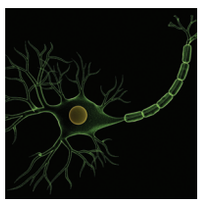
Invasion

Major finding: Schwann cell contact induces cancer cell dispersion and perineural invasion.

Mechanism: Schwann cells promote cancer cell protrusions away from neighboring cells in an NCAM1-dependent manner.

Impact: Cancer cells exploit normal Schwann cell nerve repair programs to promote perineural invasion.

SCHWANN CELLS PROMOTE CANCER CELL INVASION



In a variety of malignancies, cancer cells can invade along nerves in an aggressive perineural invasion, which is associated with pain and paralysis as well as reduced survival. A better understanding of the regulation of perineural invasion may aid in the development of improved therapeutic strategies. Schwann cells are a type of glial cell that supports neuronal guidance during nerve repair, similar to cells from the tumor microenvironment contributing to cancer cell invasion. Deborde and colleagues hypothesized that the ability of Schwann cells to guide cells, remodel the matrix, and secrete paracrine signals during neuronal repair might facilitate cancer cell invasion. Analysis of histologic sections from 8 patients with pancreatic adenocarcinoma revealed increased perineural invasion, with more Schwann cells expressing GFAP, a marker for a Schwann cell subtype that facilitates repair during neuronal guidance, than matched control sections. Similar results were observed in thyroid cancer, salivary duct carcinoma, and cutaneous squamous cell carcinoma. Further, in a xenograft model of perineural invasion, cancer cells increased the number of GFAP$^+$ Schwann cells. The presence of GFAP$^+$ Schwann cells in 3-D cancer cell sphere cultures disrupted the spheres and enhanced invasion by promoting dissociation of individual cells, formation of linear cell chains, and disruption of cancer cell contacts by intercalating between cells. At Schwann cell contact sites, cancer cells formed protrusions and migrated toward Schwann cells, which depended on the presence of NCAM1, which has been correlated with the presence of perineural invasion. Invasion of pancreatic cancer cells injected into the sciatic nerves of NCAM1 knockout mice was decreased compared to WT mice. Taken together, these findings indicate that NCAM1 is a critical mediator of Schwann cell–induced cancer cell invasion, and suggest that disruption of Schwann cell–cancer cell contacts may reduce tumor invasion. ■

Deborde S, Omelchenko T, Lyubchik A, Zhou Y, He S, McNamara WF, et al. Schwann cells induce cancer cell dispersion and invasion. J Clin Invest 2016;126:1538–54.

Hepatocellular Carcinoma

Major finding: Systemic deletion of *Akt1* and *Akt2* is lethal in adult mice, whereas hepatic deletion accelerates HCC.

Mechanism: Hepatic deletion of *AKT1* and *AKT2* promotes FOXO1-driven inflammation, leading to HCC.

Impact: Isoform-specific AKT inhibitors may be better tolerated than pan-AKT inhibitors.

HEPATIC DELETION OF *AKT1* AND *AKT2* INDUCES HEPATOCELLULAR CARCINOMA

The serine/threonine AKT family kinases (AKT1, AKT2, and AKT3) are frequently activated in cancer, and pan-AKT inhibitors are in clinical trials, making it important to understand the systemic effects of deletion of each isoform. Wang, Yu, and colleagues characterized systemic combined deletion of *Akt* isoforms in adult mice. While inducible deletion of *Akt1* in an *Akt3* null background was tolerated, combined systemic deletion of *Akt1* and *Akt2* was toxic and led to inflammation, hypoglycemic shock, and death. Hepatic deletion of *Akt1* in *Akt2*-null mice was tolerated, but the mice exhibited reduced body weight and developed spontaneous hepatocellular carcinoma (HCC). The initiation of liver carcinogenesis is often associated with liver injury and inflammation. Consistent with this observation, hepatic deletion of *Akt1* in *Akt2*-null mice led to increased serum levels of injury-associated liver enzymes and inflammatory markers, such as interleukin-6 (IL6) and tumor necrosis factor alpha (TNFα). Hepatic tumor sections were characterized by increased proliferation and macrophage infiltration. Mechanistically, inflammation in *Akt1*/*Akt2*-deleted livers was driven by FOXO1-mediated transcription, and subsequent deletion of FOXO1 reversed liver inflammation and tumorigenesis in the context of *Akt1*/*Akt2* loss. Increased IL6 production and high levels of protumorigenic STAT3 signaling were observed within tumor-associated hepatocytes, and RNA sequencing revealed an upregulation of gene signatures associated with aggressive human hepatocellular carcinoma. Although deletion of either *Akt1* or *Akt2* alone did not inhibit carcinogen-induced HCC, *Akt2* deletion contributed to increased lung metastasis originating from primary liver tumors. Together, these data show that while systemic loss of *AKT1* and *AKT2* is lethal, hepatic deletion of the two *AKT* isoforms accelerates hepatocarcinogenesis due to FOXO1-driven liver injury and inflammation, and suggest a need for AKT isoform–specific inhibitors, which may be better tolerated than pan-AKT inhibitors and prevent liver damage and inflammation. ■

Wang Q, Yu W-N, Chen X, Peng X-d, Jeon S-M, Birnbaum MJ, et al. Spontaneous hepatocellular carcinoma after the combined deletion of Akt isoforms. Cancer Cell 2016 Mar 17 [Epub ahead of print].

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