Abstract

Purpose: Metastasis remains a major hurdle in treating aggressive malignancies such as pancreatic ductal adenocarcinoma (PDAC). Improving response to treatment, therefore, requires a more detailed characterization of the cellular populations involved in controlling metastatic burden.

Experimental design: PDAC patient tissue samples were subjected to RNA sequencing analysis to identify changes in immune infiltration following radiotherapy. Genetically engineered mouse strains in combination with orthotopic tumor models of PDAC were used to characterize disease progression. Flow cytometry was used to analyze tumor infiltrating, circulating, and nodal immune populations.

Results: We demonstrate that although radiotherapy increases the infiltration and activation of dendritic cells (DC), it also increases the infiltration of regulatory T cells (Treg) while failing to recruit natural killer (NK) and CD8 T cells in PDAC patient tissue samples. In murine orthotopic tumor models, we show that genetic and pharmacologic depletion of Tregs and NK cells enhances and attenuates response to radiotherapy, respectively. We further demonstrate that targeted inhibition of STAT3 on Tregs results in improved control of local and distant disease progression and enhanced NK-mediated immunosurveillance of metastasis. Moreover, combination treatment of STAT3 antisense oligonucleotide (ASO) and radiotherapy invigorated systemic immune activation and conferred a survival advantage in orthotopic and metastatic tumor models. Finally, we show the response to STAT3 ASO + radiotherapy treatment is dependent on NK and DC subsets.

Conclusions: Our results suggest targeting Treg-mediated immunosuppression is a critical step in mediating a response to treatment, and identifying NK cells as not only a prognostic marker of improved survival, but also as an effector population that functions to combat metastasis.