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Targeting Mre11 Nuclease Overcomes Platinum Resistance and Induces Synthetic Lethality in Platinum Sensitive XRCC1 Deficient Epithelial Ovarian Cancers

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Abstract : Platinum resistance is a clinical challenge in ovarian cancer. Platinating agents induce DNA damage which activate Mre11 nuclease directed DNA damage signalling and response (DDR). Upregulation of DDR may promote chemotherapy resistance. Here we have comprehensively evaluated Mre11 in epithelial ovarian cancers. In clinical cohort that received platinum- based chemotherapy (n=331), Mre11 protein overexpression was associated with aggressive phenotype and poor progression free survival (PFS) (p=0.002). In the ovarian cancer genome atlas (TCGA) cohort (n=498), Mre11 gene amplification was observed in a subset of serous tumours (5%) which correlated highly with Mre11 mRNA levels (p<0.0001). Altered Mre11 levels was linked with genome wide alterations that can influence platinum sensitivity. At the transcriptomic level (n=1259), Mre11 overexpression was associated with poor PFS (p=0.003). ROC analysis showed an area under the curve (AUC) of 0.642 for response to platinum-based chemotherapy. Pre-clinically, Mre11 depletion by gene knock down or blockade by small molecule inhibitor (Mirin) reversed platinum resistance in ovarian cancer cells and in 3D spheroid models. Importantly, Mre11 inhibition was synthetically lethal in platinum sensitive XRCC1 deficient ovarian cancer cells and 3D-spheroids. Selective cytotoxicity was associated with DNA double strand break (DSB) accumulation, S-phase cell cycle arrest and increased apoptosis. We conclude that pharmaceutical development of Mre11 inhibitors is a viable clinical strategy for platinum sensitization and synthetic lethality in ovarian cancer.

Keywords : MRE11; XRCC1, ovarian cancer, platinum sensitization, synthetic lethality
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