961 TUMOR-INFILTRATING MUCOSAL-ASSOCIATED INVARIANT T CELLS (MAIT) FROM PATIENTS WITH PANCREATIC CANCER RECOGNIZE SHARED TUMOR ANTIGENS IN AN MR1-RESTRICTED FASHION

[1]Jéssica Kamiki*, [1]Patrícia António, [1]Rodrigo Eduardo, [1]Sara Cascais, [1]Bernardo Marinheiro, [1]Andreia Maia, [1]Eric De Sousa, [1]Joana Lerias, [1]Carolina Gorgulho, [1]Mireia Castillo-Martin, [1]Markus Buechler, [1]Antonio Beltran, [1]Carlos Carvalho, [2]Ridong Chen, [2]Sam Jeong, [1]Markus Maeurer. *[1]Champalimaud Foundation, Lisbon, Portugal; [2]Human Cell Inc., Napperville, IL, United States*

Background Pancreatic adenocarcinoma (PDAC) is one of the most lethal cancers with a 5-year survival rate of 10%.[1] Standard chemotherapeutics have failed to produce relevant increased survival for patients with pancreatic cancer.[2] Cellular immunotherapies are a viable option to achieve anti-tumor directed clinically relevant treatment modalities.

Mucosal-associated invariant T-cells (MAIT) are defined by the restricted usage of the invariant Vα7.2 T-cell receptor (TCR) α-chain combined with different TCR β-chains that bridge innate and adaptive immune responses. MAIT produce pro-inflammatory cytokines[3,4] and are present in primary and metastatic cancer lesions.[4,5] MAIT may contribute to control malignant cells by either MR1-restricted recognition of cancer cells and/or by production of anti-cancer directed cytokines induced by tumoral-associated bacterial species. A set of bacterial species has been associated with improved survival in patients with PDAC.[6,7] We studied the role of MAIT in tumor-infiltrating lymphocytes (TIL) from patients with PDAC.

Methods MAIT were identified in PDAC specimens by immunohistology. Freshly harvested tumor specimen allowed to expand TILs from patients with PDAC and to selectively isolate MAIT by immunomagnetic sorting. MR1-restricted recognition and cancer specificity was tested in an autologous tumor cell recognition model- blocked by antibodies against MR1 and in a MR1+ allogeneic tumoral cell line via MR1-siRNA downregulation defined by IFN-γ production. Phenotypic and functional analysis of MAIT was carried out by flow cytometry and ELISAs. Deep TCR-sequencing of tumor tissue and TIL was performed to gauge TCR diversity and spatial transcriptomics to localize Vα7.2 cells associated with MR1 and immune effector gene expression.

Results PDAC lesions are positive for MR1 and Vα7.2+ cells defined by immunohistology and spatial transcriptomics. MAIT were isolated and found to be specifically reactive against autologous tumor determined by IFN-γ and IL-17A production. The majority of MAIT resided in the effector-memory pool (CD45-CCR7-) and tested positive for CD8, CD161 and CD26. Reactivity against a panel of candidate bacteria associated with patient survival was confirmed by cytotoxicity and a CD107a degranulation assay.

Conclusions MAIT infiltrate into PDAC lesions, they recognize the tumor in a MR1-restricted fashion defined by IFN-γ release and cytokine production could be augmented by a defined set of bacterial species. MAIT represent biologically relevant immune cells that may aid to kill cancer cells. Anti-tumor directed TCRs can be used as a molecular blueprint to construct anti-cancer directed transgenic immune cells restricted by commonly shared MR1.

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Ethics Approval This study was approved by the Champalimaud Foundation Ethics Committee and by Ethics Research Committee of NOVA Medical School of NOVA University of Lisbon.

Consent For each patient, written informed consent and approval by the Ethical Committee of the Champalimaud Foundation will be obtained. The study will be in compliance with the Declaration of Helsinki.

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