Conclusions: HLDF6 peptide exhibited antitumor activity in mice with experimental hemoblastosis, which was characterized by the inhibition of the primary tumor growth and the potentiation a cytostatic effect of CP. Besides, it has been shown that HLDF6 had a direct antiproferative effect on tumor cells.

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Antitumor activity of fragments of the HL-60 cell differentiation factor in mice with Lewis lung carcinoma

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Background: In the course of studies of the HL-60 cell differentiation factor two peptide fragments, hexamer HLDF6 and octamer HLDF8, with antiproliferative, differentiating and apoptogenic properties were identified (Kostanyan et al, 1995; 1999). It has been demonstrated that HLDF6 was an effective antitumor agent in mice with NSO myeloma (Kostanyan et al, 2000). The peptide had steroidogenic properties (Rzhevsky D.I., 2003), which made us think that it could influence the growth of hormone-dependent tumors. In this connection the aim of the present paper was to study antitumor activity of HLDF fragments in mice with transplanted Lewis lung carcinoma (LLC).
Materials and Methods: HLDF6 and HLDF8 peptides were i.p. administered to tumor-bearing female C57Bl/6 mice in a dose of 25 mg/kg five times at an interval of 24 h, with the first injection 24 h or 12 days after LLC transplantation. Cyclophosphamide (CP, 50 mg/kg) was i.p. administered on day 11 after transplantation. The mouse groups that were given saline, CP or the peptides in equivalent doses were used for comparison. Antitumor activity of the peptides was evaluated by the dynamics of the tumor growth node and the parameters of metastatic spreading of the tumor in lungs.
Results: It has been shown that administration of HLDF6 and HLDF8 peptides at different times after tumor transplantation did not have an effect on the primary tumor growth and did not enhance a cytostatic effect of CP. At the same time the injections of HLDF6 and HLDF8 at the early stage of the tumor development markedly decreased the number of lung metastases (by 40 and 48%, respectively, as compared to controls). Administration of HLDF6 in combination with CP caused a decrease in the parameters of metastatic spreading as compared to the animals injected with CP alone. When the peptide was administered prior to CP at the early stage of tumor process, a 20% decrease in the number of metastases was observed. Five-fold administration of HLDF6 at the late stage of the tumor development following the injection of CP decreased the number of lung metastases by 2.6 times and increased the animal life expectancy by six days.
Conclusions: HLDF6 and HLDF6 peptides did not have a marked effect on the Lewis lung carcinoma growth when they were used alone or in combination with cyclophosphamide. However, these peptides attenuated the process of metastatic spreading of the tumor and enhanced cytostatic effect.

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Different regulation of growth signal according to HER2 amplification status in primary breast cancer

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Background: HER2 amplification affects the cell proliferation through the modulation of multiple G1 cell cycle regulators in breast tumor cells.
Materials and Methods: We analyzed expression profiles of retinoblastoma protein (pRB) and p27Kip1 according to the HER2 amplification status on tissue microarray (TMA) from 153 breast cancers.
Results: HER2 amplification was observed in 39 (25.5%) of 153 breast cancers. The frequency of HER2 amplification was significantly increased in high grade tumors ($p = 0.023$). pRB was expressed in 54 (39.5%) of 114 tumors without HER2 amplification whereas it was expressed in 27 (69.2%) of 39 tumors with HER2 amplification. pRB expression was significantly associated with HER2 amplification. p27Kip1 expression was preserved in 75 (49%) of 153 tumors. p27Kip1 expression was preserved in 57 (50%) of 114 tumors without HER2 amplification whereas its expression was preserved in 18 (46.2%) of 39 HER2-amplified tumors. There was no significant relationship between HER2 amplification and p27 expression. We analyzed the change of proliferative index (PI) according to the HER2 amplification status. In 39 HER2-amplified tumors, PI was increased in 66.7% of pRB negative tumors. In contrast, PI was increased in 22.3% of 27 pRB expressing tumors. Degree and frequency of PI increase was significantly decreased in pRB expressing tumors ($p = 0.036$). The change of PI was also analyzed according to the p27Kip1 expression, but the association between PI and p27Kip1 was not observed in HER2 amplified tumors. In 114 HER2 non-amplified tumors, PI was increased in 21 tumors (36.8%) out of p27Kip1 repressed tumors. In contrast, PI was increased in 12 tumors (24.5%) out of 57 tumors with p27Kip1 preservation. The PI was significantly decreased in the tumors with p27kip1 expression ($p = 0.001$). The association between pRB expression and PI was not observed in these tumors.
The PI of the breast cancers was associated with pRB expression in HER2 amplified tumors whereas it was associated with p27Kip1 expression in HER2 non-amplified tumors. The results of the current study indicate that the cell proliferative activity of the breast cancer is under different regulation of growth signals according to HER2 amplification status.

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Influence of the long-term action of the flavonoid: curcumin or quercetin on the DNA damage induced by etoposide in the LT12 cell line

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Background: Plant flavonoids like curcumin or quercetin are famous for their numerous beneficial properties including antioxidant, anti-inflammatory and anticarcenogenic effects. Recently great hope has been lying in the introduction of flavonoids to chemotherapy as an adjuvant therapy. The aim of such a therapy is to minimize the side-effects of chemotherapy without decreasing the antitumor/antineoplastic effects of cytostatics. The aim of study was to ascertain the influence of curcumin or quercetin on the DNA damage induced by etoposide in the LT12 cell line derived from rat BNML leukemic model.
Materials and Methods: LT12 cells were treated for 24, 48 and 72 hours in the presence of curcumin or quercetin in the concentration range 0−20 μM. After those times (without discarding flavonoids), the cells were simultaneously treated with etoposide at a concentration of 1.5 μM for 1 hour. Then the amount of DNA damage was estimated by a single cell electrophoresis in agarose gel using Comet assay 2.6 software.
Results: When used in low doses (1−10 μM), neither curcumin nor quercetin caused DNA damage, even when they were present in the culture medium for 72 hours. High doses of quercetin (20 μM) caused a statistically significant DNA damage. After its 24-hour presence in the culture medium, curcumin induced DNA damage; that damage was very severe after 48 and 72 hours (above 95%; not measurable by the program). On the other hand, curcumin in the concentration range 1−10 μM and quercetin in the contrentation range 1−5 μM, present for 24 hours in the culture medium, protected against the DNA damage induced by etoposide. Such an effect did not appear during a longer action (48 or 72 h) of the flavonoids; on the contrary, an increase in the amount of DNA damage was then observed. After 48 and 72 hours and already at a concentration of 10 μM, curcumin increased the amount of DNA damage induced by etoposide, while quercetin only at a concentration of 20 μM enhanced the DNA-damaging action of etoposide.
Conclusions: The effect of the flavonoids tested is dose- and time-dependent. A shorter time (24 h) of their action may attenuate the effect of cytostatics by causing lesser damage to tumor cells. A longer action (48 and 72 h) of the flavonoids may enhance the effect of etoposide by causing a larger amount of DNA damage. Curcumin exerts a stronger effect than does quercetin via an increase in the amount of DNA damage induced by etoposide in rat leukemic LT12 cells.
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