Editorial

Depletion of tumor associated macrophages by anti-BAG3 treatment complements PD-1 blockade in pancreatic cancer

Yi Sun[1,2], Robert J. Torphy[1], Yuwen Zhu[1]

[1]Department of Surgery, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA; [2]Hepatopancreatobiliary Surgery Department I, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing 100142, China

Correspondence to: Yuwen Zhu, PhD, Department of Surgery, RC1-North Building, P18-8116, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA. Email: yuwen.zhu@ucdenver.edu.

Comment on: Iorio V, Rosati A, D'Auria R, *et al.* Combined effect of anti-BAG3 and anti-PD-1 treatment on macrophage infiltrate, CD8+ T cell number and tumour growth in pancreatic cancer. Gut 2018;67:780-2.

Received: 06 August 2018; Accepted: 09 October 2018; Published: 23 October 2018.
doi: 10.21037/apc.2018.10.01
View this article at: http://dx.doi.org/10.21037/apc.2018.10.01

New literature published in *Gut* has shown that combined treatment of anti-BAG3 mAb and anti-PD-1 mAb in pancreatic cancer can eliminate tumor-associated macrophages (TAMs), increase tumor infiltrating CD8+ T cells and result in tumor growth suppression (1). These findings highlight the potential of BAG3 (Bcl-2-associated athanogene 3) as a therapeutic target in conjunction with immune checkpoint blockade in the treatment of pancreatic cancer.

Pancreatic cancer, of which pancreatic ductal adenocarcinoma (PDAC) is the most common type, is predicted to be the second leading cause of cancer-related death in the USA and Europe by 2030, according to recent epidemiological projections (2). Less than 7% of 5-year survival rate rank PDAC the poorest prognosis cancer in gastrointestinal cancers (3). Surgical resection is the only option to cure PDAC; however, the majority of patients have unresectable disease at diagnosis. The resistance of PDAC to conventional therapies, including chemotherapy, targeted therapy and radiotherapy, further makes this disease deadly. Thus, a better understanding of tumor biology and the development of novel therapeutic strategies are urgently needed.

Despite the promising results of immune therapies in melanoma and non-small cell lung cancer, no clinical benefit was found for these agents in PDAC (4,5). The tumor microenvironment has recently been recognized as an important factor in the genesis and development of cancer and likely impacts the effectiveness of immune therapies. Therefore, there is increasing interest in targeting the tumor microenvironment to aid in the promotion of effective anticancer immunity, which has led to innovative therapeutic combinations. These combinations might help to overcome the resistance of PDAC to immune therapy. The work by Iorio *et al.* demonstrates a novel combination of macrophage depletion through targeting BAG3 in the tumor microenvironment in order to improve the response of PDAC to immune checkpoint blockade.

BAG3 was first described as a co-chaperone of the heat shock protein 70 (HSP70) which can be induced in response to stress. BAG3 is constitutively expressed in several primary tumors and tumor cell lines, and promotes cancer survival role through numerous mechanisms. The author's previous work has shown that BAG3 is expressed in PDAC and the expression levels in PDAC correlated with patient survival (6). BAG3 protein, secreted by PDAC cells, binds to TAMs and activates them to release cytokines and factors which supports tumor growth, metastatic spread, and suppresses T cell infiltration and activation. Analysis of tumor biopsies from tumor-bearing mice treated with anti-BAG3 mAb demonstrated that both the number of infiltrating macrophages and the level of macrophage-released cytokines were markedly decreased in the anti-BAG3 treatment group. This study demonstrated that blocking BAG3 activity results in potential anti-tumor immune effects with an increased number of CD8+ tumor infiltrating lymphocytes. From these findings, the authors concluded BAG3 has a role in interacting with TAMs to suppress CD8+ lymphocytes influx or subsistence in tumor

tissues. These results showed a potential effectiveness of anti-BAG3 treatment in fighting PDAC.

The main reasons for the failure of immune checkpoint inhibitor monotherapies in PDAC are low tumor immunogenicity and low tumor T cell infiltration and activation. The relatively low mutation burden in PDAC compared to other solid tumors yields few neoantigens. The poor efficacy of immune therapy in PDAC due to its decreased neoantigen burden is difficult to therapeutically manipulate (7). A subset of patients who have T cell inflamed tumors tend to respond to immune checkpoint blockade therapy. However, most tumors are non-inflamed with low levels of T cell infiltration and low levels of T cell activation due to upregulation of PD-1 expression on T cells. The tumor microenvironment, composed of tumor stroma, can act as a physical and chemical barrier to inhibit T cell infiltration and activation in tumors (8,9). The tumor microenvironment can potentially be therapeutically manipulated to improve the anti-tumor immune response.

The innovation of this study by Iorio *et al.* was focusing on blocking the PD-1 pathway concurrently with depletion and/or deactivation of the immunosuppressive cells within the tumor microenvironment. Various sources of PD-L1 expressed on immunosuppressive cells and tumor cells interact with PD-1 expressed on effector T cells and causes a programmed-death cascade in T cells, thereby maintaining tumor-tolerance. Anti-PD-1 mAb is a well-known immune therapy which has been approved by the FDA for several solid malignancies with promising response by preventing PD-1 from being activated. TAMs are one type of immunosuppressive cell that has been shown to induce PD-L1 expression (10). Thus, depletion and/or deactivation of TAMs was expected to result in a decrease in PD-L1 expression and enhance the efficacy of anti-PD-1 treatment. According to the results of this study, both of the monotherapy groups achieved similar anti-tumor activity. However, combination treatment of anti-PD-1 mAb and anti-BAG3 mAb produced a synergistic effect with improved anti-tumor activity.

