PATIENT-DERIVED TUMOR ORGANOID REVEAL MECHANISMS OF IMMUNE EVASION WHICH CAN GUIDE DECISIONS IN ADOPTIVE CELL THERAPY FOR COMMON EPITHELIAL CANCERS

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Background Adoptive cellular transfer (ACT) of autologous tumor-infiltrating lymphocytes (TIL) is capable of inducing durable clinical responses in patients with advanced solid malignancies,¹ however response rates are low. Limitations in personalized cancer modeling have been obstacles to understanding tumor-specific mechanisms of immune evasion. Patient-derived tumor organoids (PDO) can be efficiently grown from common solid tumors and show genetic fidelity to whole exomic sequencing (WES) of the source tumor. We investigated their use in evaluating patient-specific immune responses in vitro and selecting T-cells for adoptive cellular immunotherapy.

Methods PDO were established from metastatic deposits from patients with colorectal, breast, and pancreatic cancers and with their tumors of origin, were subjected to WES and RNAseq. They were then included in immunologic recognition assays with autologous TIL and cloned T-cell receptors (TCR) against shared mutations. TIL neoantigen reactivity was defined by screening against mutations using minigenes or synthetic peptides expressed by autologous antigen presenting cells.

Results PDO were successfully grown from 18/22 tumors from 15 patients. These cultures demonstrated a high degree of genetic fidelity to their parental tumors with near-complete retention of clonally expressed mutations. Organoid lines from 11 of these patients were utilized in recognition screening with autologous TIL or PBL transduced with relevant TCRs. TIL recognized 5/7 organoids tested, and this allowed the isolation and cloning of many of the TCRs responsible. Nineteen available TCRs predicted to be reactive with patient-specific neoantigens were also tested against relevant organoids, and only nine were found to be reactive. In most instances where such TCRs could not recognize organoid, tumor-specific defects in neoantigen processing or presentation or HLA-LOH events were either functionally or genetically identified.

Conclusions To improve response rates to neoantigen-directed adoptive T-cell therapy, a better understanding of tumor immune evasion mechanisms is needed. The inability to grow autologous tumor lines from common epithelial cancers has been a major obstacle. We demonstrate that PDO can be efficiently established and are genetically representative of their parental tumors. Importantly, these organoids can reveal defects in neoantigen processing or surface presentation as well as HLA loss-of-heterozygosity that would preclude immune recognition. PDO may be a valuable tool for screening for tumor reactivity and selecting T-cells and TCRs for clinical use.

Trial Registration The study protocol was registered under <https://clinicaltrials.gov> under NCT00068003.

REFERENCE

1. Zacharakis N, Chinnasamy H, Black M, et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. *Nat Med*. 2018;**24**:724–730.

Ethics Approval All samples were derived from study participants who granted written, informed consent to be enrolled

on a clinical protocol approved by the Institutional Review Board at the NCI (Bethesda, MD).

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