EDITORIAL

A Pancreatic Cancer Patient-Derived Xenograft Model for Adoptive Immunotherapy Using Autologous Tumor-Infiltrating Lymphocytes

Pancreatic cancer, in particular pancreatic ductal adenocarcinoma (PDAC), shows a devastating prognosis with a five-year survival rate less than 11%,[1] and it is projected to become the second leading cause of cancer-related deaths by 2040.[2] Available treatment options such as polychemotherapies as well as targeted agents demonstrate limited clinical efficacy in PDAC patients.[3–5]

In the past years, immunotherapies have demonstrated promising results for the treatment of solid cancers such as melanoma,[6] esophageal cancer,[7] and colorectal cancer;[8] however, only marginal efficacy was observed in pancreatic cancer patients.[9] This is likely due to its highly immunosuppressive tumor microenvironment[10] and a comparatively low mutational burden.[11] Still, the presence of tumor-infiltrating lymphocytes (TILs), in particular $CD8^+$ cytotoxic T cells, is associated with better clinical outcomes and increased overall survival in PDAC.[12] On the contrary, $Foxp3^+$ TILs are linked to worse prognosis in PDAC patients.[13] Various studies are now focusing on using adoptive cell therapies (ACTs), in which autologous TILs are isolated from patients and expanded/engineered in vitro to be reinfused in large numbers to potently attack tumor cells. Current clinical trials, however, show mixed efficacy of ACT therapies in PDAC cases, underscoring the urgent need to model and mechanistically decipher the interaction between pancreatic tumor cells and TILs.[14]

In this issue, a study by Nilsson et al employed *IL2*-humanized-NOG (non-obese severe combined immune deficient interleukin-2 chain receptor γ knockout mice) patient-derived xenografts (PDXv2s) to model autologous TIL-based therapy for PDAC.[15] From 29 patient biopsies, percutaneous transplantation into immunocompromised NOG mice resulted in 11 PDX tumors. In line with previous results,[16] PDX tumors displayed histological similarities to the parental tumors. In addition, PDX tumors maintained their transcriptional subtype, in terms of classical and basal-like signatures,[17] as well as mutational alterations. Applying deconvolution to bulk RNA sequencing results revealed that PDX tumors lost patient-derived immune and stroma cells, which correlated with the absence of expression of HLA-A/-B/-C by immunohistochemistry. In parallel to tumor growth in PDX models, autologous TILs were expanded in vitro. This expansion process was successful in 6 biopsy samples in which PDX tumors ($n = 11$) were also available. As previously demonstrated by the group for melanoma, long-time survival and antitumor activity of injected autologous TILs require a constant source of IL2 in vivo.[18] Therefore, analogous to their melanoma model,[18] in vitro expanded autologous TILs were transplanted into PDAC-bearing PDXv2 mice. Importantly, in 3 out of 6 PDXv2 mice, tumor regression was observed after ACT. PDXv2 mice not receiving TILs showed no tumor regression.

Limitations of this study include that the authors did not further characterize the expanded patient-derived TILs regarding T-cell type ($CD4^+$ or $CD8^+$ cells). As the authors of the study discussed, Poschke et al showed a clonal selection process occurring during TIL expansion, which leads to a loss of predominant TILs and an outgrowth of newly emerging TILs resulting in a reduced tumor-killing capacity.[19] This might explain why in 3 out of 6 treated PDXv2 mice, TIL infusion was not effective in tumor reduction.

Overall, this model is an exciting and promising tool to explore adoptive immunotherapies for PDAC, allowing to improve therapeutic efficacy of TILs possibly by genetic engineering. Another avenue might be to perform and investigate combinatorial treatments such as a combination of chemoradiation and immune checkpoint inhibition which is also currently being tested in early clinical trials of pancreatic cancer.[20] In the future, larger preclinical cohorts are needed in order to validate the efficacy of TIL-based treatment and investigate underlying molecular mechanisms as well as possible selection criteria which ultimately are needed for successful translation into the clinic and improvement of PDAC patient care.

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