Title: The role of the estrogen receptor GPER1 in ferroptosis disorders in mouse model of mucopolysaccharidosis type I

Regulated cell death is a universal process occurring in all living organisms, aimed at maintaining or restoring homeostasis under stressful conditions. This form of cell death enables proper organismal development and the elimination of unnecessary and potentially harmful cells. Several types of regulated cell death have been identified so far, including apoptosis, necrosis, necroptosis, and others. Ferroptosis, one of the latest discoveries in this field, is dependent on the accumulation of reactive oxygen species resulting from intensified iron metabolism and increased lipid peroxidation. This distinguishes ferroptosis from other well-known types of regulated cell death.

Unfortunately, the mechanisms that regulate this process are not yet fully understood. Recent reports indicating the regulation of ferroptosis by lysosomes (based on the process of autophagy-related ferroptosis) draw attention to lysosomal storage diseases as conditions where disruptions in the intensity of ferroptosis may significantly impact the development of disease symptoms.

Lysosomal storage diseases are a group of disorders caused by mutations in genes encoding lysosomal enzymes involved in the degradation of various molecules, leading to their accumulation in lysosomes. Mucopolysaccharidosis type I (MPS I) is characterized by defective degradation of compounds called glycosaminoglycans (GAGs), leading to their accumulation in lysosomes and damaging the proper functioning of cells, tissues, organs, and ultimately the entire organism. Unfortunately, the therapies available for MPS I are unable to alleviate all the symptoms of the disease, despite normalizing GAG levels.

It turns out that research on ferroptosis in lysosomal storage diseases has never been conducted. Preliminary studies carried out by the Principle Investigator (PI) indicated not only an increase in ferroptosis markers (iron concentration and lipid peroxidation) but also the role of one of the proteins, the estrogen receptor GPER, in regulating ferroptosis.

Therefore, the aim of this project will be to investigate the role of GPER in the development of MPS I symptoms and to determine its impact on the intensity of ferroptosis, along with elucidating the exact mechanism by which GPER regulates it.

The studies will be conducted on a mouse model of MPS I and on healthy control mice. The mice will be divided into groups receiving either a GPER agonist, to activate it, or a GPER antagonist, to block it. The impact of modulating GPER activity on disease progression will be assessed using various behavioral tests to measure motor activity, cognitive abilities, muscle strength, and anxiety disorders. Additionally, the effect of GPER activity modulation on disease markers at the molecular level (GAG levels, lysosome activity, and morphology) will be examined in these tissues. Furthermore, the influence of GPER activity modulation on the process of ferroptosis will be determined to understand whether GPER regulates this process positively or negatively and how it does so.

The results of the studies planned in this project will define the role of GPER in regulating ferroptosis and, consequently, in the progression of the disease. Understanding the factors regulating cell death in MPS I will not only have intrinsic scientific value but may also identify potential therapeutic targets for this rare disorder.