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Autocrine human growth hormone expression leads to resistance of MCF-7 cells to tamoxifen

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Background: Tamoxifen is the most common antiestrogen used in Treatment of estrogen positive breast cancer but its adverse effect and also resistance to this drug are serious challenges in treatment of breast caner. Characterization of mechanisms responsible for these adverse effects can lead to design more efficient therapeutic strategies to treatmentof breast cancer.
Materials and Methods: Here we prepared a cellular model of autocrine expression of human growth hormone (hGH), by production of stable MCF-7 cell line expressing hGH, to evaluation of autocrine expression of hGH effects on response of cells to tamoxifen. By using of microculture tetrazolium test (MTT) we compared tamoxifen antiproliferative effects between MCF-HGH, MCF-7 cells expressing active hGH, and MCF-MUT, MCF-7 having translation deficient hGH coding region. To finding that which of esterogen receptors are responcible to difference between MCF-HGH and MCF-MUT cells response to tamoxifen, we performed real-time RT PCR reaction using primers specific for either of esterogen receptor (ER)-a, Er-β or G-coupled estrogen receptor (GPR30) and beta-actin as housekeeping gene.
Result: MTT results show that tamoxifen treatment of MCF-MUT cells leads to inhibiotion of cell proliferation. But autocrine expression of growth hormone in human breast adenocarcinoma cell line, MCF- 7, in MCF-HGH cells results that treatment of cells by tamoxifen not only does not decrease cell proliferation, but also, partially, increase it. real-time RT PCR results show that expression levels of ER-a and Er-β does not change under effect of autocrine hGH, while expression level of GPR30 in MCF-HGH cells is 4.5 fold higher than its expression level in MCF-MUT.
Conclusion: Our results suggest, autocrine hGH results to non-responsive phenotype of MCF-HGH cell to antiproliferative effects of tamoxifen. This effect may be as a result of upregulation of G-coupled estrogen receptor, GPR30, which does not inactivates by tamoxifen. These conclusion suggests, determination of autocrine hGH expression status of breast tumor cells can help to design appropriate therapeutic strategies in treatment of breast cancer patients.

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Correlation of BRCA1, DAXX, TXN, TXR1 and TSP1 tumoral expression with resistance to docetaxel-based chemotherapy in patients with advanced/metastatic Non Small Cell Lung Cancer

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Background: Taxanes are among the most active antitumor agents in the treatment of Non-Small Cell Lung Cancer (NSCLC). However, an increasing number of patients being treated with taxanes develop resistance that finally limits chemotherapeutic efficacy. The prognostic and predictive value of tumoral expression of 5 genes *(BRCA1*, *DAXX*, *TXN*, *TXR1* and *TSP1)* related with the mechanism of actions of taxanes was evaluated in patients with NSCLC treated with first-line docetaxel-based chemotherapy.
Material and Methods: Tumor samples from 184 patients, with stage IIIB (with pleural effusion) or IV NSCLC were analyzed for *BRCA1*, *DAXX*, *TXN*, *TXR1* and *TSP1* mRNA levels by quantitative real-time PCR, from microdissected cells derived from patients' primary tumors.
Results: The mRNA levels of the *BRCA1*, *DAXX* and *TXN* were significantly correlated with each other. Also, the mRNA levels of *TXR1-TSP1* were inversely correlated (Spearman's test: −0.38; $p = 0.002$). Low *TXR1* mRNA levels were associated with higher response rate (RR $p = 0.0014$), longer median time to tumor progression (TTP $p < 0.003$) and median overall survival (mOS $p = 0.004$), while high *TSP1* expression was also, correlated with higher RR ($p = 0.021$), longer TTP ($p < 0.0001$) and mOS ($p < 0.0001$). In addition, patients whose primary tumors presented higher *BRCA1* mRNA expression experienced higher RR ($p = 0.002$) in comparison with those with low *BRCA1* tumoral expression. Higher *DAXX* mRNA levels were significantly correlated with prolonged survival ($p = 0.028$) and a trend for higher RR ($p = 0.07$) and improved TTP ($p = 0.1$). No significant association was found for *TXN* expression. Multivariate analysis demonstrated that high *TXR1*/low *TSP1* expression was an independent prognostic factor for decreased TTP (HR 2.6; 95% CI: 1.7−4.1; $p < 0.0001$) and mOS (HR 3.4; 95% CI: 2.1−5.7; $p < 0.0001$).
Conclusions: These data indicate the *TXR1-TSP1* mRNA expression could be used for the prediction of taxanes' resistance in the treatment of NSCLC and merits further evaluation.

