

Metal chelators affecting iron metabolism as a tool to investigate undiscovered aspects of ferroptosis

Iron metabolism plays an important role in many cellular processes. As one of the main micronutrients, iron is involved in almost all processes related to energy metabolism, namely glucose, lipid and amino acid metabolism. This metal also plays a key role in regulated cell death - ferroptosis, the mechanism of which is associated with loss of antioxidant capacity and impaired mitochondrial function resulting from increased concentrations of reactive oxygen species formed in the Fenton reaction. Ferroptosis is also associated with cellular energy production, so iron is the linking element between these processes. This type of cell death, discovered relatively recently, still has quite a few areas to explore, so in this project we plan to conduct a detailed analysis of the molecular targets associated with this phenomenon. Our previous studies on the anticancer effects of compounds from the thiosemicarbazone group indicate that these compounds, as metal chelators, including iron in particular, are a good tool for studying processes related to metal ion metabolism.

The number of diseases of the central nervous system, including brain tumors, is increasing as the population grows. Despite the development of medicine and the increased availability of research methods, there are still types of tumors whose treatment is difficult and the prognosis of patients is low. One of the most dangerous types of tumors is glioblastoma (GBM), which involves an area of the brain. Its location often precludes surgical removal, due to its occupation of an area responsible for key vital functions. The second major limitation of GBM treatment is the ineffective delivery of drugs to the brain, due to the existence of the blood-brain barrier (BBB), whose primary function is to protect our body's most important organ. It is estimated that about 98% of small-molecule drugs and 100% of large-molecule drugs do not pass through the BBB. Therefore, in this project, we plan to address this problem and conduct permeability prediction studies using computational methods and experimentally test the passage of the tested compounds through the BBB. Preliminary studies are promising, as they indicate that the test compounds have better BBB permeability than currently used drugs, increase drug permeation in combination therapies, and show strong anti-tumor activity, especially against GBM.

The main goal of this project is to investigate the mechanisms responsible for triggering the process of ferroptosis applicable to GBM therapy. Compounds complexing metal ions, affecting cellular pathways related to iron metabolism, are a promising tool to study these processes. The project envisions the use of sequencing methods to identify new molecular targets associated with ferroptosis. On the basis of the studies performed so far, a research hypothesis has been put forward that chelators from the thiosemicarbazone group, affecting cellular iron metabolism, may be a tool for a deeper understanding of the process of ferroptosis. The next step will be to verify the results at the gene and protein level using available molecular biology techniques and computational methods. The final step of the project will be to conduct tests on an *in vivo* mouse model to confirm the hypothesis. The overarching goal is to improve the efficacy of GBM treatment along with enriching the basic knowledge of ferroptosis. This comprehensive approach can significantly advance the understanding of BBB permeability and improve drug delivery to the brain.