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Antitumor effects of mitochondrial targeted peptide in the solid form of Ehrlich's carcinoma

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Mitochondria play an important role in energy production through ATP synthesis, maintenance of redox homeostasis, and regulation of cell survival and apoptosis. The described functions are directly related to the devel-

opment of cancer. Basically, tumor cells use aerobic glycolysis, which is known to trigger processes associated with cancer progression, accompanied by increased chemoresistance, migration and invasive potential, etc. Reducing the potential of the mitochondrial membrane increases the resistance of cells to apoptosis, since most apoptotic pathways are mediated through mitochondria. Various mitochondrial defects in tumor cells lead to the formation of reactive oxygen species and, as a result, to mutations in the mitochondrial genome.

The aim of this work is to investigate the possible antitumor effects of a mitochondrial target peptide (MTP) with MM 751.688 (MTP-FF; formula: $C_{42}H_{44}BrN_2O_4P+$) on the development of solid form of Ehrlich carcinoma (CE).

Materials and methods. A suspension of ascitic CE cells ($6 \cdot 10^6$) was injected subcutaneously on the back of Af mice and the growth of solid carcinomas was monitored for 17 days. Subcellular fractions of tumor cells were obtained by differential centrifugation and the activity of catalase, superoxide dismutase (SOD), lactate dehydrogenase (LDH), the content of lactate, pyruvic acid (PVA), ATP, apoptosis factors Bcl2 and Bax were determined. Biochemical studies of various subcellular fractions of the mouse tumor were performed using Biotek ELx-808 (USA) and ChemWell (USA) analyzers.

Results. In the experiment, a 99% survival rate of the tumor was observed. With subcutaneous administration of MTP, the tumor volume decreased throughout the entire follow-up period. By day 11, the difference in tumor volume values in mice from the "Tumor+MTP" group compared to the "Tumor" group was significantly reduced (17%, $p<0.05$), and by day 18, this difference reached 23%.

An increase in LDH activity was found in the clarified homogenate and, especially, in the cytosolic fraction, that is the evidence of the activation of glycolysis in tumor cells under the action of the peptide.

A significant increase in catalase activity in the cytosol and mitochondria of carcinoma cells was observed under the influence of MTP by 47 and 22%, respectively. Given that the peptide caused 23% suppression of the development of the carcinoma tumor, it is possible to assume the activation of peroxidation processes, possibly due to inflammatory processes in the tumor cells.

The activity of SOD after introduction of MTP significantly increased in the cytosolic fraction by 22 %. Since the tumor process is associated with increased generation of reactive oxygen species (ROS), which can play a dual role in carcinogenesis, acting, on the one hand, as a factor of tumor

progression, and, on the other hand, at high concentrations can stimulate apoptosis and necrosis, thereby damaging the cancer cell.

Under the influence of the peptide, the content of ATP and lactate in the cytosolic fraction increased by 60 and 21.5%, respectively, with a decrease in the concentration of PVA, which ones again is evidence of the activation of glycolysis in tumor cells under the action of the peptide. In the same fraction, under the action of MTP, an increase in the antiapoptotic factor Bcl2 by 31.2% was found, while the level of Bax remains unchanged, indicating a possible role of necrotic pathway involved into tumor cell death.

Conclusion. Under the influence of the studied peptide on the development of Ehrlich's carcinoma, the activation of glycolysis characteristic of tumor cells, increased generation of reactive oxygen species, and an increase in the antiapoptotic factor Bcl2 were shown, which led to a significant suppression of tumor growth.

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