Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive neoplasm characterized by a marked fibro-inflammatory microenvironment, the presence of which can promote both cancer induction and growth. Therefore, selective manipulation of local cytokines is an attractive if unrealized therapeutic approach. T cells possess a unique mechanism of activation of p38 MAPK downstream of T cell receptor (TCR) engagement by phosphorylation of Tyr-323 (pY323). This alternative p38 activation pathway is required for pro-inflammatory cytokine production. Here we show in human PDAC that a high percentage of infiltrating pY323$^+$ T cells was associated with large numbers of TNFα and IL-17-producing CD4$^+$ tumor-infiltrating lymphocytes (TIL) and aggressive disease. The growth of murine pancreatic tumors was inhibited by genetic ablation of the alternative p38 pathway, and transfer of wild type CD4$^+$ T cells but not those lacking the alternative pathway enhanced tumor growth in T cell-deficient mice. Strikingly, a plasma membrane-permeable peptide derived from Gadd45α, the naturally-occurring inhibitor of p38 pY323$^+$, reduced CD4$^+$ TIL production of TNFα, IL-17A, IL-10, and secondary cytokines, halted growth of implanted tumors, and inhibited progression of spontaneous K-ras-driven adenocarcinoma in mice. Thus, TCR-mediated activation of CD4$^+$ TIL results in alternative p38 activation and production of pro-tumorigenic factors, and can be targeted for therapeutic benefit.