Poster 19: PD-L1 and Interferon Type 1 as a Potential Novel Cancer Cell-Autonomous Mechanism of Chemoresistance in a Patient Derived Model of High Grade Serous Ovarian Cancer.

Presenting Author: Ashlyn Conant, Loma Linda University

Topic
Ovarian

Objectives
To better understand the molecular mechanisms contributing to therapy resistance in high grade serous ovarian cancer (HGSOC), our group developed a chemo-resistant and -sensitive pair of patient-derived (PDX) HGSOC cells via chronic, long term cisplatin exposure. RNA sequencing revealed that type 1 interferon (IFN-1) production and signaling, as well as JAK/STAT signaling, were among the most enriched pathways in the resistant cells. PD-L1 RNA was also found to be significantly higher in the resistant cells. An interferon related DNA damage signature (IRDS), as well as high PD-L1, have been associated with low level, chronic interferon signaling and therapy resistance in other cell types, although this mechanism is poorly defined and represents a novel resistance mechanism in HGSOC. Our hypothesis is that chronic IFN-1 production and signaling is driven by high expression of PD-L1, resulting in IRDS expression and cisplatin resistance in HGSOC cells.

Methods
Using one platinum sensitive PDX sample, one platinum resistant PDX sample, and a pair of chemo-resistant and -sensitive PDX HGSOC cells, RT-qPCR and flow cytometry were completed to evaluate the expression of IFNs, associated JAK/STAT signaling pathway members, and IRDS genes or proteins. To determine if a causal relationship between treatment with cisplatin, PD-L1, IFN-1 signaling, and resistance exists, cells were treated with their respective IC50 of cisplatin for 48 hours and proteins were analyzed using flow cytometry. To elucidate the role of PD-L1 in promoting resistance via interferon and IRDS expression, PD-L1 (CD274) was knocked down, and IFN-1 and IRDS RNA or protein were assessed. An MTT cell viability assay was performed to evaluate baseline response to cisplatin, as well as the effect of PD-L1 knockdown on response to cisplatin.

Results
Consistent with what is known about HGSOC, there is marked heterogeneity in PD-L1, IRDS, and IFN-1-associated gene expression at baseline, unstimulated cellular states. Notably, upon stimulation of sensitive and resistant cells with cisplatin, baseline PD-L1, pSTAT1, and total STAT1 expression in both resistant cell lines, and one sensitive cell type, increased. Knockdown of PD-L1 resulted in a decrease in resistance and some IRDS gene expression, although these did not reach statistical significance.

Conclusions
These data suggest that upon treatment with cisplatin, regardless of resistance status, there is activation of JAK/STAT signaling, as determined by an increase in pSTAT1 and total STAT1, in most cases. The increase in PD-L1 expression, along with the activation of the IFN-1 associated signaling pathway, upon cisplatin treatment suggests that PD-L1 may contribute to IFN production, signaling, and consequent IRDS expression and associated

therapy resistance. Further PD-L1 knockdown will be completed to validate this potential mechanism.

Uploaded File(s)
Abstract Table or Graph
NWNUUGRI-2092655-1-ANY(1).pdf