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Titel des Beitrags: Administration of Gemcitabine After Pancreatic Tumor Resection in Mice Induces an Antitumor Immune Response Mediated by Natural Killer Cells.

Abstract: Even after potentially curative R0 resection, patients with pancreatic ductal adenocarcinoma (PDAC) have a poor prognosis owing to high rates of local recurrence and metastasis to distant organs. However, we have no suitable transgenic animal models for surgical interventions. To induce formation of pancreatic tumor foci, we electroporated oncogenic plasmids into pancreata of LSL-KrasG12D × p53fl/fl mice; mutant Kras was expressed in p53fl/fl mice using a sleeping beauty transposon. We co-delivered a transposon encoding a constitutively active form of Akt2 (myrAkt2). Carcinogenesis and histopathologic features of tumors were examined. Metastasis was monitored by bioluminescence imaging. Tumors were resected and mice were given gemcitabine, and tumor recurrence patterns and survival were determined. Immune cells were collected from resection sites and analyzed by flow cytometry and in depletion experiments. After electroporation of oncogenic plasmids, mice developed a single pancreatic tumor nodule with histopathologic
features of human PDAC. Pancreatic tumors that expressed myrAkt2 infiltrated the surrounding pancreatic tissue and neurons and became widely metastatic, reflecting the aggressive clinical features of PDAC in patients. Despite early tumor resection, mice died from locally recurring and distant tumors, but adjuvant administration of gemcitabine after tumor resection prolonged survival. In mice given adjuvant gemcitabine or vehicle, gemcitabine significantly inhibited local recurrence of tumors, but not metastasis to distant organs, similar to observations in clinical trials. Gemcitabine inhibited accumulation of CD11b+Gr1intF4/80int myeloid-derived suppressor cells at the resection margin and increased the number of natural killer (NK) cells at this location. NK cells but not T cells were required for gemcitabine-mediated antitumor responses. Gemcitabine administration after resection of pancreatic tumors in mice activates NK cell-mediated antitumor responses and inhibits local recurrence of tumors, consistent with observations from patients with PDAC. Transgenic mice with resectable pancreatic tumors might be promising tools to study adjuvant therapy strategies for patients.

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