Overcoming sPD-L1-induced immune checkpoint inhibitor (ICI) resistance

Jacob J. Orme, M.D. Ph.D.; Jeffrey L Winters, M.D.; Haidong Dong, M.D. Ph.D.

Division of Medical Oncology, Mayo Clinic; Department of Laboratory Medicine and Pathology, Mayo Clinic; Department of Urology, Mayo Clinic

Background

- Over 3 million patients receive PD-(L)1 immune checkpoint inhibitors (ICI) for cancer each year.
- Unfortunately, fewer than half of treated tumors respond to ICI therapy.
- This response is difficult to predict.

Methods and Results

- Figure 1: Serum sPD-L1 levels were measured in a retrospective cohort of patients with melanoma. In a multivariate Cox proportional hazards analysis, high sPD-L1 prior to treatment predicted worse survival (HR 1.49; 95% CI 1.06-2.09; p=0.025) when accounting for advanced age (not significant), sex (not significant), late stage (p=0.002) and high serum LDH (p=0.01).
- Figure 2: Wild-type 786-0 renal cancer cells with DMSO vehicle control versus protease inhibitors over 48 hours and cell supernatants sPD-L1 and cell surface PD-L1 (GFP C terminus, ATZ N terminus) were measured. Inhibitors of ADAM10/ ADAM17 blocked PD-L1 cleavage.

Results

Figure 1: sPD-L1 predicts poor outcomes in metastatic melanoma.

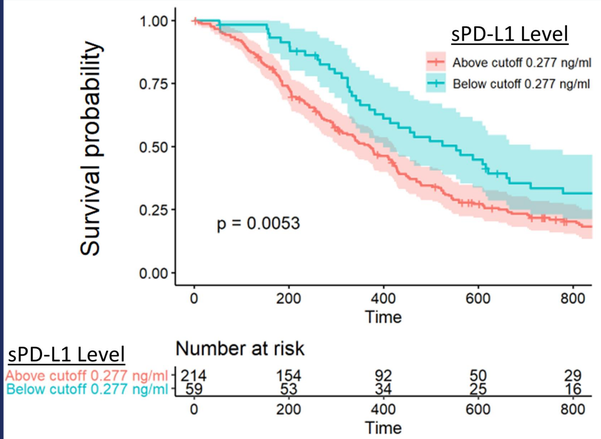


Figure 2: ADAM10 and ADAM17 cleave PD-L1 to produce sPD-L1.

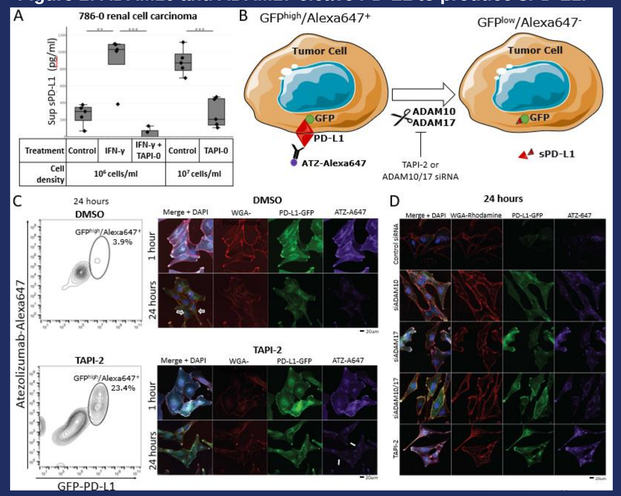


Figure 3: sPD-L1 limits tumor cell killing by peripheral bloodmononuclear cells (PBMCs).

