RESEARCH WATCH

Tumor Microenvironment

Major finding: Hedgehog signaling in tumor-associated stromal cells suppresses pancreatic cancer progression.

Mechanism: Stromal depletion via Shh inhibition enhances tumor vascularity and accelerates tumor growth.

Impact: Patients with poorly differentiated pancreatic tumors may respond to antiangiogenic therapy.

STROMAL CELLS INHIBIT PANCREATIC TUMOR GROWTH AND ANGIOGENESIS

Tumor-associated stromal cells have been shown to promote the growth and progression of many cancers, supporting the development of therapeutic agents targeting the tumor microenvironment. Canonical Hedgehog signaling via the sonic hedgehog (Shh) ligand stimulates expansion of desmoplastic stroma in pancreatic ductal adenocarcinoma (PDAC), suggesting that Shh may regulate pancreatic tumor growth. Using an autochthonous mouse model of PDAC, Rhim and colleagues found that conditional deletion of Shh in pancreatic epithelial cells resulted in depletion of tumor-associated stromal cells, but unexpectedly accelerated tumor progression and decreased survival. These more aggressive tumors exhibited Hedgehog pathway activation specifically in mesenchymal-derived stromal cells and were characterized by an undifferentiated histology, enhanced proliferation, and increased vascular density and perfusion, suggesting that paracrine Hedgehog signaling may indirectly suppress tumor angiogenesis in PDAC. In support of this idea, chronic pharmacologic inhibition of Hedgehog signaling phenocopied genetic Shh deletion, promoting the formation of poorly differentiated, highly vascular, aggressive tumors. Further more, in patients with PDAC, an undifferentiated tumor phenotype was associated with decreased stroma, reduced canonical Hedgehog activity, and increased vessel density. Consistent with a dependence of these tumors on enhanced vascularity, treatment with a VEGFR2 blocking antibody selectively diminished tumor cell proliferation, augmented tumor necrosis, and prolonged survival in mice harboring Shh-deficient PDAC. Although additional work is necessary to further define the mechanisms by which stromal depletion regulates PDAC growth, these results provide evidence that stromal cells can inhibit tumor angiogenesis and progression in pancreatic cancer and may explain the failure of Hedgehog inhibitors targeting tumor stroma in clinical trials. In addition, these findings suggest that the subset of patients with undifferentiated PDAC may benefit from antiangiogenic therapy.


Immunotherapy

Major finding: Treatment with anti-CD137 mAb improves cetuximab efficacy by enhancing immune responses.

Mechanism: Cetuximab induces CD137 on NK cells, and CD137 targeting stimulates ADCC and adaptive immunity.

Impact: Dual antibody therapy may be beneficial in EGFR-positive cancers, including KRAS-mutant tumors.

CD137 ACTIVATION AUGMENTS THE EFFICACY OF EGFR-TARGETED THERAPY

The EGFR-targeting mAb cetuximab is approved for the treatment of head and neck and colorectal cancers; however, many patients show limited response or no response to cetuximab, including those with KRAS-mutant tumors. The antitumor activity of cetuximab requires antibody-dependent cell-mediated cytotoxicity (ADCC) driven by natural killer (NK) cells, suggesting that strategies that enhance ADCC may improve the efficacy of cetuximab. Kohrt and colleagues found that expression of CD137 (also known as TNFRSF9 or 4-IBB) on NK cells was upregulated in response to cetuximab-treated EGFR-positive tumor cells both in vitro and in tumor-bearing mice. Dual treatment with cetuximab and an agonistic anti-CD137 mAb augmented NK cell-mediated ADCC of tumor cells and synergistically suppressed tumor growth in mice more efficiently than did cetuximab treatment alone, resulting in prolonged survival. Intriguingly, sequential treatment with cetuximab followed by anti-CD137 mAb induced regression of both KRAS-wild-type and KRAS-mutant tumors, suggesting that this therapeutic approach may overcome cetuximab resistance. This improved antitumor activity was dependent on NK cells as well as a CD8+ T-cell adaptive immune response, with increased IFNγ production and epitope spreading beyond EGFR. Of note, cetuximab therapy in patients with head and neck cancer was correlated with increased CD137 expression on circulating and intratumoral NK cells, particularly among patients harboring high-affinity Fc-receptor III alleles, and an increased proportion of EGFR-specific CD8+ T cells. These results define a therapeutic strategy that enhances the efficacy of cetuximab by sequentially targeting tumor cells and tumor-associated NK cells and stimulating cross-talk between innate and adaptive immune cells. In addition, these findings suggest that this approach may be more broadly useful for the treatment of EGFR-expressing tumors.
