NON-CANONICAL PEPTIDE SOURCES BROADEN THE LANDSCAPE OF TARGETABLE ANTIGENS IN Pancreatic CANCER


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Background Aberrant translation of the non-coding genome in cancer can generate novel peptides capable of presentation by major histocompatibility complex class I (MHC-I; HLA-I in humans) and these non-canonical peptide sources can broaden the landscape of potentially targetable antigens in low-to-intermediate mutational burden malignancies. While emerging evidence suggests that translation of unannotated open reading frames (uORFs) can give rise to MHC class I-associated peptides (MAPs) across a range of malignancies, it is currently unknown to what extent these translation products are truly cancer-restricted and how effectively the resulting non-canonical MAPs (ncMAPs) can elicit a T cell response.

Methods We leveraged twelve pancreatic cancer (PDAC) patient-derived organoids (PDOs) to purify the malignant compartment from low tumor cellularity tumor specimens. We developed a cutting-edge proteogenomics pipeline, coupled with high-depth immunopeptidomics to identify pancreatic cancer MAPs derived from somatic mutations, retained introns, and uORFs. To investigate the cancer-specificity of ncMAPs, we developed a translation-centric analysis pipeline that examines translation of uORFs encoding ncMAPs across a range of healthy tissues, including healthy thymus. To evaluate for immunogenicity, we employed a highly sensitive ex vivo platform to prime and expand ncMAP-specific cytotoxic T lymphocytes (CTLs) and evaluate cytolytic potential.

Results We demonstrate that ncMAPs are abundant and predominate over mutation-derived peptides in the pancreatic cancer immunopeptidome, establishing a novel class of recurrent cancer-restricted epitopes available for immune recognition. We observed widespread translation and MHC-I presentation of numerous ncMAPs across many healthy tissues, highlighting the importance of our translation-centric approach to assess cancer-restriction. Excitingly, we nominated over 500 ncMAPs that exhibit cancer-specific translation patterns. Approximately 30% of ncMAPs exhibited bona fide cancer-restricted translation patterns, and a substantial subset of these were shared among patients. We next interrogated immunogenicity using a highly sensitive ex vivo vaccination platform and demonstrated that the majority of cancer-restricted ncMAPs evaluated were highly immunogenic. Remarkably, the proportion of ncMAPs harboring immunogenic potential was substantially higher than mutation-derived neoepitopes and tumor-associated antigens, underscoring their therapeutic potential relative to traditional immunotherapy targets.

Conclusions These findings demonstrate that aberrant translation in pancreatic cancer can give rise to recurrent cancer-restricted ncMAPs capable of recognition by cytotoxic T lymphocytes. Collectively, our findings furnish a novel set of recurrent, cancer-restricted immunotherapy targets not subject to central tolerance. We believe these findings will prompt translation-centric investigations in other solid tumors. We envision that these novel antigens will augment ongoing efforts to treat pancreatic cancer patients with vaccines and cell-based therapies.

Ethics Approval Informed consent was obtained from patients at least 18 years old with pancreatic cancer under Dana-Farber/Harvard Cancer Center Institutional Review Board (IRB)-approved protocols 11–104, 17–000, 03–189, and/or 14–408 for tissue collection, molecular analysis, and organoid generation.

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