PROTOCOLLO DEL PROGETTO DI RICERCA

MODIFYING LYSOSOMAL ENZYMES TO IMPROVE SECRETION AND BRAIN DELIVERY [SURE]

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Diseases: Lysosomal Storage Diseases, in general Mucopolysaccharidosis, type III Mucopolysaccharidosis, type I Mucopolysaccharidosis, type VI

Summary

Mucopolysaccharidoses (MPS) are lysosomal storage diseases (LSD) caused by the body's inability to produce specific enzymes. Normally, the body uses enzymes to break down and recycle materials in cells. In individuals with MPS, the missing or defective enzyme prevents the proper recycling processes, resulting in the storage of materials in virtually every cell of the body. As a result, cells do not perform properly and may cause progressive damage throughout the body, including the heart, bones, joints, respiratory system and central nervous system. While the disease may not be apparent at birth, signs and symptoms develop with age as more cells become damaged by the accumulation of cell materials. The central nervous system is the predominant target of damage in most MPSs and MPS patients experience severe mental retardation and neuropathological decline. Gene therapy is a therapeutic option for several inherited diseases. The aim of gene therapy is to substitute the defective gene with a functional one. In these therapeutic approaches modified non-pathogenic virus is used as vehicle to transport the gene in the affected tissues. In this study we will test the efficacy of a therapeutic approach based on the delivery, via intravenous injection, of an aden-associated virus (AAV) bearing a functional copy of the gene coding for the specific lysosomal enzyme that is deficient in the MPS. We will use AAV vectors with a tropism to the liver, so that upon injection the virus will reach the liver that consequently will produce the functional enzyme. The functional lysosomal enzyme will be then secreted from the liver and will enter into the brain throughout the blood torrent. The most important innovation of the therapeutic protocol we will develop in this study consist in the fact that the lysosomal enzyme will be opportunely modified to be secreted more efficiently from the liver and to enable crossing of the blood-brain barrier which constitute the major obstacle for the therapeutic agent to reach and transduce the brain.

Scientific publications

2012 - MATRIX BIOLOGY - Arteaga-Solis, E; Settembre, C; Ballabio, A; Karsenty, G
Sulfatases are determinants of alveolar formation

2013 - EMBO MOLECULAR MEDICINE - Sorrentino, NC; DOrsi, L; Sambri, I; Nusco, E; Monaco, C; Spampanato, C; Polishchuk, E; Saccone, P; De Leonibus, E; Ballabio, A; Fraldi, A - Cites: 1 (*)
A highly secreted sulphamidase engineered to cross the blood-brain barrier corrects brain lesions of mice with mucopolysaccharidoses type IIIA

2012 - AUTOPHAGY - Di Malta, C; Fryer, JD; Settembre, C; Ballabio, A - Cites: 1 (*)
Autophagy in astrocytes A novel culprit in lysosomal storage disorders