Exosomal PD-L1: an effective liquid biopsy target to predict immunotherapy response

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Up-regulation of programmed death-ligand 1 (PD-L1) may allow cancer cells to evade the host immune system by recognizing the immune checkpoint programmed death-1 (PD-1) on T cells to promote self-tolerance by suppressing T-cell inflammatory activity [1]. Blocking the interaction between PD-L1 and PD-1 has positive anti-tumor effects [2]. Recently, several antibodies targeting the PD-L1/PD-1 pathway have been approved by the administration for the treatment of various tumors. However, only a minority of patients respond to the therapies [3]. Therefore, a deeper insight into the mechanisms of the immune evasion is urgent to improve the efficacy of these treatments.

In recent work by the Guo and Xu groups, they reported that melanoma cells released PD-L1⁺ extracellular vesicles, mostly in the form of exosomes, into the circulation to counter the anti-tumor immunity, unveiling a mechanism by which tumor cells systemically suppress the immune system [4]. The PD-L1 expressed on extracellular vesicles, which predominantly targets PD-1⁺ CD8 T cells, could be up-regulated by interferon-γ (IFN-γ). This finding suggests that PD-L1⁺ extracellular vesicles are able to counteract the immune pressure at the effector stage. In patients with metastatic melanoma before and during anti-PD-1 antibody pembrolizumab treatment, the amount of circulating exosomal PD-L1 may reflect different states of anti-tumor immunity (Fig. 1). Higher levels before treatment may hint at the ‘exhaustion stage’ of T cells where they can hardly be reactivated by the anti-PD-1 therapy. However, a significant increase in the level of circulating exosomal PD-L1 after several weeks of treatment would be a predictor of the adaptive response of the tumor cells to T-cell reinvigoration, stratifying the non-responders in the clinic. The authors found no obvious increment in circulating exosomal PD-L1 during the treatment of non-responders, possibly due to the failure of eliciting a sufficient T-cell response or an adaptively down-regulated response to IFN-γ from tumors. The adaptive resistance mechanism is to prevent antigen presentation and also to escape IFN-γ-induced anti-tumor effects. This study investigates in great depth the fundamentals of developing circulating exosomal PD-L1 as an indicator for clinical outcomes and offers

![Diagram](https://example.com/diagram.png)

**Figure 1.** (a) The interactions between circulating exosomal PD-L1 and T cells at different situations. (b) Tracking the levels of circulating exosomal PD-L1 may help to predict patients’ response and identify the possible reasons for success (orange and yellow) or failure (blue and green) for anti-PD-1 therapy.

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possible explanations for the unsatisfactory response rate of anti-PD-1 therapies.

These findings offer novel insights into the tumor-immunosuppression mechanism and provide the rationale for applying exosomal PD-L1 as an effective biomarker for immunotherapy as a complement to tissue biopsy, with the advantages of its non-invasive nature, accurate representation and real-time monitoring, although more basic studies and long-term clinical trials are needed to further confirm the detailed action mechanisms of PD-L1-positive extracellular vesicles and their clinical impact. This work has broadened the scientific community’s understanding of PD-L1-mediated tumor immune evasion and the clinical significance of PD-L1 on extracellular vesicles, which would help to develop strategies for accurate monitoring of immunotherapy response and to improve treatment efficacy. In addition to exosomal PD-L1, blood-based tumor mutational burden (bTMB) also can be a clinically actionable biomarker for anti-PD-L1 therapy [5]. It is believed that, in the near future, with further understanding of the immune escape mechanism, there will be more markers or multiple markers combined to predict the immune treatment effect.

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