ADAPTING ORTHOTOPIC MURINE MODELS OF PANCREATIC CANCER TO ENHANCE ADOPTIVE T CELL IMMUNOTHERAPY

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Background Pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumor with poor prognosis and low survival in patients (~12% at 5-years). Immunotherapy approaches, including adoptive T cell therapy, have not appreciably impacted PDAC patients. This poor outcome is due in part to the hostile tumor microenvironment (TME) which limits T cell trafficking and persistence. We posit that murine models serve as useful tools to study the fate of adoptively transferred T cells in vivo. Currently, genetically engineered mouse models (GEMM) for PDAC are considered a ‘gold-standard’ given their ability to recapitulate many aspects of human disease. However, these models have limitations, including marked tumor variability across individual mice and cost of colony maintenance.

Methods We characterized the immunologic features and evaluated trafficking of adoptively transferred T cells into orthotopic models using two mouse cell lines, KPC-Luc and MT-5, isolated from KPC-GEMM mouse models (Kras^{LSL-G12D/+}p53^{-/-} and Kras^{LSL-G12D/+}p53^{LSL-R172H/+}, respectively). These cells were implanted into the pancreas of syngeneic, immune competent, C57BL/6 mice and features of the TME were assessed. We engineered murine T cells with a lentiviral vector encoding a chimeric antigen receptor targeting murine mesothelin and signals CD3\(\zeta\) and 41BB (Meso -41BB\(\zeta\)-CAR T cells). Cells were adoptively transferred into mice bearing orthotopic KPC-Luc or MT-5 tumors following lymphodepletion via total body irradiation.

Results Although tumors are driven by both oncogenic Kras and harbored similar genetic insults to the trp53 gene, the MT-5 orthotopic model best recapitulates the cellular and stromal features of the TME found in PDAC GEMM. In contrast, the KPC-Luc model demonstrates significantly more immune infiltration (CD4\(^+\) and CD8\(^+\) T cells; F4/80\(^+\) cells) and less stroma (\(\alpha\)-smooth muscle actin, Picosirius red). The MT-5 model had similar immune infiltration (CD4\(^+\) T cells: 2.5\% ± 2 in KPC-GEMM and MT-5 vs 7.5\% in KPC-Luc tumors, \(p<0.005\)) and stromal protein content upon flow cytometry and histological analysis versus the KPC-GEMM. Analysis of tumor infiltrating lymphocytes (TIL) revealed the stroma-rich MT-5 orthotopic mouse model, but not the KPC-Luc mouse model, had limited infiltration of Meso-CAR T cells (15\% ± 15 live cells in KPC-Luc vs 1\% ± 2 in MT-5 tumors, \(p<0.01\)).

Conclusions Our data establish reproducible models that are useful for modeling stroma-rich and stroma-devoid PDAC tumors and enable in-depth study of how to overcome barriers that limit anti-tumor activity of adoptively transferred T cells. Ongoing studies are also interrogating how similar genomic profiles of PDAC tumors influence immune cell composition in the TME.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0267