RESEARCH FINAL REPORT

The Effects of RAPTA-EA1 on Conformation, Binding and Ubiquitination of BRCA1 RING protein

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ABSTRACT

The RAPTA-EA1 complex [ruthenium(II)-arene 1,3,5-triaza-7-phosphaadamantane (pta) complex with an arene-tethered ethacrynic acid ligand] has been reported to overcome drug resistance developed to the current platinum-based treatments. However, the exact mechanism of action of RAPTA-EA1 remains largely unexplored. To address this concern, we have investigated the effects of RAPTA-EA1 on conformation, binding and ubiquitination of the BRCA1 RING protein. Changes in the conformation, binding constants and thermal stability of ruthenium-BRCA1 adducts were observed, causing inactivation of the RING heterodimer BRCA1/BARD1-mediated E3 ubiquitin ligase activity. Moreover, treatment of the BRCA1 RING protein with RAPTA-EA1 in combination with the PARP inhibitor, olaparib, resulted in a synergistic effect. These findings could provide an alternative approach to finding an effective therapeutic ruthenium-based agent, and demonstrated that the BRCA1 RING domain protein was a promising therapeutic target for breast cancers.