POPULAR SCIENCE ABSTRACT

Application of small drugs in the epigenetic therapy of malignant brain gliomas

Gliomas make up the vast majority of primary malignant brain tumors. They are characterized by aggressive dynamic growth, which means that despite comprehensive therapy (surgical removal of the tumor, radio- and chemotherapy) the prognosis for these cancers remains very poor. For the most aggressive of them, glioblastoma (GBM), the average life expectancy is about 12 months from diagnosis. Due to the infiltration of the tumor surrounding the brain, chemotherapy could be the most effective treatment. However, its use is limited due to the blood-brain barrier (BBB), which hinders the penetration of drugs into the brain. However, resistance to the chemotherapeutics used and frequent and rapid relapses of the disease are observed. Therefore, there is an urgent need to develop new drugs that would significantly affect the effectiveness of glioblastoma treatment.

It is well known that carcinogenesis is associated with the change in the oxidation-reduction potential of the cell and the overproduction of reactive oxygen species (ROS). That leads to cellular stress and numerous damage to cell components, including DNA. As a result of DNA modification, disturbances occur at the epigenetic level, which are faster and more extensive than genetic mechanisms, and therefore that level of observation seems to be most promising in such an etiologically complex phenomenon as cancer. The tumorigenesis process can be monitored by two markers: DNA methylation (5-methylcytosine, m^5C) - the main epigenetic marker, and 8-hydroxyguanine (8-OH-dG) - a marker of cell oxidative damage. DNA methylation functions as a "switch" that activates or inhibits gene expression. Increased methylation (hypermethylation) of the promoter regions of genes leads to the inhibition of their function, as in the case of common genetic mutations. But in cancer, also global genome hypomethylation is particularly important. It leads to uncontrolled gene expression, including activation of oncogenes. The reduction of 5-methylcytosine contents in DNA occurs as a result of oxidative stress. The increased contents of 8-OH-dG in DNA is an independent and direct marker of oxidative damage to nucleic acids.

It has been noticed that some drugs, such as valproic acid (VPA), dexamethasone (DEX), metformin (MET), cannabidiol (CBD), tetrahydrocannabinol (THC), in addition to their basic applications, improve also the survival in patients suffering from glioma. However, the mechanism of their positive effect on the treatment of these brain tumors remains unknown.

The aim of this project is to analyze the effects of VPA, DEX, MET, CBD and THC on epigenetic changes in DNA and attempt to explain their positive effects at the level of genome expression regulation. This will be done by determining the total m^5C contents in the DNA of glioma, as well as 8-OH-dG to assess the damage process during chemotherapy. It is also known that stem cell formation is induced during cancer chemotherapy, while epigenetic changes and chromatin remodeling are involved in the formation of cancer stem cells. Stem cell behaviors is also controlled by H3K27me3 histone demethylases (Jmjd3 and Utx) in activation of reprogramming in cancer stem cells. Also these epigenetic markers will be analyzed.

The research will be carried out on glioblastoma cell lines to be exposed to VPA, DEX, MET, CBD and THC at various concentrations and incubation times. The total content of 5-methylcytosine and **8-hydroxyguanine** will be determined in isolated DNA of glioma cells. Also the histone demethylases activity will also we determined.

The approach we propose is **new**, **original** and **unique** worldwide, because for the **first** time it proposes comprehensive **epigenetic** characteristics of the effects of **drugs** on cancer treatment in the context of **oxidative stress**, which is the driving force of carcinogenesis. The obtained results will allow **optimization** of the methods of treatment of malignant brain tumors. Project results will have a huge impact **on neuro-oncology,** providing the basis for further **basic and clinical research**.