Pharmacologic inhibition of Discoidin Domain Receptor 2 (DDR2) sensitizes homologous recombination proficient ovarian cancer models to treatment with olaparib.

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Topic: Ovarian

Objectives
Discoidin Domain Receptor 2 (DDR2) is a tyrosine kinase receptor which binds fibrillar collagen type 1. Previous work from our lab demonstrated that genetic inactivation of DDR2 increases sensitivity to olaparib in homologous recombination (HR) proficient ovarian cancer models through induced HR deficiency and decreased pentose phosphate pathway activation. This leads to decreased nucleotide biosynthesis and increased DNA damage. This study aimed to demonstrate increased sensitivity to olaparib with pharmacologic inhibition of DDR2 and to further understand the cell signaling mechanism of DDR2 inhibition increasing sensitivity to olaparib.

Methods
Two high grade serous HR proficient ovarian cancer cell lines were used, ES2 and UWB1 with genetic re-expression of BRCA1 (UWB1 BRCA1 wt). A small molecule allosteric inhibitor of DDR2 was used for pharmacologic inhibition. Western blot was used to detect changes in HR pathway protein expression after DDR2 inhibition. Cell viability after treatment with or without 1uM of the DDR2 inhibitor and olaparib was quantified using MTS assays. Flow cytometry was used to quantify cell cycle changes relative to DDR2 expression.

Results
Western blot confirmed both cell lines expressed DDR2 and showed decreased expression of p-DDR2 and p-AKT, a downstream effector, after treatment with the DDR2 inhibitor thus confirming that the inhibitor inhibits the DDR2 pathway. MTS viability assays showed no cell death with inhibitor treatment alone. However, treatment with the DDR2 inhibitor increased sensitivity to olaparib with a 99% reduction (0.03 uM vs 42 uM) and 14% reduction (122 uM vs 141 uM) in IC50 in ES2 and UWB1 BRCA1 wt cell lines, respectively. Notably, the DDR2 inhibitor altered expression of proteins involved in DNA damage repair. We found decreased expression of ATM, a known inducer of the pentose phosphate pathway, and decreased expression of p-CHK1, a key regulator of S phase progression. Cell cycle changes using flow cytometry showed genetic inhibition of DDR2 increased the length of S phase in both ES2 and UWB1 BRCA1 wt cells. Finally, DDR2 inhibition did not change the expression of PARP1 (poly(ADP ribose) polymerase 1) but did decrease PARylation, a post-translational modification of proteins catalyzed by PARP, suggesting that DDR2 inhibition impairs PARP1 activity.

Conclusions
Pharmacologic inhibition of DDR2 increases sensitivity to olaparib in HR proficient ovarian cancer models through impaired DNA damage repair by decreasing pentose phosphate pathway activation, disrupting cell cycle regulation and impairing PARP1 activity. This adds to prior evidence that genetic inactivation of DDR2 induces functional HR deficiency and increases DNA damage. Taken together, these results provide strong evidence in support of DDR2 inhibition as a therapeutic target for HR proficient ovarian cancers.