic reprogramming of the tumor microenvironment including a marked reduction in myeloid-derived suppressor cells and immune-suppressive macrophages, increased Th1 differentiation of CD4<sup>+</sup> T cells, and expansion and activation of cytotoxic CD8<sup>+</sup> T cells. These data suggest that endogenous microbiota promote the crippling immune-suppression and that the microbiome has marked potential as a biomarker and therapeutic target. We will also discuss bidirectional metabolic cross-talk between the cancer cells and the innate immune compartment.