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PD-L1 biology in response to chemotherapy in vitro and in vivo in ovarian cancer

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Objective

PD-L1 is an immune checkpoint molecule expressed by a variety of tumors, including ovarian, which binds to circulating PD-1 expressing effector T cells allowing for tumor escape from the immune system. PD-L1 blockade prevents PD-L1/PD-1 interaction and is currently explored as therapy of solid tumors. Ovarian cancer patients receive combination cisplatin/taxane chemotherapy as standard of care. Chemo-induced effects on tumor PD-L1 expression have been only partially addressed. We studied here the effect of platinum/taxane exposure on PD-L1 expression in vitro and in vivo.

Methods

Human (OVCA 420 and OVCA432) and mouse (2F8) ovarian cancer cell lines were exposed to increasing doses of cisplatin and paclitaxel for different time periods. PD-L1 expression was analyzed with flow cytometry and Western blot. Through continuous exposure in vitro of mouse 2F8 ovarian cancer cells to increasing doses of cisplatin we have derived a new cisplatin-resistant line (2F8-Cis). In vivo, we have challenged n=37 mice IP with 0.8 million 2F8 cells. Tumor-bearing mice were treated with cisplatin, anti-PD-L1 antibody, both drugs, or isotype control every two weeks for three doses starting at day 14 post-inoculation. Tumor- and ascites-derived cancer cells were analyzed with flow cytometry.

Result

Exposure of OVCA420 and OVCA432 to cytotoxic doses of cisplatin or paclitaxel trigger PD-L1 up-regulation. Similarly, 2F8-Cis cells show increased cell surface PD-L1 compared to parental 2F8 cells, providing the rationale for combination therapy with PD-L1 blockade. In vivo treatment of mice with aggressive 2F8 tumors respond well to cisplatin and anti-PD-L1 individually with increased survival (median 45 days versus 24 days for isotype control, p=0011). At necropsy, anti-PD-L1 therapy significantly reduced tumor burden (1.48 g versus 0.25 g, p=0.0294). Tumor cells cultured from cisplatin-only treated mice expressed higher levels of PD-L1, in line with our in vitro results. A higher percentage of PD-1 expressing cells were found amongst the tumor cells in these cultures versus cisplatin/anti-PD-L1 treated mice. Although high dose anti-PD-L1 immediately following cisplatin administration can control tumor burden (0.48 g), it does not significantly prolong survival (median 29 days). We are currently testing an alternative therapeutic schema exploring a lower anti-PD-L1 dose and a different timing post-chemo.

Conclusion

Tumor cells upregulate PD-L1 in response to chemotherapy exposure and combination PD-L1 blockade in conjunction with chemotherapy effectively controls tumor burden. Optimization of timing and dosage for this combination therapy will likely increase its therapeutic benefit.

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