

Project title: Stimulation of various autophagy induction pathways in the light of efficiency of glycosaminoglycan degradation in neuronopathic types of mucopolysaccharidoses

Objective of the project

Mucopolysaccharidoses (MPS) belong to the group of lysosomal storage diseases caused by excessive accumulation of compounds called glycosaminoglycans (GAGs) in the cells of patients. The accumulation of these linear sugar chains leads to damage of physiology of individual cells and the whole organism. There are 11 types and subtypes of MPS which are characterized by a common spectrum of symptoms such as bone deformity, coarsening of facial features, forehead highlighting, organomegaly and impaired sensory organs, changes in the circulatory system or respiratory system. Patients do not usually live to adulthood.

The simplest therapeutic strategy would be to provide the patient with enzymes that would stimulate the removal of accumulated GAG from cells. This strategy brings very good results in the case of MPS types which symptoms affect only somatic organs. However, in the case of MPS types affecting the central nervous system (MPS I, II, IIIA, IIIB, IIIC, IIID and VII) this strategy does not bring good results because the molecules (enzymes) used in it do not cross the barrier that surrounds the brain (the blood-brain-barrier). Therefore, alternative therapeutic strategies for these types of MPS are still being sought.

Recent studies on the use of genistein, one of flavonoids currently tested in clinical trials on MPS, have shown that this compound is able to stimulate the lysosomal biogenesis, organelles with digestive functions within the cell. Stimulation of lysosomes leads to accelerated degradation of accumulated GAG in cells. The discovery of this mechanism of action of genistein suggests that other compounds that can stimulate lysosomal biogenesis could also be effective in the treatment of neuronopathic MPS types, especially as natural compounds with such properties are often very small molecules crossing the blood-brain-barrier.

Therefore, the aim of this project is to test known safe compounds that stimulate lysosomes for their ability to stimulate degradation of GAGs, and to create more effective mixtures of these compounds in this respect.

Research to be carried out

The research will be conducted on fibroblast lines taken from patients with neuroponopathic MPS types/subtypes. These cells will be incubated in the presence of selected inducers of autophagy (a process induced in cells due to increased lysosomal biogenesis) or mixtures thereof (to increase the GAG degradation efficiency) for various periods of time. Selected molecules are already known for their positive effects on accumulated macromolecules in different diseases, such as Alzheimer's, Parkinson's, Huntington's diseases or amyotrophic lateral sclerosis. Both the GAG degradation efficiency and the cytotoxicity of selected substances/mixtures will be measured. Studies on the mechanisms of action of these substances will include both the efficiency of the autophagy induction and the possible impact on GAG biosynthesis.

Reasons for choosing the research topic

Genistein is currently the only substance tested in clinical trials for MPS types that affect the central nervous system. The studies included in this project may not only expand the pool of potential drugs for this incurable disease but also contribute to the effectiveness of genistein itself by combining it with other inducers of GAG degradation. Mixtures of this type show much greater therapeutic potential than each of the tested compounds individually.