Background

PD-L2 expression is shown to be as or more predictive of response to PD-1 blockade than PD-L1. PD-L2 traditionally was dismissed as functionally redundant to PD-L1 varying only in pattern of expression. We hypothesize that PD-L2 engages PD-1 to generate a distinct inhibitory signal from that of PD-L1, and antibody mediated blockade and depletion of PD-L2+ cells may promote anti-tumor immunity that is superior to PD-L1 blockade alone.

Methods


Results

We validated that human PD-L2, unlike murine PD-L2, generates a purely co-inhibitory signal in human T cells, albeit with a reduced inhibitory potential relative to PD-L1. We discovered significant differences in downstream T cell signaling pathways generated by PD-L1 versus PD-L2 through PD-1 engagement. Human PD-L1 and PD-L2 differentially modulated T cell effector function and proliferation with PD-L2 preferentially arresting T cells in S-phase of cell cycle. PD-L1 and PD-L2 also differed in the temporal kinetics of dephosphorylation of the membrane proximal proteins in the TCR-CD3 signaling complex. We observed that combination blockade of PD-L1 and PD-L2 improves on blockade of PD-L1 alone resulting in increased production of IL-2 and IFNγ in primary human mixed lymphocyte reactions. Our data in a syngeneic murine model of EL4 showed that effector-function capable PD-L2 blocking antibodies are therapeutically superior to PD-L1 or PD-L2 blockade alone.

Conclusions

We are the first to report on T cell immunoregulatory functions of PD-L2 which are distinct from those of PD-L1, and demonstrate that the more tumor-selective expression pattern of PD-L2 relative to PD-L1 provides a therapeutic advantage to effector-function capable PD-L2 antibodies.

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REFERENCES


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