ENGINEERING OPTIMAL CAR T CELLS TO OVERCOME PANCREATIC TUMORS WITH SECRETED ANTAGONISTIC PEPTIDES

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Background Chimeric antigen receptor (CAR) T cell therapies have shown remarkable clinical efficacy in hematological cancers, but still face significant obstacles in the treatment of solid tumors such as pancreatic ductal adenocarcinoma (PDAC). Two hurdles in developing effective CAR T therapies for PDAC are the identification of ideal tumor-associated antigens (TAA) to target and overcoming a complex tumor microenvironment (TME). We hypothesize that the optimal CAR T cell to treat PDAC both recognizes an ideal TAA and is protected from immune suppression from the TME. Here, we propose the ectodomain of Muc16 (Muc16CD) as a viable TAA expressed in PDAC tumors (figure 1) and antagonizing vasoactive intestinal peptide (VIP), an immunosuppressive neuropeptide, to overcome the PDAC TME.

Methods CAR T cells were generated to specifically target Muc16CD and express a novel, potent VIP receptor (VIPR) antagonist (antVIPR) peptide. CAR T cells were assayed in vitro and in vivo against human VIP-expressing PDAC cell lines (Panc1) and PDX cell lines.

Results We first assayed patient-derived xenograft (PDX) PDAC cell lines for Muc16CD and VIP expression to establish the clinical relevance of these targets (figure 1). Interestingly, despite modest Muc16CD expression on PDX lines, anti-Muc16CD CAR T cells had cytotoxic function in vitro (figure 1) and reduced tumor burden in mice engrafted with orthotopic PDX PDAC tumors. Next, we investigated whether VIP is immunosuppressive for CAR T cell function. VIP limits the proliferative capacity of CAR T cells, which can be reversed by treatment with VIPR antagonist peptides. We therefore engineered novel antVIPR-secreting CAR T cells that provide continuous and localized delivery of antVIPR peptides within the TME. AntVIPR expression by CAR T cells impacts their phenotype as these cells have improved cell viability and express less VIP and VIPRs at baseline. Functionally, antVIPR CAR T cells have a proliferative advantage after antigen-stimulation and enhanced activation compared to parental CAR T cells. Finally, treatment with antVIPR CAR T cells reduces tumor burden and improves overall survival in mice bearing human VIP-expressing PDAC tumors (figure 2).

Conclusions Collectively, this data demonstrates that the combination of targeting Muc16CD and VIP with a novel CAR T cell can improve anti-tumor efficacy against PDAC. Ongoing experiments are determining the mechanisms by which locally secreted VIPR antagonists can modulate the PDAC TME using an orthotopic syngeneic PDAC mouse model with the long-term goal of translating antVIPR-secreting CAR T cells for the treatment of PDAC.

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REFERENCES
(purple) show improved survival compared to parental anti-Muc16CD CAR T cells (red).