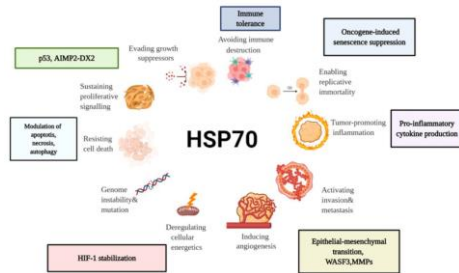


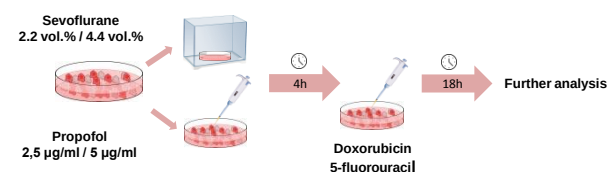
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Heat shock protein 70 (HSP70) is a key component of cell protection. Functions of HSP70 in cancer cells are multiple and ultimately lead to an increase in proliferative signaling, migration ability, invasiveness, and decrease in cell death, including elevated resistance to chemotherapy (Fig. 1).



The role of HSP70 makes this molecule an attractive target for anticancer therapy. There is an active search for HSP70 inhibitor molecules, which demonstrate quite prominent antitumor activity *in vitro* and *in vivo*.

To assess whether HSP70 expression is dependent on sevoflurane and propofol, we took three cell lines: A549 human lung carcinoma, CT26 murine colorectal carcinoma, and DLD1 human colorectal carcinoma. Propofol was added to the cell culture medium at concentrations of 2.5 and 5 µg/ml. To assess the effect of sevoflurane, cells were placed in a specially designed chamber containing predominantly measured volume concentrations of sevoflurane (2.2 and 4.4 vol. %). The anaesthetic doses in the experiment were equal to those used in clinical practice. To exclude the influence of the solvent on HSP70 induction, cells were exposed to fat emulsion corresponding in lipid composition to propofol 5 µg/ml. The exposure time with anaesthetics and control drugs was 4 hours which is commensurate with the approximate duration of anesthesia in oncosurgical interventions. In order to test whether HSP70 expression would be potentiated by stress factors, we exposed the cells to chemotherapy drugs such as 5-fluorouracil at 5 and 50 µg/mL and doxorubicin at 1 and 5 µM. After 18 hours of exposure, the cells were lysed, and the lysates were subjected to protein electrophoresis in a polyacrylamide gel (Fig. 2, 4). The relative concentration of HSP70 was determined by measuring the intensity of the pixel fluorescence using Li-Cor Image Studio™ Lite Quantification Software and normalized to the fluorescence of GAPDH bands and control samples. The experiment was repeated 3 times.



A549

CT26

DLD1

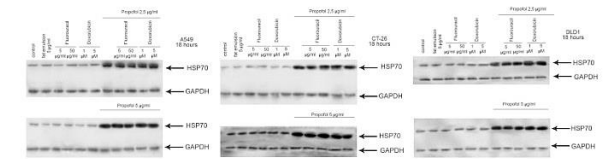
Legend:

- Control
- Fat
- No anaesthetic
- Propofol 2.5 µg/kg
- Propofol 5 µg/kg
- Sevoflurane 2.2 vol. %
- Sevoflurane 4.4 vol. %
- 5-fluorouracil 50 µg/ml
- No chemotherapy
- Doxorubicin 1 µM
- 5-fluorouracil 5 µg/ml
- Doxorubicin 5 µM

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Propofol significantly increased the expression of HSP70 in a dose-dependent manner in all studied cell cultures (Figure 3). The maximum effect was observed in A549 pulmonary adenocarcinoma cells: after the exposure to propofol at a concentration of 2.5 µg/ml, an increase in HSP70 expression was observed by 5.3 times, and after the exposure to propofol at a concentration of 5 µg/ml, by 7.6 times. Chemotherapeutic drugs did not significantly affect the synthesis of HSP70. Exposure of cells to sevoflurane also did not lead to a significant increase in HSP70 expression.



Thus, propofol is an inducer of HSP70 expression in cancer cells, which has been demonstrated in three cell lines. It remains to be studied how this property of propofol affects proliferation, the ability to invade and metastasize, immunogenicity, and apoptosis of cancer cells. To date, no published large prospective study is comparing the effects of inhalation versus intravenous anaesthesia in oncology, and the VAPOR-C study (NCT04316013) is currently recruiting patients to compare the effects of these two types of anaesthesia on oncological patients prognosis. Further study of the possible HSP70-mediated protective effect of propofol *in vitro* and *in vivo* is needed, since this phenomenon may have a significant impact on the patient's outcome.