Editorial Commentary

PD-1 expression on tumor cells: a new target for cancer therapy

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In this editorial commentary, we discussed the potential of programmed death-1 (PD-1) expression on tumor cells as a novel target for the treatment of non-small cell lung cancer (NSCLC) patients based mainly on the findings reported by Rotolo and colleagues (1). We focused on PD-1 expression on tumor cells as a biomarker for combination chemotherapy with anti-PD-1 antibodies and cytotoxic agents as well as future perspectives for PD-1 targeted cancer therapy (*Figure 1*).

Anti-PD-1 blockade is one of the most frequently used immune checkpoint inhibitors in multiple settings, including monotherapy, combination therapy with cytotoxic agents (2), neoadjuvant therapy (3), and post-chemoradiation therapy (4), for patients with NSCLC. While the most common mechanism for the anti-tumor effects of anti-PD-1 blockade is an increase in T cell activity in the tumor microenvironment (5-7), a lymphocyte-independent function was recently reported in melanoma (8-10). Kleffel and colleagues reported that human melanoma tumor tissues frequently contained PD-1-expressing tumor cell subsets. Moreover, an anti-PD-1 antibody inhibited lymphocyte-independent tumor growth in murine models via the mTOR pathway (8). Sanlorenzo and colleagues demonstrated that BRAF and MEK inhibitors increased the number of PD-1-positive melanoma cells, indicating the potential of lymphocyte-independent synergism with anti-PD-1 antibodies (9). In the study that is the focus of this editorial commentary, Rotolo and colleagues reported the novel lymphocyte-independent anti-tumor efficacy of an anti-PD-1 antibody in human and murine NSCLC cell lines (1). The baseline expression of PD-1 in NSCLC cell lines was low and increased after the administration of cisplatin. PD-1 expression was enhanced in stem-like NSCLC pneumospheres, derived from NSCLC cell lines cultured within a defined serum-free medium, exhibiting characteristics reminiscent of stem cells. The anti-PD-1 antibody showed lymphocyte-independent anti-tumor efficacy *in vitro* and *in vivo*, and its combination with cisplatin exerted synergistic anti-tumor effects. A question refers to the variance in downstream signaling of PD-1 observed between T cells and tumor cells. Anti-PD1 antibody blocks the growth of PD-1-positive tumor cells, but not PD-1-expressing T cells. Comparison of downstream signaling of PD-1 between T cells and tumor cells will clarify the rational of anti-PD-1 therapy.

The study by Rotolo and colleagues focused on the expression of PD-1, not programmed death-ligand 1 (PD-L1), in NSCLC cells. PD-L1 is currently used as a biomarker to predict the efficacy of anti-PD-1 antibody therapy for NSCLC patients (11,12), whereas PD-1 expression has not been reported to be a predictive biomarker of anti-PD-1 treatment outcome in clinical settings. A critical issue for NSCLC patients without driver mutations is that there are currently no useful biomarkers for combination therapy with anti-PD-1 antibodies and cytotoxic agents. PD-L1 expression is not used as a biomarker for the combination therapy with anti-PD-1 antibodies. The findings obtained by Rotolo and

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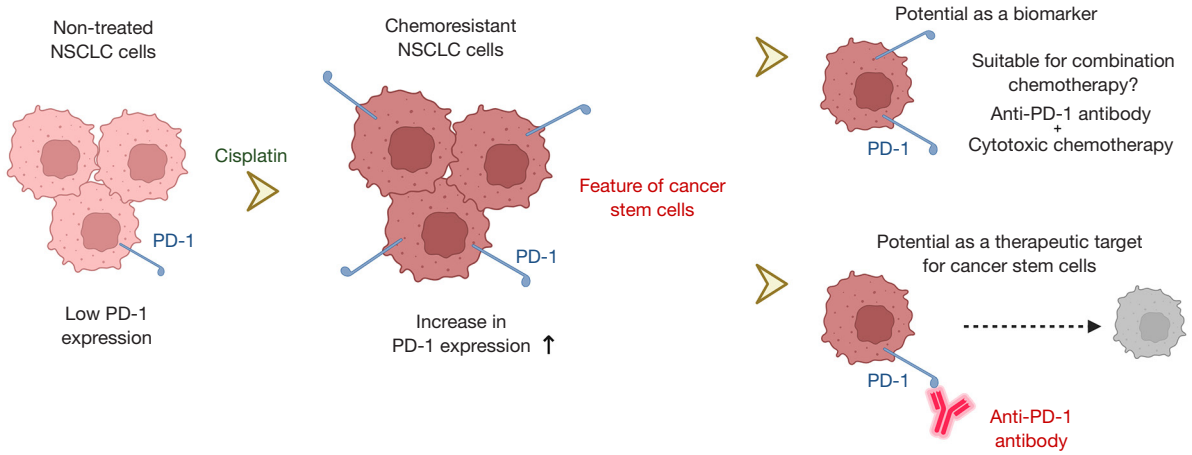

