Targeting Energy Metabolism for Precision Cancer Therapy: Novel Inhibitors of LDH-A and PDK1 as Potential Strategies to Starve Non-Small Cell Lung Cancer and Malignant Pleural Mesothelioma Cells

Research project objectives

Non-small cell lung cancer (NSCLC) and malignant pleural mesothelioma (MPM) are two chest cancers with high patient mortality, due to late-stage diagnosis and inefficient therapy. The five-year survival rate of patients with NSCLC is approximately 30%, and one of the main environmental causes affecting its development is smoking. MPM is a very rare cancer with a five-year survival rate of only 12%, associated with asbestos exposure and develops even 20-40 years after exhibition. Although in Europe, at the beginning of the 21st century, a ban on the use of asbestos products was introduced, it is still present in the environment and the number of MPM cases is increasing. One of the problems encountered in NSCLC and MPM therapy is their high resistance. The key reason for this resistivity is the ability of cancer cells to change their metabolism, thanks to which they can adapt to unfavorable conditions, which are induced, among others, by treatment. In both NSCLC and MPM, oxygen-depleted areas are observed, which shift energy production from glucose (the main energy substrate) in oxygen-dependent metabolism to anaerobic glycolysis. This makes them more aggressive with an increased ability to metastasize. The aim of our research is to inhibit the described metabolic changes, so as to re-sensitize cancer cells to standard chemotherapy. Many studies indicate the ineffectiveness of monotherapy, which is why we will use the multidirectional inhibition of energy processes by targeting glucose transporters (GLUT-1) in cells, which is the main energy substrate, as well as lactate dehydrogenase (LDH-A), superactive in anaerobic conditions, and kinase dehydrogenase pyruvate (PDK1), involved in the mitochondrial respiration.

Research project methodology

The cellular effects caused by the use of a combination of the LDH-A, PDK1 and GLUT-1 inhibitors will be tested *in vitro* and *in vivo*. Cellular analyzes will include testing the cytotoxicity of this combination of inhibitors, changes in nucleotide concentrations, mitochondrial respiration, glycolysis, as well as apoptosis and histone lactylation in several NSCLC and MPM cell lines. In addition, we will check the ability of these inhibitors to inhibit the migration of cancer cells: the process responsible for metastases. In the next step, we will create 3-dimensional cultures that are characterized by an environment similar to that observed in cancer, with a hypoxic core. These studies will be used to transfer the experiments to *in vivo* conditions in the mouse model of NSCL and MPM, where we will study changes in the size of tumors after administration of LDH-A, PDK1 and GLUT-1 inhibitors. The last important step of the project will be the analysis of the level of GLUT-1, LDH-A and PDK1 proteins in the tissues of patients with NSCLC and MPM in order to select patients for personalized treatment using an appropriate mix of drugs.

Expected impact of the research project on the development of science

The innovation of our research is the fact that we will focus not only on inhibiting the growth of NSCLC and MPM cancer cells but also on trying to understand the mechanisms occurring during the inhibition of LDH-A, PDK1 and GLUT-1. Moreover, we will be the first to test a combination of these three inhibitors, trying to inhibit the energy metabolism of cancer cells in a multidirectional way. The comprehensiveness of our research is based on the transition from *in vitro* to *in vivo* conditions, with the analysis of patient tissues, so as to exhaust the possibilities of preclinical research as much as possible with the prospect of transferring them also to research at the clinical level.