Effects of respiratory mechanical forces on the pharmacological response of lung cancer cells to chemotherapeutic agents.

In vitro screening of chemotherapeutic agents is routinely carried out in static monolayer cell cultures. However, drugs administered to patients act in the presence of various microenvironments in vivo. For example, in lung tumors, mechanical forces are constantly present and do affect the physiological response of the lung tissue to a variety of therapeutic agents. We hypothesized that mechanical forces may affect the response of lung tumors to chemotherapeutic agents and studied the effects under simulated conditions. First, we examined the effects of simulated forces that approximate normal respiration on the proliferation and morphology of NCI-H358 and A549 cell lines. Then, we studied the effects of the simulated forces on the ability of Paclitaxel, Doxorubicin, Cisplatin, Zactima and an experimental drug to induce cytotoxicity in both cell lines. Cells were treated with the drugs in the presence or absence of simulated forces (20% maximum strain and 15 cycles/minute) that approximate human lung expansion and contraction. Cell proliferation and the effectiveness of the drugs were assessed. Using a standard exponential cell growth model, it was determined that mechanical forces significantly reduced the proliferation of both cell lines. Interestingly, forces also significantly lowered the effectiveness of all drugs except Zactima in A549 cells, while in NCI-H358 cells, Zactima was the only drug that demonstrated an increase in effectiveness owing to applied forces. Our results demonstrate that mechanical forces have significant impact on cell survival and
chemotherapeutic efficacy and may be of significance in engineering improved screening assays for antitumor drug discovery.

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