Focal Adhesion Kinase Inhibition Enables Efficacy of Checkpoint Immunotherapy in Pancreatic Cancer

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ABSTRACT

Checkpoint immunotherapies are promising agents with the potential to improve patient outcomes in several types of cancer. Unfortunately, to date, single-agent immunotherapy has achieved limited clinical benefit in patients with pancreatic ductal adenocarcinoma (PDAC). This may be due to the presence of the uniquely immunosuppressive tumor microenvironment present in PDACs, which creates a barrier to immune surveillance by T cells. Critical obstacles to immunotherapy in PDAC tumors include the dense desmoplastic stroma that acts as an immune T cell infiltration, and high numbers of tumor-associated immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs).

To understand which signaling pathways in pancreatic cancer cells might drive this suppressive tumor microenvironment, we analyzed the correlation between high-density signaling molecules and tumor-infiltrating leukocytes using tumor tissue from 50 PDAC patients. Of the pathways evaluated, we found that focal adhesion kinase (FAK) activity was elevated in human PDAC, which was correlated with highly fibrotic tumors with poor CD8+ T cell infiltration. The end FAK kinase inhibitor VS-4718 and FAK shRNA in the tumor cells were each effective in reducing FAK activity in fibroblasts. Importantly, the FAK inhibitor VS-4718 and FAK shRNA in the tumor cells were each effective in increasing CD8+ T cell infiltration into the PDAC tumors in vivo. Taken together, these data suggest that FAK inhibition increases immune surveillance programs in PDAC tumors by overcoming the fibrotic and immunosuppressive microenvironment, rendering tumors more responsive to immunotherapy. These data provide rationale for the clinical evaluation of a FAK inhibitor in combination with checkpoint immunotherapies in patients with pancreatic and other cancers.

CONCLUSIONS

• We are now testing this approach clinically. (see NCT-02546531 on clinicaltrials.gov)

Future Directions

• FAK inhibition renders previously unresponsive pancreatic tumors sensitive to immunotherapy.