Editorial

# Current and emerging perspectives on immunotherapy for pancreatic cancer

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*Comment on:* Zhang Y, Velez-Delgado A, Mathew E, *et al*. Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer. Gut 2017;66:124-36.

**Abstract:** Pancreatic cancer (PC) is an extremely lethal disease and despite significant advances in cancer therapy, including chemotherapy, radiation, surgery, or targeted therapy, the current treatment strategies remain insufficient to cure PC patients due to the development of chemoresistance of pancreatic tumors. The ineffective nature of these strategies highlights the need for a better approach to improve patients' survival. This need for better treatment has prompted the rise of immunotherapy in PC treatment. Specifically, these types of therapy have sought to attack the tumor's defense mechanisms while simultaneously inducing an immune response that would be used to eradicate the tumor itself. In PC, increased T-regulatory cells, myeloid derived suppressor cells and tumor associated macrophages while reduced cytotoxic T-cells and natural killer (NK) cells establish an immunosuppressive environment. A recent publication by Zhang *et al*. highlights the specific pathways by which myeloid cells suppress immune response, and how the reduction of these cells can induce regression of the tumor itself. They also suggest how a combined therapeutic regimen of mitogen-activated protein kinases (MAPK) inhibition with immunotherapy modulates different immunosuppressive pathways. In this perspective, we will also discuss recent achievements in the immunotherapy for PC.

**Keywords:** Immune checkpoint; immunotherapy; pancreatic cancer (PC); pancreatic ductal adenocarcinoma (PDAC); programmed cell death protein 1 (PD-1)

Submitted Feb 01, 2017. Accepted for publication Feb 07, 2017.
doi: 10.21037/tcr.2017.03.48
**View this article at:** http://dx.doi.org/10.21037/tcr.2017.03.48

## Introduction

Pancreatic ductal adenocarcinoma (PDAC), which is derived from glandular tissues of exocrine parts of the pancreas, accounts for approximately 90% of pancreatic cancer (PC) and is a lethal malignancy with increasing incidence, poor prognosis, and lower survival rates (1-3). In fact, recent studies indicate that, on average, the survival rate for one-year PC is approximately 20%, while the survival rate for five-year is about 5% (4,5). During diagnosis, the cancer has often metastasized beyond the pancreas, making treatment much more difficult. An estimated 53,070 new cases of PC are expected to occur and about 41,780 people will die of this disease in the US in 2016 (6). PC is expected to become the second leading cause of cancer mortality only to lung cancer by 2030 (7). Despite significant advances in cancer therapy, including chemotherapy, radiation, surgery, or targeted therapy, the current treatment strategies remain insufficient to cure PC patients due to the development of chemoresistance of pancreatic tumors to these strategies

(8,9). The ineffective nature of these current treatment strategies highlights the need for a better approach to improve patients' overall survival (OS).

This need for better treatment has prompted the rise of immunotherapy in PC treatment (10). Specifically, these types of therapy have sought to attack the tumor's defense mechanisms while simultaneously inducing an immune response that would be used to eradicate the tumor itself (11). In order to understand the role of immunotherapy in combination therapy, it is important to understand the role of the immune system in the PDAC tumor microenvironment (TME).

In this perspective, we will discuss some of the recent combined therapeutic strategies to enhance anti-tumor immune response in PC.

## Immune network in PDAC

PDAC is characterized by a dense desmoplastic reaction in which proliferating tumor cells co-exist with pancreatic stellate cells, fibroblasts, immune cells, and extracellular matrix (ECM) proteins, including collagen I and III that permanently interact and influence each other (12). In this TME, immune cells make up about 50% of tumor cell mass to suppress the immune system and promote angiogenesis in order to metastasize (11,13). Certain immune cells are upregulated and downregulated in PC in order to create an environment conducive to tumor growth (11). Cells such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Treg), fibroblasts, mast cells, and others are upregulated in the TME, ultimately creating a niche for the PC to grow that is insulated from immune response (11,13-15). MDSCs are heterogeneous population of myeloid progenitor cells, comprising granulocytes, macrophages, and dendritic cells (DCs) that play a key role in tumor initiation, progression, metastasis, angiogenesis, chemoresistance and cancer immune evasion via suppressing T-cell cytotoxicity against tumor cells (16-18). On the other hand, certain cells are downregulated in order to suppress the immune system (11). These cells include natural killer (NK) cells, CD8+ T cells, and others that serve to promote immune response by attacking the tumor's defense and ultimately the tumor itself.

