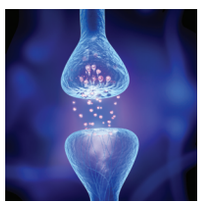
Gastric Cancer

Major finding: Nerve- and tuft cell–derived acetylcholine upregulates NGF and activates YAP in gastric cancer.

Mechanism: NGF drives TRK-mediated innervation and TRK/YAP-mediated epithelial stem cell expansion.

Impact: The acetylcholine–NGF axis may be a target for the treatment of gastric cancer.

NERVE GROWTH FACTOR DRIVES GASTRIC TUMORIGENESIS VIA ACETYLCHOLINE



The enteric nervous system, which is located within the walls of the gastrointestinal (GI) tract, directly and indirectly regulates mucosal regeneration by driving cholinergic signaling in muscarinic receptor–positive crypt cells and by interacting with stem-like doublecortin-like kinase 1–positive ($DCLK1^+$) tuft cells, respectively. Recently, nerves have been shown to infiltrate the tumor microenvironment and release neurotransmitters, such as acetylcholine, to promote tumor growth; reciprocally, tumors secrete neurotrophic factors, such as nerve growth factor (NGF), which signal through neurotrophic receptor tyrosine kinases (NTRK) to stimulate nerve outgrowth and cancer cell growth. To elucidate the role of tuft cells in nerve–cancer cell cross-talk, Hayakawa, Sakitani, and colleagues interrogated acetylcholine signaling in transgenic mouse models. In a carcinogen-induced mouse model of gastric cancer, an increase in tuft cells expressing choline acetyltransferase (ChAT), which is responsible for acetylcholine synthesis, occurred during the early stages of tumorigenesis, followed by subsequent loss of $ChAT^+$ tuft cells and increased axonal growth of cholinergic nerves. Collectively, these changes resulted in increased acetylcholine production and signaling, which induced the upregulation of NGF in gastric epithelial cells and tumors. Analysis of transgenic mouse models that conditionally express NGF or ablate the muscarinic receptor 3 (M3R) in mouse gastric epithelium showed that NGF promoted axonogenesis, M3R-mediated cholinergic signaling in tuft cells regulated mucosal proliferation and the expansion of clonal stem cells, and the NGF/cholinergic signaling axis stimulated GI dysplasia and tumor initiation. Consistent with these findings, inhibition of NGF reduced allograft tumor growth and innervation of the peritumoral mucosa in an NTRK-dependent manner. Mechanistically, NGF-driven upregulation of M3R-mediated cholinergic signaling promoted YAP activation to drive WNT signaling in APC-dependent tumor growth. Taken together, these findings further elucidate the acetylcholine-dependent signaling axis underlying gastric tumor initiation by nerve–cancer cell cross-talk and suggest that targeting this pathway may be a potential therapeutic strategy for patients with GI cancers. ■

Hayakawa Y, Sakitani K, Konishi M, Asfaha S, Niikura R, Tomita H, et al. Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling. Cancer Cell 2016;31:21–34.

Metabolism

Major finding: PDACs gain necessary amino acids via macropinocytosis and degradation of extracellular proteins.

Approach: Miniaturized plasma exchange with labeled albumin allows direct observation of protein catabolism *in vivo*.

Impact: Increased albumin uptake by PDACs may allow for improved therapeutic delivery via albumin conjugation.

PANCREATIC TUMORS EXHIBIT ENHANCED EXTRACELLULAR PROTEIN CATABOLISM

Amino acids are required for the growth of many cancer cells and may be obtained via the scavenging and catabolism of extracellular protein through macropinocytosis. Although many pancreatic cancers have elevated levels of some amino acids, it has not been directly shown that extracellular proteins are catabolized *in vivo*. As albumin is the most abundant extracellular protein in blood and tissue and serum albumin is reduced in patients with cancer, Davidson, Jonas and colleagues used labeled albumin in a miniaturized plasma exchange assay to determine if albumin is used as a tumor nutrient source *in vivo*. Compared to control mice, mice bearing pancreatic ductal adenocarcinomas (PDAC) exhibited increased levels of labeled albumin-derived amino acids in the blood, indicative of albumin degradation. Further, the concentration of labeled albumin peptides and labeled amino acids was higher in PDAC tissue compared to normal pancreas, suggesting that tumors exhibited increased albumin uptake and breakdown compared to normal pancreas. Using an implantable device to deliver fluorescently labeled albumin to the tumor microenvironment of PDAC tumors revealed that PDAC cells internalized albumin via macropinocytosis. Albumin degradation was detected in pancreatic cancer cells, but not detected in nontumor regions of the pancreas. In addition, labeled fibronectin was also internalized by PDAC cells, but not normal pancreas cells, suggesting that pancreatic tumors can consume other extracellular proteins in their environment. The lysosome was involved in catabolism, as degradation of albumin could be reduced by the lysosomal inhibitor hydroxychloroquine. Moreover, inhibiting macropinocytosis resulted in local tumor amino acid depletion, further confirming that a large portion of tumor amino acids are derived from macropinocytosis and catabolism of extracellular proteins. The development of methods to directly observe albumin catabolism provides direct evidence of extracellular protein degradation by pancreatic tumors and suggests a mechanism by which albumin conjugation may improve therapeutic agent delivery. ■

Davidson SM, Jonas O, Keibler MA, Hou HW, Luengo A, Mayers JR, et al. Direct evidence for cancer-cell-autonomous extracellular protein catabolism in pancreatic tumors. Nat Med 2016 Dec 26 [Epub ahead of print].