Cellular mechanisms and effects *in vivo* of selective lactate dehydrogenase A inhibitors in experimental models of mesothelioma

Description for general public

Background and aim of the project

Malignant Pleural Mesothelioma (MPM) is a poorly promising cancer, particularly refractory to treatment that is derived from pleural cells, the serous membrane that surrounds the lungs. One of the main reasons for the development of pleural mesothelioma is asbestos exposure. Although the production of asbestos has been almost completely eliminated, an increase in the number of cases of MPM is still noticeable. Cells of aggressive forms of tumors, including mesothelioma, are less sensitive to treatment because of their adaptation to function under hypoxic conditions prevailing in the tumor microenvironment. These cells undergo a metabolic modification associated with a change in energy supply from oxygen-dependent metabolism to anaerobic glycolysis, which gives an advantage to tumor cells present in the hypoxic environment where oxidative phosphorylation is restricted. One of the key enzymes involved in the glycolysis is the muscular isoform of lactate dehydrogenase (LDH-A), the increased activity of which is present in cancer cells with significant metastatic capacity and is associated with their high survival during hypoxia. LDH-A inhibition, and the simultaneous cutting off of cancer cells from the possibility of anaerobic energy production can be effective in treating cancer. The aim of this project is to examine the mechanism of action and to evaluate the therapeutic possibilities of compounds that inhibit LDH-A activity in experimental systems that resemble the course of pleural mesothelioma.

Research to be carried out in the project

The mechanism of action and the antitumor effect of LDH-A inhibitors will be tested in vitro and in vivo. The effect of these compounds on growth, invasiveness, metabolism and gene expression in cells isolated from MPM, spheroids obtained from MPM under normoxia and hypoxia conditions will be investigated. In addition, in order to check the specificity of the observed effects, the activity of LDH-A inhibitors in non-neoplastic cells, such as vascular endothelial cells and inflammatory cells, will be analyzed. Combination studies of LDH-A inhibitors with commonly used drugs for MPM therapy, such as pemetrexed, cisplatin and carboplatin, and targeted drugs such as vandetanib will also be carried out. In order to provide selective compounds that inhibit LDH-A activity, which can then be used in preclinical studies, a synthesis of new LDH-A inhibitors will be performed, preceded by computer molecular modeling. A rich collection of samples from healthy tissues and malignant pleural mesotheliomas and a collected clinical database available to the project team will be used to investigate the relationship between biological changes associated with LDH-A and clinical parameters.

Expected impact of the research project

Current anti-cancer therapies do not address resistance mechanisms caused by altered cancer cell metabolism. There are only a few compounds that have inhibitory properties against the increased glycolytic activity of invasive cancer cells. This research project proposes testing new LDH-A - selective inhibitors. The results of studies using unique metabolic reprogramming features of MPM cells can be used to develop drugs for selective anticancer therapy, as well as to optimize new technologies for detecting prognostic factors. In addition, the results of the research proposed in the project can help improve the effectiveness of standard treatment methods by identifying new biomarkers that will help optimize the use of aggressive therapies in patients at risk of failure of conventional therapies. The methodological and technological knowledge gained as part of the project implementation will also be used in diagnostics and therapy in many other types of cancer with similar metabolic changes.