ISSN 2471-142X

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Editorial

PD-1/PD-L1 Blockade: A New Promising Therapy for the Treatment of Pancreatic Cancer?

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Article information
Received: February 28th, 2018; **Accepted:** March 1st, 2018; **Published:** March 1st, 2018

Cite this article
Gagliano N, Sommariva M. PD-1/PD-L1 blockade: A new promising therapy for the treatment of pancreatic cancer? *Pancreas Open J.* 2018; 2(1): e5-e7. doi: 10.17140/POJ-2-e007

Programmed cell death protein 1 (PD-1), a member of the CD28 family, is an immune-checkpoint receptor expressed on a variety of immune cells, such as T-cells, monocytes, B-cells, dendritic cells, and tumor-infiltrating lymphocytes (TILs).[1] PD-1 major role is to limit the activity of T-cells in peripheral tissues at the time of an inflammatory response to constrain autoimmunity and tissue damage.[1,2] Engagement of PD-1 by one of its two known ligands (PD-L1 and PD-L2) inhibits kinases involved in immune cell activation.[2] Interestingly, PD-1 has an opposite function in T_{reg} lymphocytes.[3]

In the tumor microenvironment (TME), PD-1/PD-L1 axis represents one of the mechanism utilized by tumor cells to avoid immune surveillance.[4] Many different tumors express high-level of PD-L1 including breast, urothelial, ovarian, cervical, colorectal, gastric, pancreatic, and non-small-cell lung cancer (NSCLC), melanoma, and glioblastoma.[5] PD-L1 is also expressed on tumor-infiltrating dendritic cells and macrophages. PD-L1$^+$ cells are able to induce T-cell apoptosis protecting tumor cells from being killed T-cells and interfering with PD-1/PD-L1 axis is described to reactivate the immune response against cancer.[6]

Immunotherapy with monoclonal antibodies targeting PD-1 or PD-L1 represents a powerful weapon in the oncology field. Clinical studies demonstrated that this type of therapy exerted benefits in different types of cancers. Durable objective (partial or complete) responses following anti-PD-1 therapy in patients with advanced melanoma (31-44% of patients), non-small-cell lung cancer (NSCLC; 19-20%) and renal cell carcinoma (RCC; 22-25%).[7-9]

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal human cancer, with a 7% 5-year overall survival rate, and represents the fourth leading cause of cancer-related deaths in the USA.[10] The 5-year survival for all stages of the disease remains <5%, due to the high incidence of recurrence and metastases dissemination. Even in early stages, pancreatic cancer is particularly difficult to treat. The primary therapeutic strategies include the surgical removal of the tumor and chemotherapy, but less than 20% of people with pancreatic cancer are eligible for surgery.[10,11] Moreover, the disease is often resistant to chemotherapy and chemoresistance is a very common phenomenon.[12] Current therapies remain poorly effective at treating late-stage disease; thus, there is an urgent need for new and effective treatment options for this type of cancer.

PDAC cells live in a TME playing a key role as a modulator of their phenotype, behavior, and chemoresistance. The TME contains extracellular matrix (ECM) components, growth factors and other soluble mediators, and different stromal cells including fibroblasts, inflammatory and pancreatic stellate cells as well as cells of the immune system, such as T- and B-lymphocytes, and tumor-associated macrophages, having either tumor-suppressive or tumor-promoting properties depending on the tissue context and cellular stimuli.[13-15] The immune system is strongly involved in cancer progression and resistance to therapy.[13,14]

Immunotherapy has emerged as a new therapeutic option in cancer treatment through its gradual acceptance as standard of care for hematological and solid malignancies, showing a potential to become a standard treatment for PDAC. Different clinical trials in pancreatic cancer using immune checkpoint inhibitors alone or in combination with other therapeutic agents are under clinical evaluation. However, results of early clinical trial showed that anti-PD-1/anti-PD-1 axis blockade as single-agent therapy (anti-PD-L1 monoclonal antibody) did not produce clinical benefits

in pancreatic cancer patients. The lack of efficacy of this type of therapy can be explained by the fact that pancreatic cancer creates a non-immunogenic tumor microenvironment, limiting the activity of immune checkpoint therapies and, indeed, it can be classified as "cold" tumor (from an immunological point of view).[16-18]

First, one of the most peculiar characteristics of pancreatic cancer is that the tumor cells represent only 20% of the tumor mass, while the remaining 80% is constituted by desmoplastic stroma.[19] This stroma is characterized by high infiltration of cells with immune suppressive activity such as myeloid-derived suppressive cells (MDSCs),[20] T-regulatory cells (T_{regs}),[21] and tumor-associated macrophages (TAMs).[22] They reduced the anti-tumor functionality of $CD8^+$ T-cells determining an impairment of tumor recognition and destruction. Indeed, they are reported to represent a mechanism of resistance to immune checkpoint therapy.[23]

Second, the mutational load in pancreatic cancer is very low compared with other tumor hystotypes. The cumulative mutational load determines the expression of neoantigens which are recognized and attacked by the immune system as non-self antigens.[24-26] Cancers with high mutational load can be recognized easier by immune cells, compared to cancer with low mutational load.[24]

Third, infiltrating T-cells in the microenvironment of pancreatic cancer do not provide sufficient T-cell responses. Although, a high number of $CD8^+$ T-cells is significantly associated with longer disease-free survival and overall survival in PDAC patients, in the majority of patients $CD8^+$ T-cells are scarce and/or show decreased expression of activation markers suggesting an impaired infiltration and/or quiescence of tumor-infiltrating T-cells.[14,23] Different mechanisms concur to determine the dysfunction of intratumoral T-lymphocytes. Due to their genomic instability, pancreatic cancer cells can modulate the expression MHC molecules making themselves less immunogenic.[27] They can also increase the expression of immune checkpoint receptor ligands (e.g., PD-L1) and upregulate immunosuppressive molecules (IL-10, IDO, TGF-β).[23,28,29]

Nowadays, PDAC remains a challenge for oncologist and immunotherapy may represent the future standard treatment for this type of cancer even if the available clinical data reported its inefficacy as single agents. However, understating the biological complexity of PDAC TME will allow to elucidating all the mechanisms of resistance to PD-1 signaling blockade therapy paving the way to the identification of new therapeutic combination strategies.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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