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Short Communication
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Detection of PDL-1 as of Biomarker in Checkpoint Blockade Therapy

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Short Communication

Immune checkpoints are a series of pathways which can regulate T cell activity as either co-inhibitory or co-stimulatory signals [1]. Increasing evidences confirmed that Immune checkpoints play important roles in tumor evasion from antitumor immune responses (Figure 1) [2]. Clinical trials using antibodies targeting immune checkpoints, especially programmed cell death protein 1 (PD-1) and its ligandPD-1 ligand (PD-L1 or B7-H1), have shown revolutionized beneficial effects inmany patients with high clinical stages cancers which are usually resistant or refractory to conventional chemoradiation therapy. However, the objective responses are variable among each individual patient [3]. Thus, it has become a top priority to identify biomarkers that can predict patient responses to the immunotherapy.

PD-L1 Expression as Biomarker

It is widely accepted that tumor cells over express PD-L1 to inhibit T cell responses [4]. Higher expression of PD-L1 on tumor cells has been shown a better prognosis after checkpoint blockade intervention [5]. Thus, the expression of PD-L1 has been selected as companion diagnostics for PD-1/PD-L1 blockade therapy (Table 1) [6]. It has been found that both tumor cells and tumor associated stromal/immune cells express PD-L1. Due to the lack of conditional knockout mice, the contributions of PD-L1 from different cell populations are still not well-defined. Most studies analyze the PD-L1 protein level in tumor cellsto grade the expression. Some recent studies emphasize the role of the PD-L1 expression in immune cells to predict the response rate of PD-L1 checkpoint inhibitor treatment. (Table 1)(Figure 2) [7].

In spite of the fact that a higher potential response rate in patients with high level of positivity of PD-L1 expression in tumor tissues, clinical responses were also observed in some patients that were essentially negative for PD-L1 in tumor tissues [3]. The underlying mechanisms is still undetermined for patients who respond to PD-L1 blockade therapy with negativePD-1 expression in tumor tissue. Several potential hypothesis have been proposed. First, temporal and spatial heterogeneity of PD-L1 expression may lead to false-negative result duet to the limitation of tumor sampling especially in small core biopsy of clinical sample. Only a small fragment of the tumor tissues can be collected at certain time points, which may not be representative of the entire tumor tissue [8]. Second, the sensitivity of immunohistochemistry (IHC) is suboptimal to evaluate the PD-L1 expression. PD-L1 antigen may not be detected in the conventional IHC due to the tissue degeneration, fixing artifact in formalin fixed paraffin embed tissue (FFPE) sample and different type of antigen retrieval process in different labs. Furthermore, the lack of standardization as shown in Table 1, several different antibody clones with different cut-off values have been utilized to quantify the PD-L1 expression in different studies. One sample negative in one assay/study may turn out to be positive in others. Third, the expression of PD-L1 can be somehow upregulated in adjacent to nonspecific chronic inflammation responses, especially by interferon-gamma and TNF-alpha. It is possible that some PD-L1 negative tumor tissue may turn out to be positive after prolonged therapies.

Biomarkers other Than PD-L1 Expression

Besides PD-L1 expression, several other biomarkers are also being developed as to predict patient responses to PD-1/PD-L1 blockade therapies. Defects in DNA repair mechanisms, such as microsatellite instability/mismatch repair deficiency (MSI/MRD), are associated with an increased somatic mutation loads. It has been shown that tumor mismatch repair status can also be used to predict the clinical responses to checkpoint blockade therapy [9]. Recently, FDA has approved Keytruda for the treatment of patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers. This is the first approval a cancer treatment based on a common

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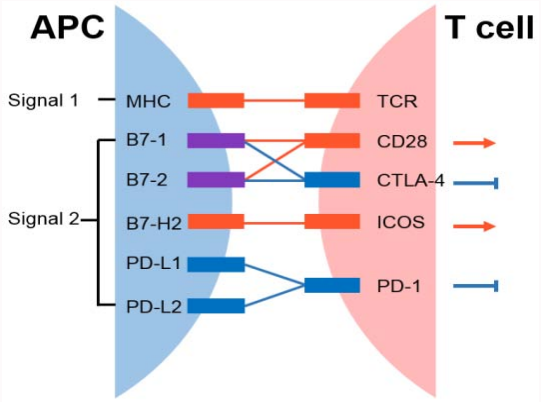

Figure 1: Immune checkpoints regulate T cell activation. Immune checkpoints provide co-inhibitory or co-stimulatory signals, which lead to T cell suppression or activation.

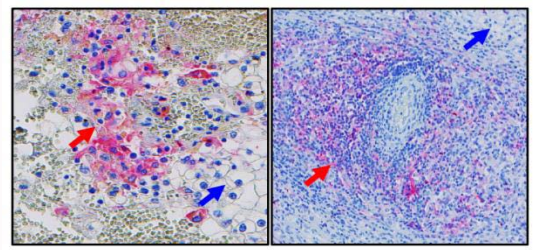

Figure 2: Typical immunohistochemical staining of PD-L1 in tissues from renal cell cancer (RCC) patients. Blue arrow: tumor cells; red arrow: PD-L1 positive macrophages.

Tabel 1: PD-L1 immunohistochemical assays as companion diagnostics.

Antibody	22C3	28-Aug	SP142	SP263
Host	Mouse	Rabbit	Rabbit	Rabbit
Companion therapy	Keytruda	Opdivo	Atezolizumab	Durvalumab
Cells	Tumor	Tumor	Tumor and immune	Tumor
Cutoffs	50%	1, 5, or 10%	5% of tumor or 50% of immune	25%

biomarker rather than the location of the primary tumor. Other widely acceptedbiomarkeris the entire tumor mutation burden [10]. In fact, many tumors that respond well to checkpoint blockade therapy usually have higher mutation burdens [11]. The caveat still remains as 0a clear cut-off value for tumor mutation burden is not established. In addition, the requirement for high-throughput sequencing and relative high cost limit further development of the test.

Conclusion

With the explorative growing clinical trials on checkpoint blockade therapies in cancers, it has become an utmost need to identify reliable biomarkers to predict patient responses. In spite of the rapid progress of biomarker development of caner immunotherapy, the current assays are still not perfect due to the lack of selectivity, specificity, accuracy, and precision. Further investigations are needed in order to improve the current test or develop novel assays.

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