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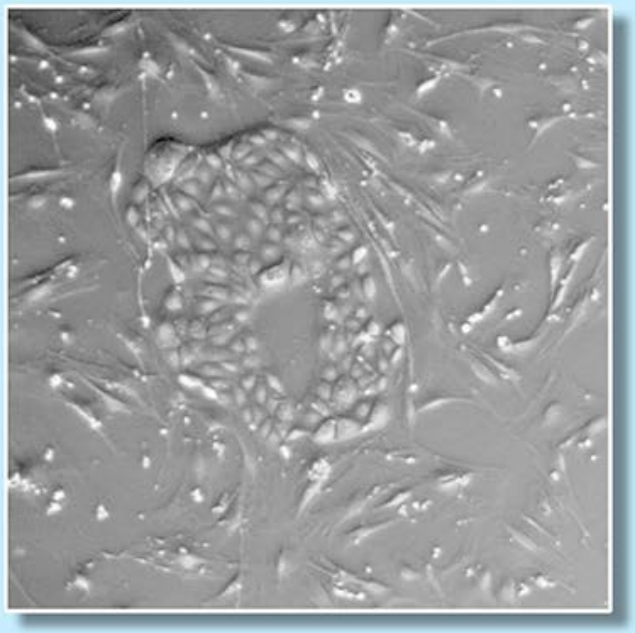

Pancreatic Cancer Patient-derived Xenograft Cells in Culture

Inhibiting JNK in Combination with FOLFOX Chemotherapy Synergistically Suppresses Pancreatic Cancer Cell Growth

Pancreatic cancer is the 3rd leading cause of cancer deaths in the United States. A cocktail combining folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) has an established efficacy in treating pancreatic ductal adenocarcinoma (PDAC) and is amenable to further drug combination, but the cellular signaling response to FOLFOX has not been determined. This study investigates the pathway involving c-Jun N-terminal Kinases (JNK), which previous data suggest is upregulated following FOLFOX treatment. We hypothesized that PDAC cells resist FOLFOX chemotherapy treatment in part by upregulating JNK, and that inhibiting this pathway could act synergistically with FOLFOX to treat PDAC. Patient-derived xenograft cell lines were treated with varying doses of either FOLFOX, an irreversible inhibitor of JNK, or both. Western blotting was then used to quantify the amounts of JNK, c-Jun, and other kinases and compare these values between the different treatments. We found that JNK and its downstream effector c-Jun are rapidly (within 4 hours) upregulated in response to FOLFOX treatment. In addition, irreversible inhibition of JNK led to the rapid inactivation of c-Jun. Furthermore, an MTT cell viability assay was performed on the same treatment groups, which showed that FOLFOX and irreversible inhibition of JNK synergize to inhibit cell line growth. These findings suggest that targeting JNK using an irreversible inhibitor could act synergistically with FOLFOX to treat PDAC.