The Warburg effect in breast cancer - role of cadmium as the activator of HIF-1 alpha

In the mid-1920s a German biochemist, Otto Warburg showed, along with his colleagues, that under aerobic conditions cancer cells metabolize glucose to lactate (in other words they undergo "fermentation"). Fermentation is a process that occurs typically under anaerobic conditions, when lack of oxygen does not allow the cells to produce energy by oxidative phosphorylation (in mitochondria). However, in tumor cells, this process occurs regardless of the oxygen concentration. This metabolic reprogramming was called **Warburg effect** (or aerobic glycolysis). Intriguingly, its causes as well function, remained unclear. It is believed that tumor cells prefer to metabolize glucose to lactate (preceded by a process of intensive glycolysis), as that allows them to obtain not only energy, but also a necessary substrates required for growth and division. In addition, the Warburg effect protects cells from the toxic effects of reactive oxygen species which are generated by mitochondria as a result of oxidative phosphorylation. Thus, the Warburg effect is an adaptive mechanism created by cancer cells to survive. The Warburg effect is also very important for the survival of tumor cells under hypoxia, an effect that often accompanies solid tumors. Hypoxia significantly reduces the anticancer effects of drugs, so the Warburg effect contributes to the development of drug resistance.

Although the Warburg effect has been discovered over 90 years ago, it gained scientific interest only in the last 10 years. Currently numerous studies are conducted in order to identify novel drugs, targeting the Warburg effect. A key factor regulating the Warburg effect is **HIF-1α (hypoxia inducible factor 1 alpha)**. Importantly, it was shown that both the Warburg effect and activation of HIF-1α are associated with the phenomenon of resistance to **tamoxifen**. This therapeutic agent is used to treat hormone-dependent breast cancer, but treatment is often associated with the development of resistance. The proposed project will focus on the mechanism of tamoxifen resistance, with respect to the role of carcinogenic element in this process - cadmium. The rationale for the study is supported by recent reports indicating the ability of **cadmium** to increase the expression of HIF-1α in breast cancer cells, This suggests that cadmium, due to the activation of HIF-1α, also affects the Warburg effect. Studies on the effect of carcinogens on energy metabolism in the context of the Warburg effect have not been conducted so far. Importantly, cadmium is widespread in the human environment. Although it is present at low concentrations, long-term exposure to this metal leads to its accumulation in the body because it is poorly excreted. The effects of long-term environmental exposure to cadmium are poorly understood, therefore there is a need for research in this area, particularly with reference to breast cancer, for which cadmium is considered to be one of the risk factors.

Research hypothesis assumes that:

1) long-term environmental exposure to cadmium, leading to accumulation of this element in the breast tissue, affects the Warburg effect in breast cancer cells through the activation of HIF-1α;
2) the effect of Cd accumulation in breast cancer cells reduce the therapeutic response to tamoxifen due to the Warburg effect.

The hypotheses will be verified by examination of tumor tissues obtained from 150 breast cancer women, as well as by an *in vitro* experiment, conducted in human breast cancer cell line (MCF-7 cells).