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Editorial

EDITORIAL

PD-L1 Expression in Pancreatic Cancer

Lei Zheng

Affiliations of authors: Sidney Kimmel Comprehensive Cancer Center, Department of Oncology, Graduate Program in Cellular and Molecular Medicine, Department of Surgery, The Skip Viragh Center for Pancreatic Cancer, and The Bloomberg-Kimmel Institute of Cancer Immunotherapy, The Johns Hopkins University School of Medicine, Baltimore, MD.

Correspondence to: Lei Zheng, MD, PhD, Department of Oncology, Johns Hopkins University School of Medicine, 1650 Orleans Street, CRB1, Room 488, Baltimore, MD 21287 (e-mail: lzheng6@jhmi.edu).

Pancreatic ductal adenocarcinoma (PDAC) has the most dismal prognosis among all major solid malignancies, with five-year survival of approximately 6% (1). PDAC is also highly resistant to chemotherapy and radiotherapy (2). Although there have been successful developments of targeted therapies for other cancers, little progression has been made finding new therapies for PDAC despite promising results from preclinical studies (3).

Cancer immunotherapy has made clinically significant breakthroughs in the last decade. Ipilimumab, a monoclonal antibody that blocks the immune checkpoint cytotoxic T lymphocyte antigen-4 (CTLA-4), was the first in the class of immune checkpoint inhibitors approved by the United States Food and Drug Administration (FDA) for the treatment of cancer diseases (4). Since 2014, other checkpoint inhibitors including programmed death-1 (PD-1) and programmed death-1 ligand-1 (PD-L1) blocking antibodies have been approved by the FDA to treat melanoma, non–small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, bladder cancer, and Hodgkin's lymphoma (5–23). Anti-PD-1 or PD-L1 antibodies were shown to induce objective responses in approximately 20% to 30% of patients with these FDA-approved indications and in approximately 20% of patients with other malignancies that are still being tested in clinical trials (24). Many of these responses are durable. However, despite the success of developing agents blocking CTLA-4 and PD-1/PD-L1 as single therapy in a growing list of cancer types, treating PDAC with single-agent immune checkpoint inhibitors has not been effective (5,25–27).

In prior studies, it was shown that membranous PD-L1 expression is scarce in PDACs (28–30). Lack of PD-L1 expression is thought to account for the ineffectiveness of anti-PD-1/PD-L1 antibodies in treating PDACs. PD-L1 expression is shown to be activated in tumor cells either by oncogenic signaling or by inflammatory cytokines, particularly interferon gamma, as a result of adaptive immune response (31). PDAC lacks effective T cell infiltration and thus the inflammatory signaling needed to activate PD-L1 expression (29,32,33). Whether oncogenic signaling may activate PD-L1 expression in PDACs has been poorly studied.

In this issue of the Journal, Lu et al. describe that human mixed lineage leukemia protein-1 (MLL1) and PD-L1 are highly expressed in the majority of the 13 human PDAC specimens that they tested (34). MLL1 is a histone H3-lysine 4 (H3-K4) methyltranferase, and its rearrangement is thought to underlie the oncogenesis of certain types of acute leukemia (35). In the study described by Lu et al., the majority of tumor cells express MLL1 in 11 out of the 13 PDAC specimens tested. MLL1 was shown to directly bind to the H3K4 trimethylation (H3K4me3)–enriched promoter of the *CD274* gene and catalyze H3K4me3 to induce the expression of PD-L1 from the *CD274* gene. PD-L1 was suggested by Lu et al. to be expressed in 60% to 90% of tumor cells in all 13 PDAC specimens. PD-L1 was detected both on cell membranes and in the cytoplasm of tumor cells in this study. By using flow cytometry, Lu et al. found that nine out of 10 PDAC cell lines expressed a high-level PD-L1. Verticillin, an MLL1 inhibitor, improved the efficacy of anti-PD-l blockade antibodies in the preclinical model of PDAC, as suggested by Lu et al., by decreasing PD-L1 expression and through an immune-mediated mechanism.

Thus, Lu et al. revealed a novel mechanism of PD-L1 activation in cancer cells and also described their different observations on PD-L1 expression in PDACs and on the efficacy of anti-PD-1 antibodies in preclinical models of PDAC, compared with prior published studies (28–30). The study by Lu et al. highlights the importance of understanding the oncogenic activation of PD-L1 and suggests that targeting epigenetic regulation of PD-L1 may enhance the efficacy of anti-PD-1/PD-L1 antibodies in treating PDACs. Lu et al. also indicated the discrepancy between their observations and prior publications on PD-L1 expression in PDACs.

Membranous PD-L1 expression has been used to select patients for anti-PD-1 antibody therapies for certain types of cancer. In such cancers, exemplified by non–small cell lung

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cancer, PD-L1 membranous expression appears to have enriched the patients who are potentially sensitive to anti-PD-1 therapies (11,21). However, not all the patients whose tumors express membranous PD-L1 respond to anti-PD-1 or anti-PD-L1 therapy. Other immune parameters such as the infiltration of CD8 cells also appear to be important for the sensitivity to immune checkpoint inhibitors (36). On the other hand, PD-L1-negative cancers can also respond to anti-PD-1/PD-L1 antibodies (12,22,37). Moreover, it remains challenging to develop a consensus method that consistently demonstrates and quantifies PD-L1 expression. There are several immunohistochemistry-based companion diagnostic tests used for selecting patients for anti-PD-1 antibody therapies as well as immunohistochemistry methods used to correlate PD-L1 expression with the responses of patients to anti-PD-1 or anti-PD-L1 antibodies in clinical trials (38). However, there is a lack of comparisons between different anti-PD-L1 antibodies used in these immunohistochemistry methods. Even employing the same antibodies, differences in the immunohistochemistry staining methods for PD-L1 may have existed in different publications (38). Thus, it would not be surprising to observe a difference in the detection of PD-L1 expression in PDACs. It is critical to reconcile differences in the observation of PD-L1 expression in PDACs.

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