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ABSTRACTS

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Molecular Mechanisms of Resistance to STAT3 inhibition in Pancreatic Cancer

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most difficult human malignancies to treat due to its intrinsic (de novo) and extrinsic (acquired) chemoresistance. STAT3 signaling is a central regulator of tumor development and progression. We have previously identified constitutively activated STAT3 as a mediator of treatment resistance. Src or EGFR activate STAT3 and promotes STAT3 mediated tumor progression. We hypothesized that STAT3 inhibition could activate Src and/or EGFR by inducing a homeostatic feedback loop, contributing to STAT3 inhibitor resistance. Understanding the molecular mechanisms mediating this chemoresistance generate new and promising targeted therapies.

Methods: We have characterized the expression of total and activated STAT3 and MAPK proteins in human pancreatic tissues (n=106), nine human PDAC cell lines and human pancreatic duct epithelial (HPDE) cells and in cell lines generated from PanIn (pancreatic intra-epithelial neoplasia) lesions established in Pdx1-cre/LSL-Kras G12D genetically engineered mice and from primary PDAC (PDA) and liver metastasis (LMP) cell lines generated from tumors established in Pdx1-cre/LSL-Kras G12D/LSL-p53 R273H genetically engineered mice. Effects of STAT3 inhibition (drug or siRNA) on phosphorylation of MAPK, Src and EGFR were performed. PDAC cells treated with combination of STAT3 and MAPK inhibitors were evaluated for the expression of total and activated STAT3 and MAPK, cyclin-D1, c-Myc and survivin, and VEGF release by ELISA. In vitro tumorigenicity was evaluated. Animals were treated with vehicle or Src kinase and EGFR inhibitors with gemcitabine and imaged by ^{18}FLT PET/CT. Drug delivery was analyzed by MALDI-MS.

Results: STAT3 activation is necessary for the malignant phenotype and affects survival in PDAC. In both human and mouse PDAC cell lines and tissues, there is an inverse correlation between activation of STAT3 and MAPK. Complete inhibition of activated STAT3, reciprocally activates MAPK, Src and EGFR. Targeting both STAT3 and MAPK, completely inhibits pSTAT3, pSrc and pEGFR activation. Combined inhibition of STAT3 and MAPK overcomes STAT3 mediated resistance and results in synergistic inhibition of c-Myc, Cyclin-D1, Survivin and VEGF. Optimal inhibition of proliferation, migration or invasion was seen with the combined treatment of STAT3 and MAPK inhibitors as compared to treatment with monotherapy.

Conclusions: STAT3 inhibition results in MAPK activation which leads to reactivation of Src and EGFR signaling and subsequent STAT3 reactivation. Combined STAT3 and MAPK inhibition results in sustained inhibition of STAT3, MAPK, Src and EGFR signaling and tumorigenicity. These results provide mechanistic evidence demonstrating MAPK as a mediator of therapeutic resistance to STAT3 inhibition. Targeting STAT3 and MAPK may be a potent treatment regimen for PDAC.