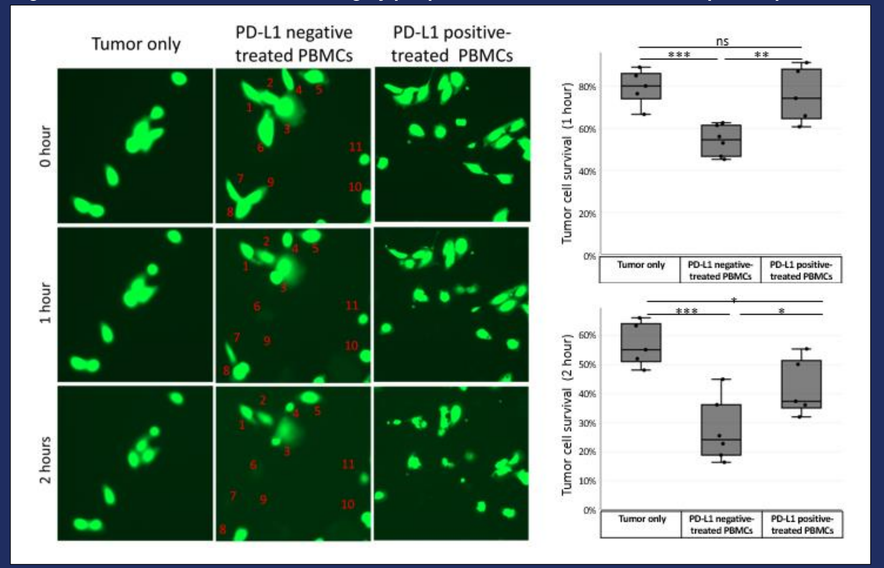
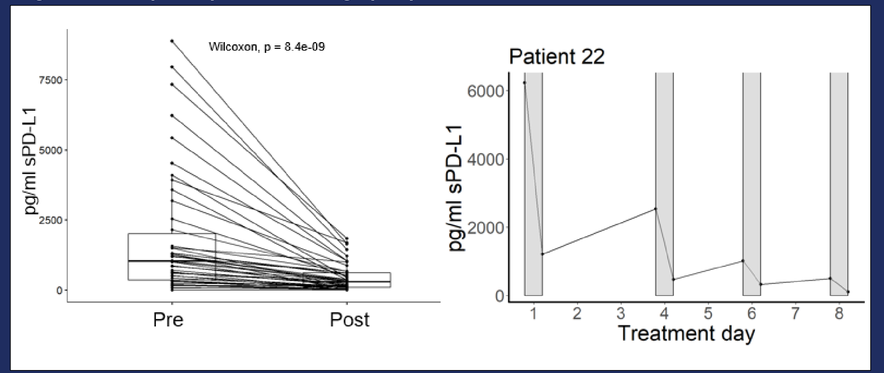


Figure 4: Therapeutic plasma exchange (TPE) removes sPD-L1 *in vivo*.



Methods and Results

- Figure 3: Peripheral blood mononuclear cells (PBMCs) were pre-treated with media, sPD-L1-negative, and sPD-L1-positive supernatant for four hours. 786-0 PD-L1-deficient cells with calcein dye were then treated with these PBMCs and tumor cell killing was measured. PD-L1-negative supernatant-treated PBMCs significantly reduced tumor cell survival at 60 and 120 minutes versus media control and PD-L1 positive supernatant-treated PBMCs.
- Figure 4: 24 patients undergoing therapeutic plasma exchange (TPE) were enrolled and gave blood samples before and after each session. TPE significantly reduced plasma sPD-L1 levels in patients receiving albumin-only (i.e. no FFP) replacement fluid. Mean 70.8% removal was seen per cycle. Example of Patient 22 shown.

Conclusions and Future Studies

- This study identifies a novel mechanism of resistance to anti-PD-1 therapy
- Furthermore, it offers a potential therapeutic intervention (TPE) to restore ICI sensitivity.
- Our pending clinical trial of this approach in melanoma has just been funded and approved.

References

Orme, J. J. et al. ADAM10 and ADAM17 cleave PD-L1 to mediate PD-(L)1 inhibitor resistance. Oncoimmunology. 9, (2020).

Orme, J. et al J. et al. Therapeutic plasma exchange clears circulating soluble PD-L1 and PD-L1-positive extracellular vesicles. J. Immunother. Cancer. 8, (2020).