Hypomethylating therapy in an aggressive stroma-rich model of pancreatic carcinoma.

Abstract:
Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy that resists current treatments. To test epigenetic therapy against this cancer, we used the DNA demethylating drug 5-aza-2'-deoxycytidine (DAC) in an aggressive mouse model of stromal rich PDAC (KPC-Brca1 mice). In untreated tumors, we found globally decreased 5-methyl-cytosine (5-mC) in malignant epithelial cells and in cancer-associated myofibroblasts (CAF), along with increased amounts of 5-hydroxymethyl-cytosine (5-HmC) in CAFs, in progression from pancreatic intraepithelial neoplasia to PDAC. DAC further reduced DNA methylation and slowed PDAC progression, markedly extending survival in an early-treatment protocol and significantly though transiently inhibiting tumor growth when initiated later, without adverse side effects. Escaping tumors contained areas of sarcomatoid transformation with disappearance of CAFs. Mixing-allografting experiments and proliferation indices showed that DAC efficacy was due to inhibition of both the malignant epithelial cells and the CAFs. Expression profiling and immunohistochemistry highlighted DAC induction of STAT1 in the tumors, and DAC plus IFN-? produced an additive antiproliferative effect on PDAC cells. DAC induced strong
expression of the testis antigen deleted in azoospermia-like (DAZL) in CAFs. These data show that DAC is effective against PDAC in vivo and provide a rationale for future studies combining hypomethylating agents with cytokines and immunotherapy.