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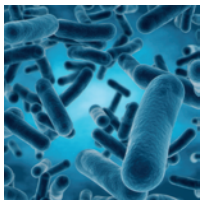
## Microbiome

**Major finding:** Distinct tumor microbiomes are associated with long- and short-term survival in patients with PDAC.

**Concept:** Tumor microbiota promote recruitment and activation of $CD8^+$ T cells and survival of patients with PDAC.

**Impact:** Modulation of the PDAC microbiome is a potential therapeutic approach for patients with PDAC.

### TUMOR MICROBIOME COMPOSITION INFLUENCES PANCREATIC CANCER SURVIVAL



Gut microbiota can regulate immune responses beyond the gut, and recent studies suggest that gut microbiota may mediate chemotherapeutic and immunotherapeutic responses. Riquelme, Zhang, and colleagues investigated the role of tumor microbial populations in the survival of patients with pancreatic ductal adenocarcinoma (PDAC). Tumor microbial diversity was characterized in two independent cohorts of patients with surgically resected PDAC who were long-term survivors (LTS) or short-term survivors (STS). Compared with STSs, LTSs exhibited increased microbial diversity and enrichment of district bacterial species that correlated with overall survival. Furthermore, higher densities of $CD3^+$ and $CD8^+$ T cells and increased numbers of granzyme $B^+$ cells were found in LTS tumors, and $CD8^+$ T-cell density correlated with the top three enriched bacterial genera in LTSs. Intratumoral microbiome composition also correlated with differential enrichment of metabolic pathways. Comparison of matched gut, tumor, and adjacent normal tissue microbiomes from three patients with PDAC showed that the gut microbiome represents approximately 25% of the tumor microbiome and is absent in adjacent normal tissue. Fecal microbial transplantation (FMT) from STSs to mice previously treated with antibiotics resulted in the presence of bacteria of human origin in both murine gut and tumor. FMT from LTSs, STSs, or healthy controls showed that mice receiving FMT from LTSs exhibited enhanced survival and increased levels of $CD8^+$ T cells and activated $CD8^+$ T cells, whereas mice receiving FMT from STSs exhibited increased levels of $CD4^+FOXP3^+$ and myeloid-derived tumor suppressor cells, and T-cell depletion blocked the antitumor effect induced by FMT from LTSs. Collectively, these results suggest that gut microbiota can colonize pancreatic tumors, change intratumoral bacterial composition, recruit and activate $CD8^+$ T cells, and prolong survival of patients with PDAC. Therefore, determining the tumor microbiome of patients with PDAC may serve as a prognostic tool, and FMT from LTS patients may have therapeutic potential. ■

*Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell 2019;178:795–806.*

## Neuroblastoma

**Major Finding:** The transcription factor BORIS promotes resistance-associated chromatin regulatory interactions.

**Concept:** Development of ALK resistance is a multistep process involving a switch from MYCN to BORIS dependency.

**Impact:** The role of BORIS in co-opting developmental networks to promote drug resistance may extend to other cancers.

### RESISTANCE TO ALK INHIBITORS IN NEUROBLASTOMA IS REGULATED BY BORIS

Overexpression of the *CTCF* paralog brother of the regulator of imprinted genes (*BORIS*; also known as *CTCFL*) has been observed in several cancers, but the relevance of this finding is unknown. Debruyne, Dries, and colleagues discovered that *BORIS* was one of the most differentially expressed genes in *MYCN*-amplified neuroblastoma cells made resistant to ALK inhibition, and this finding appeared to extend to other neuroblastoma lines and resistance to other kinases. The process of acquiring resistance to ALK inhibitors included multiple steps and was characterized by a transition from dependency on amplified *MYCN* to dependency on *BORIS* overexpression, with fully ALK-resistant cells requiring BORIS for survival. Increased occupancy of BORIS on chromatin, particularly in enhancer and promoter regions, was observed in resistant cells. The preferential binding of BORIS to open chromatin regions suggested that BORIS may regulate gene expression via chromatin looping, and high-throughput chromosome conformation capture followed by chromatin immunoprecipitation experiments provided evidence that this was the case. The superenhancer landscape of resistant cells was characterized by BORIS-positive regulatory loops, and the presence of these superenhancers was associated with greater expression of associated genes. A search for genes regulated by BORIS that were functionally connected to the resistance phenotype identified 89 genes that are highly expressed early in neural development, suggesting that BORIS mediates a switch in phenotypic state that supports resistance. Signifying the potential broader relevance of these findings, increased BORIS occupancy was observed at regulatory regions in chemotherapy-resistant Ewing sarcoma cells. However, further research is needed to determine whether the precise mechanism extends to other cancers. ■

*Debruyne DN, Dries R, Sengupta S, Seruggia D, Gao Y, Sharma B, et al. BORIS promotes chromatin regulatory interactions in treatment-resistant cancer cells. Nature 2019 Aug 7 [Epub ahead of print].*

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AACR American Association for Cancer Research

CANCER DISCOVERY

# Tumor Microbiome Composition Influences Pancreatic Cancer Survival

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