Previous literature has clearly indicated the immunosuppressive role myeloid cells play in pancreatic carcinogenesis (16). PC shows higher levels of MDSCs as compared to a healthy pancreas (15,19). A recent publication by Zhang *et al*. highlights the specific pathways by which myeloid cells suppress immune response, and how the reduction of these cells can induce regression of the tumor itself (20). They depleted the population of myeloid cells in an iKras* mice model of PC by crossing them with CD11b-diphtheria toxin receptor (DTR) mice to observe the difference in cancer initiation and progression. The results of this experimentation are in agreement with Stromnes *et al*. (15) and indicate that MDSC depletion works in tandem with CD8+ T cells to initiate PC cell death as evident by increased expression of apoptosis marker, cleaved caspase-3. To check whether this increase was due to inability of macrophage to clear dead cells or cytotoxic CD8+ T-cell response, they deplete both CD8+ T cells and myeloid cells and almost complete rescue of apoptosis was observed. This observation supports the role of myeloid cells in protecting tumor cells from T-cell cytotoxic response. MDSCs and tumor cells communicate to encourage carcinogenesis. It is thus prudent to investigate the pathways by which these cells communicate to understand the broad, over-arching mechanisms and by which tumor cells utilize other cells in their environment in proliferation and metastasis in order to establish various novel combination therapy in PC treatment.

## Combination therapy in PC

A key aspect regarding immunotherapy within combination therapy is an understanding of immune checkpoints. Immune checkpoints are set in place as inhibitory pathways used in immune responses to minimize damage caused to cells (21). Tumors are able to utilize certain immune checkpoints in allowing them to proliferate unhindered by the immune system. Specifically, these checkpoints utilize ligands and receptors in order to function, and can thus be blocked by specific antibodies that render the checkpoint useless. This presents a significant function in therapy because it inhibits immune suppression in a cancerous environment. However, the utilization of this function is rather novel. In previous endeavors for therapeutic approaches, the tumor cell was targeted directly (22). However, this process targets the inhibitory pathways, revolutionizing the approach to cancer treatment itself. Thus, the search for viable immune checkpoints being exploited by tumors is underway, and a few promising candidates have surfaced, including the programmed cell death protein 1 (PD-1) (21,22).

PD-1 is an inhibitory receptor that belongs to B7-receptor family and is induced on T cells, B cells and

 

monocytes on activation (11,23,24). Once induced, PD-1 interacts with its ligands PD-L1 (also known as B7-H1) or PD-L2 (B7-DC) to down regulate cytotoxic signals by T cells that, in turn, might favor tumor progression and poor prognosis (8,25). The distinct expression pattern of these two ligands has been observed and it has been suggested that their functions may depend on the tissue microenvironment (23). PD-L1 is expressed on many cell types, including resting T cells, B cells, DCs, macrophages, vascular endothelial cells, pancreatic islet cells and tumor cells after exposure to multiple proinflammatory mediators including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), GM-CSF, and vascular endothelial growth factor (VEGF) (22,23,26). IFN-γ and TNF-α are produced by activated T cells whereas GM-CSF and VEGF are produced by a variety of cancer stromal cells (27). Expression of PD-L2 is restricted to antigen-presenting cells (APCs) such as DCs and macrophages (8,27). PD-L2 has not gained as much attention, and its role in reducing tumor immunity is less clear (28).

