Chapter 18
Therapeutic Strategies for Lysosomal Storage Diseases by Targeting Glial Cells

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ABSTRACT

Lysosomal storage disorders (LSDs) are a group of about 70 life-threatening conditions caused by genetic defects affecting lysosomal components. The underscoring molecular deficiency leads to widespread cellular dysfunction through most tissues in the body, including peripheral organs and the central nervous system (CNS). Clinical and experimental strategies encompassing enzyme replacement, gene and cell therapies, substrate reduction, and chemical chaperones are showing considerable potential in attenuating the peripheral pathology. Microglial and astrocyte activation is a hallmark of many LSDs that affect the CNS, which often precedes and predicts regions where eventual neuron loss will occur. However, the timing, intensity, and duration of neuroinflammation may ultimately dictate the impact on CNS homeostasis. For example, a transient inflammatory response following CNS insult/injury can be neuroprotective, as glial cells attempt to remove the insult and provide trophic support to neurons.

INTRODUCTION

Lysosomal storage diseases (LSDs) are monogenic hereditary metabolic diseases affecting the functioning of a lysosomal enzyme (or its activator) involved in the degradation of complex molecules, or more rarely of a transport or membrane protein. This results in an accumulation of metabolites in lysosomes leading to cell damage: disruption of autophagy, oxidative stress, inflammation and increased apoptosis, disruption of cell signaling pathways. LSDs are rare or very rare diseases individually, since their

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incidence is between 1 in 40,000 and 1 in 1,000,000. However, their incidence as a group is greater, on the order of 1 in 5000 live births (Al-Jasmi et al., 2013; Platt et al., 2018; Poupětová et al., 2010). They include about 70 different pathologies that can be classified according to the nature of the accumulated compound or the mechanism involved (Kingma et al., 2015). The mode of transmission is most often autosomal recessive except for Fabry, Hunter and Danon diseases transmitted in an X-linked mode. Clinical orientation is essential but is not sufficient to establish the diagnosis. Specialized biochemistry and molecular biology laboratories, attached to rare disease reference centers and forming an integral part of the health sector, carry out biological examinations contributing to the diagnosis. This is classically based on the first-line biochemical study: study of the metabolite accumulated in biological fluids (plasma, urine, etc.) often by tandem mass spectrometry (MSMS) and/or measurements of enzymatic activities in the blood mostly. The molecular study confirms the diagnosis in a second time.

Attenuated forms can present a significant diagnostic problem, although severe phenotypes are easily detected. It is well known that musculoskeletal issues often prompt a patient to seek medical attention for the first time. Timely diagnosis and therapy initiation are crucial to prevent irreversible organ damage and poor quality of life, as several of these conditions can be efficiently treated with enzyme replacement. As a result, every physician needs to be knowledgeable with the hallmark signs and symptoms of lysosomal storage disorders.

Many LSDs have modest to severe involvement of the central nervous system (CNS). Post-mortem tissues and animal illness models, respectively, depict the last stage of CNS pathology and partially replicate the disease. Over the past few decades, induced pluripotent stem cell (hiPSC)-based human models have been widely used to study LSD disease in various tissues and organs, including the central nervous system. A potentially useful method for defining the impact of pathological storage on neurodevelopment, survival, and function of neurons and glial cells in neurodegenerative LSDs is neural stem/progenitor cells (NSCs) generated from patient-specific hiPSCs (hiPS-NSCs). The study of neuron-glia functional and dysfunctional interactions is also being aided by the development of novel 2D co-culture systems and 3D hiPSC-based models. These developments are helping to define the role of neurodevelopment and neuroinflammation in the onset and progression of the disease, which has significant implications for treatment timing and efficacy (Luciani et al., 2020).

THE LYSOSOMAL SYSTEM: FUNCTIONS AND USES

The lysosome is an organelle which can be spherical, ovoid, or sometimes tubular, and having a variable size between 0.1 and 2 μm, present in most plant and animal cells (Appelqvist et al., 2013). In humans, lysosomes are present in around a hundred copies in all cells of the body, except in red blood cells. Two distinct classes of proteins are present at the lysosome: a) acid hydrolases, approximately 50 in number, activated by the acidic pH between 4.5 and 5 at the lumen of the lysosome, b) membrane proteins, which are 25 in number (Mindell, 2012). These enzymes and proteins are all essential for the lysosome to perform its functions. These consist in particular of degrading macromolecules, polysaccharides, glycosaminoglycans and complex lipids into their elementary molecules respectively: amino acids, monosaccharides and free fatty acids. Lysosomal degradation products are transported outside the lysosome via specific transporters located in the lysosomal membrane (Saftig & Klumperman, 2009), or via vesicular membrane trafficking for reuse in biosynthetic pathways (Ruivo et al., 2009). (Figure 1).