Targeting TAK1 for intercepting PanIN progression to ductal adenocarcinoma in an inducible KC mouse model

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Despite advances in our knowledge of human pancreatic ductal adenocarcinoma (PDAC), targeted therapies have not yet significantly translated to an improved overall survival for patients. Pancreatic tumor microenvironment enriched by infiltrating immune cells and consisting of dense fibrotic stroma is characterized by desmoplasia, the major contributors of tumor-associated inflammation. Transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) is widely accepted as a key player in the TNF-α and TGF-β-induced signaling, and principal contributor of tumor fibrosis, inflammation and cell proliferation. Here, we show that pancreatic tumors over-express TAK1, and are associated with fibrotic-stroma and infiltrating immune cells. Also, p-TAK1(ser412) expression is correlated with progression of pancreatic intraepithelial neoplasia (PanIN) lesions to PDAC. Thus, we hypothesized TAK1 as an important target for inhibition of the tumor-associated fibrosis, inflammation and PanIN progression to PDAC.

To prove above hypothesis, we tested a selective TAK1 inhibitor, Takinib for its toxicity and efficacy against PanIN progression in the inducible Ptf1CreERT.LSL-KrasG12D (KC) mouse model. Takinib was synthesized and fed to wild type C57BL/6J mice (n=6) at 250 ppm and 500ppm in diet for 6 weeks to determine toxicity. Bodyweight gain, organ weights and serum enzyme analysis did not indicate any toxicity at the tested doses. For efficacy study, LSL-KrasG12D mice were bred with Ptf1-CreERT mice. Pups were genotyped and randomized to groups (n=12). PanINs-PDAC was induced in the KC mice by tamoxifen (oral gavage) followed by 250ppm Takinib administration in diet for 20 weeks. After termination, pancreas tissue sections were evaluated for PanIN multiplicity and PDAC incidence/spread. Administration of Takinib led to significant reduction in PanIN 1 by 54% (p<0.02), PanIN 2 by 77% (p<0.001) and PanIN 3 by 80% (p<0.02) in the KC mice compared to untreated mice. PDAC incidence was also reduced with an increase in normal pancreas in Takinib administered KC mice. Taken together our results suggest that TAK1 is a valuable target for PDAC, and Takinib possesses efficacy against the PanIN and PDAC progression in the KC mouse model warranting further studies.

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