Mucosal-associated invariant T (MAIT) cells sensing bacterial metabolites are involved in defense against pathogens and tumors. However, their role in pancreatic ductal adenocarcinoma (PDAC) is unknown. PDAC is a highly lethal malignancy with a 5-year survival rate of around 12%, largely due to late diagnoses.

High dimensional flow-cytometry of PBMCs obtained from PDAC, pancreatitis patients, and healthy donors (HD) revealed a decrease in circulating MAIT cell abundance in PDAC compared to HD, while an increase in tumor compared to healthy adjacent tissue, indicating an infiltration of PDAC tissue by MAIT cells.

The heightened intratumoral MAIT presence positively correlated with longer patient survival, increased $CD8^+$ T cell presence, and a classical PDAC subtype, while inversely with a basal subtype and activated fibroblasts abundance, suggesting a possible contribution of MAIT cells to the classical PDAC. In the presence of bacterial metabolites MAIT cells were activated by PDAC cells, which expressed the monomorphic MHC class I-related protein 1 (MR1), a key antigen-presenting protein for MAIT cells. The cytokine environment created during the disease influenced the MAIT heterogeneity. Whereas MAIT17 subtype was dominating in HD, in PDAC exhausted MAIT1 phenotype was induced at the expense of MAIT17 cells. This shift resulted in impaired PDAC protection since MAIT17 but not exhausted MAIT1 subtype correlated with a better patient survival. Analysis of PDAC patient serum revealed a correlation of IL-12 and IL-18 levels with MAIT1 and MAIT17 frequencies, respectively, suggesting their involvement in the MAIT diversification.

Thus, our data uncover, an infiltration of PDAC tissue by MAIT cells, their activation by tumor cells, and a cytokine-environment-driven diversification of their phenotype, influencing patient survival. Therefore, modulation of the cytokine environment to stabilize the protective MAIT17 subtype might be a new option for PDAC therapy.