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Dealing with chemotherapy resistance: A new road to lung cancer therapy

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Introduction: Among the fatal malignancies, lung cancer is the most common and leading cause of cancer-related deaths in the developed world. Over the past 30 years, lung cancer survival rates have not changed much. NSCLC accounts for nearly 80% of all lung cancers. Despite increasing interest in developing non-cytotoxicity drugs, systemic chemotherapy is still the most commonly practiced anti-cancer strategy for all kinds of lung cancer. But, the treatment of advanced lung cancer is restricted due to chemotherapy resistance. Chemotherapy resistance in lung cancers may be in some cases is intrinsic, but in virtually all instances, acquired resistance is developed even in the patients which initially show a good response to chemotherapy.

Objective: Conditionally replicating adenoviruses (CRAds) have already demonstrated potency as anti-tumor agents. Their tumor-specific replication on account of integrated survivin promoter results in very high tumor targeting ability sparing the normal tissues. We previously investigated its anti-tumor potential along with cisplatin in three lung cancer cells; A549, H292, and H661, and found it very efficient. Also, fortunately, CRAd in monotherapy proved very lethal against chemotherapy resistant cells of above mentioned cell lines. We have suggested cisplatin-driven upregulation of CAR as a selective vulnerability of chemotherapy-resistant cancers. Keeping in mind the heterogeneity of lung cancer, the goal of the current interrogation was to examine and verify the toxicity of CRAd using some other cisplatin-resistant cells of the same cancerous organ.

Materials and Methods: CRAd was previously engineered by our research group by replacing its E1B region with survivin promoter to regulate the replication. Two lung cancer cells, H23 and H2172, employed in current experiments were obtained from the CAS-China. The resistant cells, H23/CPR and H2172/CPR, were developed in our lab. The anti-tumor efficacy was evaluated *in vitro* through MTT assay, resazurin assay, and colony formation assay. To measure the expression of Multi-Drug Resistance and Coxsackievirus and adenovirus receptor (CAR) genes, RT-PCR was performed.

Results: We demonstrated through *in vitro* studies that cisplatin alone significantly decrease the viability of both, H23 and H2172, lung cancer cells and its combination with CRAd synergistically inhibited cancer cell survival. Also, experiments with chemotherapy resistant cells recapitulated similar results which established our hypothesis that CRAd alone is a very potent anticancer agent for resistant cells. These insights may prove to be a timely opportunity for the application of CRAd in recurrent drug-resistant cancers.

Conclusion: This study established that CRAd monotherapy could be a practical approach to deal with resistance issues. Further studies involving cancer cells of other origins are necessary to authenticate this promising anti-chemoresistance agent.

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