Poster 41: Overexpression of the microRNA let-7i does not consistently enhance sensitivity to cisplatin in vitro in patient-derived epithelial ovarian carcinoma samples

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Topic: Ovarian

Objectives

Epithelial ovarian carcinoma (EOC) is the most lethal gynecologic cancer. Decreased levels of the tumor suppressor microRNA (miRNA) family let-7 are seen in EOC and other cancers. Loss of let-7 correlates with chemoresistance and poor prognosis. Replacement of let-7 family members has been shown to increase sensitivity to platinum chemotherapy in oral and gastric cancer cells. Prior studies in our lab demonstrated let-7i was lost to a greater degree as compared to other let-7 family members in EOC patient-derived cells, and in EOC cells let-7i overexpression increases sensitivity to poly-ADP ribose inhibitors (PARPi). We hypothesized that restoring let-7i levels in EOC patient-derived cell via overexpression will increase sensitivity to cisplatin.

Methods

Let-7i overexpression (OE) was performed via lipofectamine transfection. Successful OE was confirmed via reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Sensitivity to cisplatin was characterized using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell viability assay. Using the institutional biobank, 12 patient-derived (PD) samples were identified for study; 6 had growth characteristics favorable for completion of the experiments presented here.

Results

PD1 is derived from a patient with platinum resistant EOC. PD2, PD3, PD5, PD8 and PD9 are from patients with platinum sensitive EOC. PD1, PD2, and PD9 are homologous recombination repair proficient, while PD3, PD5, and PD8 are homologous recombination deficient (HRD). Only PD8 demonstrated increased sensitivity to cisplatin after overexpression of let-7i. PD5 was more resistant to cisplatin after let-7i overexpression, and a similar trend in PD9 did not reach statistical significance. No significant difference was seen in the remaining three cell types.

Conclusions

Prior studies have demonstrated increased sensitivity to platinum chemotherapy after replacement of let-7 family members in multiple cancers. In a set of 6 patient-derived EOC samples, let-7i replacement increased sensitivity to cisplatin in only one, and increased resistance to cisplatin in two. Further studies will be needed to elucidate the pathways and characteristics resulting in these different responses to let-7i OE.

Abstract Table or Graph

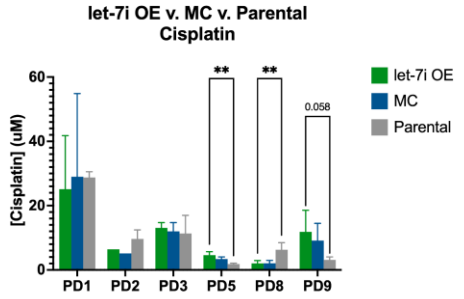

Figure 1: **Graphical depiction of Cisplatin IC50 in 6 patient derived cell types after overexpression of the microRNA *let-7i***