Immunosuppressive cells in the tumor microenvironment are composed of a variety of populations of cells including dendritic cells, myeloid derived suppressive cells (MDSC), regulatory T cells (TREGs), CD8-positive γδT cells and M2 macrophages. These immunosuppressive cells within the tumor microenvironment of PDAC prevent effector T cells from being recruited and activated by secreting TGFβ, nitric oxide synthase and arginase which all negatively affect CTL function. TAMs are the major component of MDSCs and play an important role in suppressing the cancer-related immune response. M1 subtype TAMs, which are activated by bacterial products and cytokines and have the capacity to kill tumor cells, while M2 subtype TAMs inhibit the anti-tumor immune response and promote tumor growth and metastasis. During the different stages of cancer development, TAMs might exert different functions. Ultimately, most cancers promote TAM polarization toward an immunosuppressive phenotype (M2), educated by the tumor cells (11).

The authors' previous work demonstrated PDAC cells release BAG3 which stimulates macrophage activation and the release of cancer cell-sustaining factors, such as IL-6, IL-10 and CSF-1. These cytokines attract more macrophages and drives TAM differentiation towards an immunosuppressive, tumor-promoting phenotype. When secreted BAG3 was blocked by anti-BAG3 mAb, cancer cells produced less of these tumor promoting cytokines and resulted in reduced tumor growth. IFITM-2 expressed on TAMs was identified as the receptor of BAG3 and signals through the phosphorylation of AKT and p38. Besides cytokines reduction, the density of TAM infiltration was found to be dramatically decreased in anti-BAG3 mAb treated tumor tissues compared to control and anti-PD-1 treatment groups. It might be the result of cytokines reduction that less TAMs were attracted. Or, TAMs were depleted by antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

Better understanding of the mechanism of how BAG3 interacts with TAMs to affect tumor development might help to identify a better alternative combination for PDAC immune therapy. Angiogenic promoters secreted by TAMs, such as VEGF, act on vascular and lymphatic vessels to promote angiogenesis and lymphoangiogenesis, as well as tissue remodeling (12). Correspondingly, vascular density in human cancers was found to be associated with TAM density in the cancer tissues. Resistance of tumors to current anti-VEGF therapies is also frequently associated with increased myeloid-cell infiltration. From pre-clinical studies, the mechanism of this resistance is thought to be secondary to tissue hypoxia promoting myeloid cell recruitment in an effort to promote angiogenesis. Furthermore, anti-angiogenic treatments might result in more TILs delivered to the tumor microenvironment through normalized tumor vessels. Thus, targeting TAMs concurrently with antiangiogenic therapies might be an alternative way to fight pancreatic cancer.

Despite the exciting result from the combination strategy, there is still long way to go to translate these results into clinical benefits. From clinical aspects, most

PDAC patients did not respond to the anti-PD-1 treatment except a minor group of patients with MSI-H tumors which harbor a relatively high mutation load. Based on results from mouse tumor models, the efficacy of immune therapy on subcutaneous inoculated tumors is not paralleled to the orthotopic or spontaneous PDAC tumor models. Thus, if these findings can be replicated in an orthotopic PDAC model, that would be more convincing to develop a humanized version of the anti-BAG3 antibody to conduct clinical trials for PDAC therapy.

To summarize, the authors gave us a new point of view to treat pancreatic cancer by targeting BAG3-mediated TAM depletion in conjunction with immune checkpoint blockade. We are looking forward to more details of the interactions between BAG3 and immune cells in the tumor microenvironment to be elucidated in the near future, which would help to push this therapy into clinical trials and finally benefit pancreatic cancer patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Pancreatic Cancer*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apc.2018.10.01). 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.

References

1. Iorio V, Rosati A, D'Auria R, et al. Combined effect of anti-BAG3 and anti-PD-1 treatment on macrophage infiltrate, CD8(+) T cell number and tumour growth in pancreatic cancer. Gut 2018;67:780-2.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
3. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014;371:1039-49.
4. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33:828-33.
5. Patnaik A, Kang SP, Rasco D, et al. Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors. Clin Cancer Res 2015;21:4286-93.
6. Rosati A, Basile A, D'Auria R, et al. BAG3 promotes pancreatic ductal adenocarcinoma growth by activating stromal macrophages. Nat Commun 2015;6:8695.
7. Bailey P, Chang DK, Forget MA, Lucas FA, Alvarez HA, Haymaker C, et al. Exploiting the neoantigen landscape for immunotherapy of pancreatic ductal adenocarcinoma. Sci Rep 2016;6:35848.
8. Watt J, Kocher HM. The desmoplastic stroma of pancreatic cancer is a barrier to immune cell infiltration. Oncoimmunology 2013;2:e26788.
9. Turley SJ, Cremasco V, Astarita JL. Immunological hallmarks of stromal cells in the tumour microenvironment. Nat Rev Immunol 2015;15:669-82.
10. 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.
11. Mantovani A, Marchesi F, Malesci A, et al. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017;14:399-416.
12. De Palma M, Lewis CE. Macrophage regulation of tumor responses to anticancer therapies. Cancer Cell 2013;23:277-86.

doi: 10.21037/apc.2018.10.01
Cite this article as: Sun Y, Torphy RJ, Zhu Y. Depletion of tumor associated macrophages by anti-BAG3 treatment complements PD-1 blockade in pancreatic cancer. Ann Pancreat Cancer 2018;1:32