Abstracts

341 γδ T CELLS SUPPORT PANCREATIC CANCER IMMUNITY BY ENHANCING αβ T CELL ACTIVATION

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Background The prognosis for pancreatic ductal adenocarcinoma (PDAC) remains dismal due to limited options for surgical resection, as well as minimally effective treatments for patients presenting with advanced disease.1 PDAC is remarkably resistant to immunotherapies due, in part, to a hostile tumor microenvironment, characterized by poor antigenicity, low mutational burden, and MHC class I defects.2 The value of patient-derived organoids (PDOs) centers on their ability to recapitulate the parental tumor, positioning PDOs as a promising technology to support personalized therapy initiatives.3 We aim to improve outcomes in patients with PDAC by advancing combination cell immunotherapies, utilizing PDOs to assess tumor-specific reactivity of expanded T cell products.

Methods PDOs were established from resected primary PDAC tissue. Tumor infiltrating lymphocytes (TILs) were simultaneously expanded from the resected tissue in G-REX gas permeable membrane culture systems in two phases. Prior to the initiation of the second phase, γδ T cells were negatively selected from harvested bulk TILs. The γδ-enriched and bulk TIL fractions were then rapidly expanded in separate cultures for 14 days, followed by phenotyping to identify TIL composition and immunoassays to assess TIL reactivity toward autologous PDOs.

Results Both αβ and γδ TILs were successfully expanded ex vivo 200- to 1200-fold from PDAC tissue (figure 1A). Whereas the bulk TIL cultures consisted primarily of αβ TCR+ cells, the γδ-enriched population was comprised of varying proportions of NK, αβ TCR+ , and γδ TCR+ cells (figure 1B). Interestingly, γδ TILs appeared to play an important ex vivo helper role, as αβ TCR+ cells expanded in the presence of γδ TILs demonstrated a decreased CD4:CD8 ratio (figure 1C), as well as an enhanced activation profile, with upregulation of CD27, CD56, 4–1BB, and NKG2D (figure 1D). Tumor organoids exhibited the tissue architecture and cellular morphology of ductal adenocarcinoma on H&E staining, namely, ductal structure and prominent nucleoli, confirming malignancy as determined by pathologist review (figure 2A). Both TIL cultures were functionally active, producing IFNγ following mitogenic stimulation; however, the γδ-enriched population was more potent than αβ TILs in specifically recognizing and lysing autologous PDO targets (figure 2B, C). Importantly, infiltration of γδ T cells within pancreatic tumor tissue, assessed in the TCGA database, is associated with improved overall survival (figure 2D).

Conclusions Together, these findings highlight the potential benefit from adoptive cell transfer of expanded γδ TILs—perhaps coupled with αβ TILs—in patients with PDAC.

REFERENCES

Ethics Approval All participants provided written informed consent prior to inclusion in this study, which was approved by the Institutional Review Board at the University of Pittsburgh (MOD20040316–006).

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Abstract 341 Figure 1 γδ TILs play an important ex vivo helper role, enhancing activation of αβ TCR+ cells. (A) Both αβ and γδ TILs were successfully expanded ex vivo 200- to 1200-fold from PDAC tissue. (B) The bulk TIL cultures consisted primarily of αβ TCR+ cells, whereas the γδ-enriched population was comprised of varying proportions of NK, αβ TCR+ , and γδ TCR+ cells. (C, D) Interestingly, γδ TILs appeared to play an important ex vivo helper role, as αβ TCR+ cells expanded in the presence of γδ TILs demonstrated a decreased CD4:CD8 ratio and an enhanced activation profile, with upregulation of CD27, CD56, 4–1BB, and NKG2D. Statistical significance was determined by the paired Student’s t test.

Abstract 341 Figure 2 γδ-enriched TILs more potently recognize and lyse autologous PDO-targets. (A) Representative brightfield microscopy image highlighting the varying size, shape, and density within an organoid culture. Tumor organoids exhibited the tissue architecture and cellular morphology of ductal adenocarcinoma on H&E staining, namely, ductal structure and prominent nucleoli, confirming malignancy as determined by pathologist review. (B, C) Both TIL cultures were functionally active, producing IFNγ following mitogenic stimulation; however, the γδ-enriched population was more potent than αβ TILs in specifically recognizing and lysing autologous PDO targets. Statistical significance was determined by the paired Student’s t test. (D) Infiltration of γδ T cells within pancreatic tumor tissue, assessed in the TCGA database, is associated with improved overall survival.