CANCER CELLS RESPONSE ON THE MICROTUBULE-INHIBITING DRUGS

Balabiyev A.[1], Kakpenova A.[1], Kauanova S.[1], Vorobjev I.A.*[1, 2]

[1] *National Laboratory Astana (Astana, Kazakhstan)*
[2] *A.N. Belozersky Institute of Physico-Chemical Biology and Department of Cell Biology and Histology, Faculty of Biology, M.V. Lomonosov Moscow State University (Moscow, Russia)*
skashikova@nu.edu.kz

Introduction.Cancer is one of the age-related diseases with detrimental impact on people survival. Improvement of cancer therapies is a major focus of many scientists around the world. Anticancer drugs based on the microtubules inhibition are successfully used to treat wide-range of cancers. Anti-microtubules drugs directly bind to colchicine, vinca and taxol binding sites on beta-tubulin, resulting in the impairment of spindle formation, vesicle transport, cell structure and migration. One of the modes of action anti-tubulin drugs is through causing faults in mitotic spindle function, which lead to the prolonged mitotic block and consequently to cell death. Although, drugs' high toxicity and development of resistance in patients lead to the idea of revisiting the dosage and combination therapies of anti-tubulin drugs, some sources reported that cell migration is more sensitive to microtubule inhibiting drugs than to cell proliferation in endothelial cells. Previously, we reported observations on NIH/3T3 (normal fibroblasts) cell proliferative activity, cell migration and direct test of microtubule dynamics. Thus, we aimed to identify effect of microtubule inhibitors on cancer cell lines. In addition, we compare normal cell lines with human cancer cell lines such as A549 (lung carcinoma), HT1080 (fibrosarcoma) and U118 (glioma).

Methodology. Using high-throughput microscopy we have obtained large of sets of experiments, which gave us statistically significant values. We followed up individual cells and described in detail their fates during mitosis. For cell migration evaluation we used a gold standard wound healing assay.

Results and discussion. Our results revealed that cancer cells are affected by MT binding drugs differently than normal cells. In particular, all three cancer cell lines demonstrated at least 10 times higher sensitivity to MT binding drugs compared to normal cell lines on mitotic progression. However in all cultures cells had been arrested in mitosis often escaped into interphase demonstrating mitotic slippage. We further analyzed the effect of microtubule inhibitors on cancer cell migration. For A549, HT1080 and U118 cancer cell lines, 1 μM concentration of all drugs could diminish the migration rate as low as 30%, except for more inhibitory effect of taxol on HT1080. In comparison, normal 3T3 fibroblast migration can be completely inhibited at 1 μM. The concentration curve pattern suggests that both normal and cancer cells at some point do not respond to the increasing drug dosage. We hypothesize that cancer cells possibly acquire resistance to drugs through mitotic slippage, but this mechanism requires further elucidation.

Conclusion. Overall, our results showed that microtubule binding drugs can be detrimental for cells in dose-dependent manner. Microtubule drug caused mitotic block that may result in

cell death, but can also lead to the development of polyploidy, which is the prerequisite of carcinogenesis and cancer progression. Therefore, we suggest that targeting cell motility is more important to tackle cancer cell migration and formation of metastases.

This work was supported by Grant # 0472/GF4 and TFP # 0212/PCF-14-OT(3) from MES (Republic of Kazakhstan).