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Inactivation of Notch signaling by Withaferin-A in human colon cancer

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Background: Colorectal cancer is the third most frequently diagnosed cancer and the third leading cause of cancer-related deaths in men and women in the United States. The medicinal plant, *Withania somnifera*, is extensively used in Asian herbal medicines to treat a variety of ailments, including cancer. We identified Withaferin-A (WA), a major bioactive compound in *Withania somnifera* exhibits potent anti-cancer effects on colon cancer cells that underscores the necessity of studying the molecular mode of action of WA to clarify its potential clinical merit.
Materials and Methods: To determine the effect of WA on Notch signaling we used three colon cancer cell lines (SW-620, SW-480 and HCT-116). Cell viability and apoptosis was determined using Trypan Blue exclusion assay and Annexin V-FITC staining respectively. Western Blot analysis was performed to determine WA-mediated modulation in the expression of Notch signaling proteins. To study whether WA transcriptionally regulates Notch and its downstream genes, we isolated total RNA and subjected it to RT-PCR to determine WA-mediated modulation of mRNA expression of Notch and its downstream genes.
Results: Our results suggest that WA inhibits cell proliferation and induces apoptosis in colon cancer cells (SW-480, SW-620 and HCT-116). While dissecting the mechanism of action of WA on colon cancer cells, we found that WA inhibits Notch-1 signaling, which resulted in the downregulation of pAkt and Bcl-2 expression. In addition, inhibition of mTOR signaling by WA resulted in the down regulation of pS6K and p4E-BP1 expression in SW-480, SW-620 and HCT-116 colon cancer cells. We also observed, WA activates caspase-3 and PARP cleavage suggesting that it triggers the pro-apoptotic machinery in colon cancer cells. Interestingly, WA causes a strong mitotic catastrophe by arresting the cells G2/M phase of cell cycle in colon cancer cells. Finally, oral administration of WA resulted in significant tumor regression of xenografts comprised of highly metastatic colon cancer cells in nude mice.
Conclusions: Our results suggest that WA inhibits cell viability and induces apoptosis in colon cancer cells. Additionally, we found that the biological effects of WA were due to inhibition of Notch and its downstream signaling molecules. The results from our study suggest that WA can be explored for its potential as a targeted therapy for colon cancer.

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Influence of chemotherapy on breast cancer cells in the conditions of 24-hour incubation in vitro

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Background: Nowadays the spectrum of medicaments for treatment of oncologic patients constantly extends, but there is no common opinion about therapeutic advantages of these agents and practically there are no standardized schemes of their use in a combination with traditional therapy. In our opinion more perspective method is restoration of function of lymphocytes by using of ultrasonic influence. The technique of allocation of lymphocyte stimulation factor by ultrasound influence on serum, worked out in our centre, showed the high efficiency of restoration of the lost or weakened function of immune cells.
Materials and Methods: the **s**tudy of morphological tumor structure of 28 breast cancer patients showed that selected influences significantly differ by the character and expression of changes. In our work 5 series of the experiment are presented. In the 1 series of the experiment – tumor was processed by Cycloferon. In the 2 series of the experiment – tumor was processed by Doxorubicin. In the 3 series of the experiment – tumor was processed by the combination of Cycloferon and Doxorubicin. In the 4 series of the experiment – processing of tumor by combination of Doxorubicin and autoserum after ultrasound influences on it. In the 5 series of the experiment – tumor was processed only by autoserum after ultrasound processing.
Results: In the 1 series the rise of a number of mitosis till 1.3% and insignificant induction of apoptosis till 0.8% was marked. In the 2 series the quantity of mitosis considerably decreased to 0.6% and expression of apoptosis increased to 1.5%. Simultaneously a toxic damage of cells