PD-L1 has been correlated with a poor prognosis in melanoma, renal cell carcinoma, gastric cancer, breast cancer, colon cancer, lung cancer, glioblastoma (27,29-32) including PC (8,33,34). Blockade of PD-1/PD-L1 axis by antibody therapy enhances anti-tumor immunity, leading to robust clinical responses for patients with melanoma, lung cancer, renal cancer cell carcinoma and other immunogenic cancers (35). Antibodies against PD-1 and PD-L1 have entered clinical trials with great success in patients with advanced melanoma and advanced non-small cell lung cancer (36,37). However, patients with PDAC, a non-immunogenic cancer, are reported to respond poorly to immune checkpoint blockade therapies (35,38). The unique mechanisms and sites of action of checkpoint molecules, cytotoxic T lymphocyte-associate protein-4 (CTLA-4) and PD-1 suggest that although blockade of either has poor anti-tumor immune responses in PDAC, their combined blockade could synergize to mediate robust anti-tumor immunity (39-41). This double blockade has been associated with the attenuation of suppressive functions of Tregs and increased effector functions of T cells (14,42). Colony stimulating factor 1 (CSF-1)/CSF-1 receptor (CSF-1R) inhibitors or GVAX, a granulocyte macrophage-CSF transfected irradiated tumor cell vaccine improves the efficacy of antibodies against PD-1 and CTLA-4 (42,43).

In addition, the cancer immunotherapy field has turned to other novel ideas that seem to be effective, including the use of small molecules to suppress the expression of certain enzymes.

Some of these enzymes include focal adhesion kinase (FAK) and mitogen-activated protein kinases (MAPK), or more specifically, MEK. FAK is hyper-activated in PDAC and its activity correlates with highly fibrotic tumors with poor infiltration of CD8+ cytotoxic T cells (44). FAK kinase inhibitor VS-4718, currently used in Phase I clinical trials (NCT02546531) significantly enhances the efficacy of gemcitabine and PD-1/CTLA4 antibodies in PDAC mouse models (44). Vella and colleagues tested the effect of small molecules that inhibit MEK expression on immune response using a drug called trametinib (45). In fact, this drug proved more effective with or without combination therapy than standard chemotherapeutic approaches. The BRAF kinase was discovered as a cancer-promoter, and the BRAF kinase inhibitor (BRAFi) was introduced as a therapeutic approach (45). When trametinib was combined with dabrafenib, a BRAFi drug, the survival rate without progression was prolonged by 3.5 months compared to dabrafenib treatment alone. It is clear that immunotherapy used in combination with conventional treatments is a promising field of research.

The findings from Zhang *et al*. show that myeloid cells can promote PD-L1 expression in pancreatic tumor cells through the involvement of EGFR/MAPK signaling (20). Inhibition of EGFR and MEK by Erlotinib and GSK1120212, respectively *in vivo* as well as *in vitro* reduces the expression of PD-L1 on tumor cells and in turn making them sensitized to anti-PD-1 treatment.

There are many other therapeutic strategies similar to the one mentioned above that utilize the combination of various novel and preexisting techniques to create more effective results. Deng *et al*. highlights an approach which utilizes irradiation in conjunction with a PD-L1 blockade to decrease the amount of MDSC more effectively (14). This experiment found that high-dose ionizing irradiation caused MDSC levels to go up, diminishing the effect of the treatment. Ultimately, this can cause tumor regression at a relatively high rate. After realizing that MDSC cells contain high levels of PD-L1 and play a key role in immunosuppression, Deng *et al*. chose to test anti-PD-L1 treatment with ionizing irradiation (14). This was tested in mice and caused a dramatic decrease in the number of MDSC cells, significantly reducing the chance of relapse.

He *et al*. discusses the merits of using anti-PD-1 or anti-PD-L1 antibodies with treatments that activate the immune system (27). They provided a list of anti-PD-1 (nivolumab, pembrolizumab, and pidilizumab) and anti-PD-L1 (BMS-

 

936559, MPDL3280A, MEDI4736, and AMP-224). This publication describes the recently discovered effectiveness of these therapies on their own, but also indicates that combination therapy prolongs OS significantly. Some of these other therapies that are used in conjunction with the aforementioned antibodies include chemotherapy and radiotherapy.

Another piece of literature that delves into the potential of combination therapy is Ebert *et al*. (46). Two essential treatment methods for PC have been MEK inhibitors and anti-PD-LI treatments. The researchers indicate that MEK inhibition is used concurrently with PD-L1 inhibitors to boost the efficacy of the treatment, in addition to diminishing the chance of regression. The MEK inhibition treatment was used on its own, and initially showed a shrink in the tumor size. However in some cases, the tumor began progressing again just a few weeks later. Just as with most combination therapies, both the MEK inhibition and anti-PD-L1 antibody treatments show a modest effect when used by themselves. However, MEK inhibitors use a preclinical combination mechanism with anti-PD-L1 that is not yet well understood, but has proven far more therapeutically beneficial.

