Molecular mechanism of ferroptosis impairment in mucopolysaccharidosis type I and its effects on the disease course

Regulated cell death is one of the universal processes occurring in all living organisms necessary to maintain an organism homeostasis or its restoration after stress conditions. Regulated cell death eliminates not necessary and potentially dangerous cells and has a lot of functions in organism development. Several types of regulated cell deaths were describes to date like apoptosis, necrosis, necroptosis and others. Ferroptosis is a recently discovered process. It is a regulated cell death dependent on accumulation of reactive oxygen species as products of increased efficiency of iron metabolism and lipid peroxidation, which differs from other well-known types of this phenomenon. Role of ferroptosis in living organism has just begun to be in the center of interest. Molecular mechanism of ferroptosis efficiency depends on a lot of signaling pathways and efficiency of other metabolic and cellular processes occurring in cells.

Recent discoveries on ferroptosis indicated its significant role in the pathogenesis of some human diseases. However, ferroptosis efficiency in lysosomal storage diseases has never been studied before. Lysosomal storage diseases are a group of diseases caused by mutations in one of genes encoding lysosomal enzyme involved in degradation of macromolecules, leading to storage of these compounds in lysosomes. Mucopolysaccharidoses (MPS) are characterized by defective degradation of glycosaminoglycans (GAG). Accumulated GAGs impair various cellular functions, and then tissues, organs and the whole organism. Research on ferroptosis in these diseases will be interesting because of recently described pathways linking ferroptosis efficiency and lysosomal functions.

Preliminary experiment performed by the principal investigator were conducted on models of mucopolysaccharidosis type I (MPS I). They indicated a significant impairment of ferroptosis in both cells derived from MPS I patients and the mouse model of this disease, relative to healthy controls, as revealed by decreased levels of molecular markers of this process. Because of these intriguing results, and since ferroptosis has not been studied in MPS to date, objectives of this project are:

(1) to determine molecular mechanisms leading to impaired ferroptosis efficiency in MPS I (as five molecular pathways for ferroptosis have been described to date);

(2) to test the involvement of autophagy in modulation of ferroptosis efficiency in MPS I (as the autophagy process involves lysosomes, and lysosomal functions are impaired in lysosomal storage diseases);

(3) to investigate effects of decreased efficiency of ferroptosis on the disease course (as an exact role of ferroptosis has never been determined in MPS).

Studies will be conducted on both cellular and animal models of MPS I. Patient-derived fibroblasts and healthy controls as well as the mouse model of MPS I and control wild-type animals will be employed. The project plans to investigate the role of all known pathways in decreasing the levels of ferroptosis markers as well as their dependence on GAG storage in cells and tissues. Since a role for ferroptosis is largely unknown, effects of decreased levels of markers of this process on the disease course in the MPS I mouse model will be examined following treatment with ferroptosis inducer(s).

Discovery of both mechanisms leading to modulation of ferroptosis in MPS and its role in the development of the disease might allow to identify novel therapeutic targets for this disorder. Moreover, as shown in preliminary studies, results of these experiments are the first known cases of impairment of ferroptosis in a severe disease, providing a unique opportunity to investigate cellular meaning of ferroptosis in the light of the disease mechanism which can also lead to more general conclusions.