Figure 1 A schematic overview of the present article is shown. Chemoresistant NSCLC cells expressing PD-1 have stem-like features. PD-1 expression on NSCLC cells may be used as a predictive biomarker for the treatment combination of anti-PD-1 therapy with cytotoxic agents. Anti-PD-1 antibodies have novel lymphocyte-independent anti-tumor efficacy in NSCLC via the inhibition of cancer stemness by targeting PD-1 on cancer stem cells. Created with BioRender.com. NSCLC, non-small cell lung cancer; PD-1, programmed death-1.

colleagues suggested that PD-1-positive NSCLC cells exhibited resistance to cytotoxic chemotherapy. Anti-PD-1 may be used more effectively when NSCLC relapses after the administration of cytotoxic agents for NSCLC highly expressing PD-1. The study by Rotolo and colleagues showed that the concurrent combination of an anti-PD-1 antibody with cisplatin exerted synergistic lymphocyte-independent effects on NSCLC *in vivo*. The synergistic effects of the combination of anti-PD-1 antibodies with cytotoxic agents have been attributed to immunogenic cell death induced by cytotoxic agents (13). On the other hand, the findings of lymphocyte-independent experiments conducted by Rotolo and colleagues provide a novel viewpoint of anti-PD-1 providing additional efficacy to cytotoxic agents by targeting PD-1-positive NSCLC cells. Therefore, PD-1 expression on NSCLC cells has potential as a predictive biomarker for the efficacy of anti-PD-1 therapy with cytotoxic agents (*Figure 1*). Although the study by Rotolo and colleagues mainly focused on PD-1 mRNA detection in cell lines, further investigation of PD-1 expression by immunohistochemistry (IHC) staining of human tumor tissues is needed for the development of PD-1 as a novel biomarker. Furthermore, protein profiling platforms such as digital spatial profiling (DSP) also provide insights into PD-1/PD-L1 axis in the tumor microenvironment.

The study by Rotolo and colleagues suggested that PD-1-positive NSCLC cells had stem-like features that indicated chemoresistance (*Figure 1*). The stemness of tumor cells is an important issue that needs to be overcome because it has become clear that the targeted destruction of cancer stem cells (CSCs) is required for a radical cure for malignant tumors (14,15). CSCs are a small subset of tumor cells in various cancer types that have intrinsic self-renewal and tumorigenic characteristics, which lead to chemoresistance (14). CSCs possess these properties via signaling pathways, including the Notch, WNT, Hedgehog, and Hippo pathways (14). While agents that target CSCs in all cancer types, including lung cancer, are not currently available in clinical settings, previous studies reported the development of drugs that target CSCs in NSCLC (14,16-19). For example, inhibitory antibodies against delta-like ligands 3 and 4, which are involved in the Notch signaling pathway, have been developed as novel drugs targeting CSCs and are being used in phase I and II clinical trials for NSCLC and small cell lung cancer (SCLC) patients (16,17). The anti-tumor efficacy of napabucasin has also been demonstrated via its inhibition of CSCs by targeting STAT3, a critical mediator for the maintenance of cancer stemness in NSCLC (18). While phase III clinical trials on the efficacy of napabucasin for NSCLC, colorectal cancer, and gastric cancer are now underway according to ClinicalTrials.gov (https://clinicaltrials.gov), the addition of napabucasin to conventional cytotoxic chemotherapy did not improve treatment efficacy in patients with untreated metastatic pancreatic adenocarcinoma (20). Besides

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the development of drugs that target CSCs, anti-PD-1 antibodies have been suggested to disrupt interactions between CSCs and immune cells. Various interactions between CSCs and immune cells prevent the detection of CSCs by immune cells (14). Therefore, in CSC targeted treatments, anti-PD-1 antibodies may target not only cancer stemness, but also interactions with immune cells, thereby preventing immune evasion by CSCs.

The study by Rotolo and colleagues showed the limited expression of PD-1 in NSCLC cell lines, particularly before the administration of cisplatin; however, a previous study reported that human melanoma cells frequently included cancer cell subsets that highly expressed PD-1 without the prior administration of cytotoxic agents (8). Furthermore, anti-PD-1 antibodies inhibited lymphocyte-independent tumor growth in PD-1-expressing melanoma regardless of the administration of cytotoxic agents. The analysis of PD-1 expression in tumor cells across a large cohort of human samples representing various tumor types is required. The next question refers to the impact of co-expression of PD-1 and PD-L1 in tumor cells on the tumor microenvironment. The interaction between PD-1 and PD-L1 within tumor cells potentially influences the efficacy of anti-PD-1 therapy. Concerning hyperproliferative disease following anti-PD-1 therapy, the impact of PD-1 expression in tumor cells on the pathogenesis of these conditions needs assessment. Further investigations for the application of PD-1 expression on tumor cells as a therapeutic target in various cancer types are anticipated.

In summary, Rotolo and colleagues reported increases in PD-1 expression in chemoresistant NSCLC cells and the novel lymphocyte-independent anti-tumor efficacy of anti-PD-1 antibodies against NSCLC via the inhibition of cancer stemness. Further studies will broaden the possibilities of anti-PD-1 therapy for cancer patients.

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