A different group tested anti-PD-1/PD-L1 with other treatment methods simultaneously as well (47). This complementary treatment technique is similar to the one described by Vella and colleagues, in which small molecules were used to target MEK (45). However, the treatment described by Sagiv-Barfi *et al*. utilizes small molecules in the inhibition of various tyrosine kinases, including Bruton's tyrosine kinase (BTK), a kinase presenting in an oncogenic, malignant signaling pathway, and interleukin-2-inducible T-cell kinase (ITK), a kinase important for Th2 T cells (47). This drug, called ibrutinib, is said to have immunomodulatory effects and doesn't produce a very effective treatment. In fact, some cancers are completely immune to the effects of ibrutinib due to their lack of dependence on BTK. However, the combination therapy described by them was used to treat these cancers, and significantly inhibited their growth. Furthermore, the therapy was tested on solid tumors, and had a similar effect on tumor growth. Through the discovery of this treatment technique, it is clear that combination therapy presents a novel way to approach cancer therapy.

Although MEK inhibitors work on many cancers containing the MAPK pathway, *K-Ras* mutated cancers are generally associated with MEK inhibitor resistance (48). This presents a problem in general immune checkpoint therapy. However, Zhao *et al*. indicates that a signal transducer and activator of transcription 3 (STAT3) was significantly upregulated after MEK inhibition, suggesting that this was the mechanism behind MEK inhibition resistance in K-Ras mutated PC cells (48). This discovery was critical in providing a holistic, well-targeted therapeutic approach. This experiment showed that inhibiting both MEK and STAT3 in these PC cells had a profound impact on tumor growth. The growth rate was suppressed significantly, implicating that STAT3 inhibition may play a key role in therapy while in combination with MEK inhibition.

Zhang *et al*. conducted an experiment that had a similar conclusion as Vella and coworkers, in that both papers concluded that PD-1/PD-L1 inhibitors used in tandem with MEK inhibitor drugs have an important role in tumor growth suppression (20). However, Zhang *et al*. used only MEK inhibitor drug, trametinib (GSK1120212) rather than using two inhibitors, trametinib and selumetinib (AZD6244) by Vella and group to target MEK. In addition, this publication talks about the therapeutic potential in MDSC cells in PC while Vella *et al*. talks about this therapy in regards to BRAF-mutated malignant melanoma.

## Conclusions

PC is a deadly form of cancer that is often diagnosed with a low survival rate due to a commonly late diagnosis, by which time it has already metastasized. Four basic strategies existed to address PC: surgery, ablation/embolization, radiation therapy, and chemotherapy. However, these approaches by themselves still aren't nearly as effective as they should be. With only these approaches, prognosis for PC is low. It was thus prudent for researchers to investigate alternative therapeutic approaches that would increase the overall average rate of survival. After figuring out that utilizing the immune system to induce an immune response against the tumor cells was particularly effective, researchers began to investigate the implications of combining this immunotherapy with conventional techniques. It is clear that the various combination therapies outlined by numerous recent publications have strong potential in clinical use, and will play a role in PC treatment in the near future.

## Acknowledgments

*Funding:* This work was supported by the Kansas City Area Life Science grant award (Sushanta K. Banerjee), Merit review grant from Department of Veteran Affairs (Sushanta

 

K. Banerjee), KUMC Van Goetham Family Endowed Fund (Sushanta K. Banerjee) and partly by Basic Research Development Award from Internal Medicine, KUMC (Inamul Haque).

## Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Xiaotian Sun (Department of Internal Medicine, Clinic of August First Film Studio, Beijing, China).

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.03.48). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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**Cite this article as:** Haque I, Subramanian A, Banerjee S, Banerjee SK. Current and emerging perspectives on immunotherapy for pancreatic cancer. Transl Cancer Res 2017;6(Suppl 2):S331-S336. doi: 10.21037/tcr.2017.03.48

 