Unconventional T Cells in the Pancreatic Tumor Microenvironment: Thinking Outside the Box

Sulagna Banerjee, Vikas Dudeja, and Ashok Saluja

Summary: Unlike conventional MHC-reactive T cells, unconventional T cells have emerged as an abundant component of the human immune system because of their role in tumor immunology. In this issue of Cancer Discovery, Hundeyin and colleagues have identified a population of unconventional T cells in pancreatic tumors that can reprogram the immune evasive components of the tumor to promote immunogenicity and thus are critical for the development of novel cell-based therapy in pancreatic cancer.

See related article by Hundeyin et al., p. 1288 (8).

Pancreatic cancer is among the most challenging cancers to treat. As of now, it is the third leading cause of cancer-related death in United States, with an extremely poor prognosis. Although the successful incorporation of immunotherapy in other solid tumors has resulted in better outcomes, pancreatic tumors have remained unresponsive to this line of treatment (1). Poor antigenicity of pancreatic tumor cells, which involves the ability of T cells to recognize malignant cells as foreign and thereby elicit their destruction, is considered to be one of the main reasons for the unresponsiveness of pancreatic tumors to immunotherapy (2). In addition, the robust fibroinflammatory stroma in pancreatic tumors contributes to poor response to therapy in these patients. In its unique microenvironment, with a robust extracellular matrix, inflammatory and myo-fibroblastic cells are not only deterrents for successful delivery of chemotherapy, but also affect the infiltration and function of the immune cells (3).

In all cancers, T cells have been the central focus of cancer immunotherapy. The majority of cancer immunotherapy studies have pivoted on conventional CD8αβ T cells that recognize peptide antigens presented by MHC1 molecules. In response to the tumor and its microenvironment, T cells become activated, undergo clonal expansion, and differentiate into cytotoxic T lymphocytes that have the ability to target and destroy tumor cells with specific tumor peptide–MHC Class I complexes. These responses can be further augmented by engaging CD4+ T cells to help against MHC Class II–restricted tumor peptide antigens (4). However, MHC molecules are highly polymorphic, having the ability to bind to a diverse array of peptides. Similarly, the responding T-cell antigen receptors (TCR) are equally complex and diverse, resulting in a complex, difficult-to-monitor T-cell repertoire (5). In pancreatic cancer, the immune microenvironment becomes more challenging owing to the presence of the fibro-inflammatory stroma. Studies using the spontaneous pancreatic cancer mouse models have shown that leukocyte infiltration occurs as the tumor progresses. However, the majority of these leukocytes are immunosuppressive cell types like tumor-associated macrophages (TAM), myeloid-derived suppressor cells, and regulatory T cells. Effector T cells are largely lacking from the tumor microenvironment according to these studies (6, 7). Unconventional T cells and their therapeutic potential have been largely unexplored. These T cells, which are often characterized by repeated patterns of TCR usage in unrelated individuals, have long been implicated in tumor recognition and destruction. Thus, to fully understand and exploit the pancreatic tumor immune microenvironment, it is imperative not only to study the conventional immune population within the pancreatic tumors, but also to widen our horizons to include the unconventional T lymphocytes.

In this issue of Cancer Discovery, Hundeyin and colleagues (8) investigate the previously unexplored therapeutic potential of unconventional T cells in pancreatic tumor animal models. The authors show that TCRαβ CD4+ CD8αβ NK1.1 innate ab T cells (iαβT cells) represent about 10% of the T lymphocytes infiltrating the pancreatic tumor immune microenvironment. They further showed that infiltrated iαβT cells have a distinct immunomodulatory effect and express a distinct TCR repertoire. It is well known that classically activated M1 macrophages promote polarization of CD4+ T cells to a Th1 phenotype and facilitate the entry of CD8αβ T cells. In hypoxic pancreatic tumors, however, the increased lactate efflux from the tumor cells acidifies the microenvironment and leads to an alternatively activated M2 TAM phenotype that promotes a tolerogenic Th2 CD4+ phenotype, preventing the entry of CD8αβ T cells in the tumor and making it immune evasive (9) to further drive pancreatic tumor progression. In this study, the authors showed that iαβTcs reprogrammed macrophages in a CCR5-dependent manner to an immunogenic phenotype that enhanced CD4+ and CD8αβ effector T-cell function (Fig. 1).

Previous studies have shown that TAMs drive pancreatic tumor progression by enhancing immune suppression (10). In this study, the iαβTs on one hand induced a reduction of TAMs in the pancreatic tumor microenvironment and...
on the other hand induced proinflammatory phenotypes in remaining macrophages resulting in an increase in the effector T-cell population. Upon treatment with \( \text{i\textalpha\textbeta} \) Ts, TAMs upregulated antigen presentation and T-cell chemoattraction along with IFN, STAT1, and TNF signaling. This shifted the balance toward antitumor immunity in the tumor by reducing immune suppression and promoting activation of effector T cells. This made the \( \text{i\textalpha\textbeta} \) Ts attractive vehicles for cell therapy in pancreatic cancer.

One of the challenges in exploiting the immune microenvironment as a cell therapy is the lack of \textit{in vitro} models. To overcome that and determine whether \( \text{i\textalpha\textbeta} \) Ts have the ability to immunogenically reprogram adaptive immunity in patients, the authors generated patient-derived organotypic tumor spheroids (PDOTS) from freshly harvested human tumors. FACS-sorted \( \text{i\textalpha\textbeta} \) Ts are added to these PDOTS and analyzed after 3 days. This faithfully recreated an \textit{in vitro} T-cell activation model in human patient-derived specimens. This platform showed significant induction of immunogenic activation in 3-D human systems, which can be exploited as a novel adoptive cell therapy in pancreatic cancer.

Immunotherapy is currently considered to be the best approach for treating solid tumors. The poor immunogenicity of pancreatic tumors has prevented extensive use of this therapeutic strategy in this disease. The pancreatic tumor immune microenvironment and its function in its classic and conventional setting have shown that the tumor is largely immune-evasive. In this context, pursuing novel and unconventional T-cell populations (as highlighted in the article by Hundeyin and colleagues) that can reprogram the immune-evasive components of the tumor to promote immunogenicity is extremely timely and necessary for the development of novel cell-based therapy in pancreatic cancer.

Disclosure of Potential Conflicts of Interest

S. Banerjee is a consultant/advisory board member for Minneamrita Therapeutics. A. Saluja is the Chief Scientific Officer and co-founder of Minneamrita Therapeutics. No potential conflicts of interest were disclosed by the other author.

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