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From resistance to sensitivity in non-small cell lung cancer: newly established multidrug-resistant cancer cells contribute to identifying DNA damaging agents as collateral sensitizer drugs

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Abstract

Background: Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and presents a low 5-year survival rate [1]. Standard treatment of NSCLC includes chemotherapeutic drugs, such as taxanes and platinum-based agents. However, cancer cells may acquire resistance to multiple unrelated chemotherapeutic agents, known as multidrug resistance (MDR), which significantly limits treatment options [2]. Remarkably, it was discovered that some compounds present a stronger antitumor effect on MDR cells than on sensitive counterpart cells. This phenomenon, known as collateral sensitivity, may represent an important strategy to overcome MDR [3]. **Objective:** This work aimed to establish MDR cell lines from a sensitive NSCLC parental cell line and to identify collateral sensitizer drugs by using these newly established MDR cell sublines. **Methods:** Treatment of NSCLC A549 cells with progressively increasing concentrations of paclitaxel led to the establishment of two new MDR sublines. The MDR phenotype was confirmed using the Sulforhodamine B and Rhodamine123 accumulation assays. Further characterization of the cells included analysis of selected protein expression levels by Western Blotting and evaluation of cell death and ROS production levels by flow cytometry. **Results:** The newly established cell lines were confirmed to be resistant to paclitaxel and also to other chemotherapeutic drugs from different drug classes. Moreover, the MDR phenotype of these cells was confirmed by the overexpression and increased activity of drug efflux pumps, such as P-glycoprotein. Curiously, MDR cells were more sensitive than the parental drug-sensitive cells to specific drugs involved in DNA damage, indicating that the MDR sublines presented a collateral sensitive effect to these drugs. The MDR cells presented higher DNA damage and increased ROS production than the parental sensitive cells, which could justify the higher susceptibility of the MDR cells to DNA damaging drugs. **Conclusions:** Two MDR NSCLC sublines, which may become relevant models to study collateral sensitivity and to identify compounds to overcome MDR in NSCLC, were successfully established and characterized. Most importantly, DNA-damaging drugs caused collateral sensitivity in these MDR cells, indicating that these drugs are good treatment options for NSCLC MDR patients.

Keywords: non-small cell lung cancer (NSCLC); multidrug resistance (MDR); collateral sensitivity

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