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A SURVIVIN REGULATED ONCOLYTIC ADENOVIRUS CAN IMPROVE THERAPEUTIC OUTCOME IN CHEMOTHERAPY RESISTANT LUNG CANCER

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The treatment of advanced lung cancer is restricted due to chemotherapy resistance even in the patients which initially show a good response. Author previously investigated a surviving promoter regulated conditionally replicating adenovirus (Sur-P-CRAd) for its anti-tumor potential along with cisplatin in three lung cancer cell lines; A549, H292 and H661 and found it very efficient. Also, surprisingly, CRAd in monotherapy proved very lethal against chemotherapy resistant sublines of above mentioned cells. They have suggested cisplatin-driven up regulation of CAR as a selective vulnerability of chemotherapy-resistant cancers. Keeping in mind the heterogeneity of lung cancer, this study employed two different lung cancer cells, H23 and H2126 and their resistant sublines H23/CPR, H2126/CPR, which were developed in our lab. RT-PCR and western blotting analysis confirmed that ABCB1 (MDR1) gene was overexpressed at both mRNA and protein levels in resistant sublines. Also, cocksackie-adenovirus receptor (CAR) expression found significantly up regulated in resistant cells as compared to chemo-sensitive cells. Resistant cells exhibited enhanced adenoviral transduction efficacy in X-gal staining assay which validated the up regulation of CAR. MTT assay, flow cytometry and scratch assays showed that cisplatin significantly decreases the viability of chemo-sensitive cells and its combination with CRAd synergistically inhibited cancer cell survival. Moreover, transwell assay revealed that CRAd pre-treatment restricts migratory ability of cancer cells. Epithelial to mesenchymal transition (EMT) markers investigation displayed that CRAd-treatment could reverse EMT event, but its molecular mechanism needs further elucidation. CRAd monotherapy experiments with resistant cells recapitulated similar results which established our hypothesis that CRAd alone is a very potent anticancer agent for resistant and metastatic tumors. These insights may prove to be a timely opportunity for the application of CRAd in recurrent drug-resistant cancers. Further studies are warranted to confirm the possible use of this innovative treatment approach in clinics and to move it from bench to bedside.