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Review

Alterations in membrane trafficking and pathophysiological implications in lysosomal storage disorders

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ABSTRACT

Lysosomal storage disorders are a heterogeneous group of more than 50 distinct inborn metabolic diseases affecting about 1 in 5000 to 7000 live births. The diseases often result from mutations followed by functional deficiencies of enzymes or transporters within the acidic environment of the lysosome, which mediate the degradation of a wide subset of substrates, including glycosphingolipids, glycosaminoglycans, cholesterol, glycogen, oligosaccharides, peptides and glycoproteins, or the export of the respective degradation products from the lysosomes. The progressive accumulation of uncleaved substrates occurs in multiple organs and finally causes a broad spectrum of different pathologies including visceral, neurological, skeletal and hematologic manifestations. Besides deficient lysosomal enzymes and transporters other defects may lead to lysosomal storage disorders, including activator defects, membrane defects or defects in modifier proteins. In this review we concentrate on four different lysosomal storage disorders: Niemann-Pick type C, Fabry disease, Gaucher disease and Pompe disease. While the last three are caused by defective lysosomal hydrolases, Niemann-Pick type C is caused by the inability to export LDL-derived cholesterol out of the lysosome. We want to emphasise potential implications of membrane trafficking defects on the pathology of these diseases, as many mutations interfere with correct lysosomal protein trafficking and alter cellular lipid homeostasis. Current therapeutic strategies are summarised, including substrate reduction therapy as well as pharmacological chaperone therapy which directly aim to improve folding and lysosomal transport of misfolded mutant proteins.

Contents

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Abbreviations

BBB	Blood-brain barrier
CNS	Central Nervous System
DNJ	1-Deoxynojirimycin hydrochloride
DGJ	1-Deoxygalactonojirimycin
DPPIV	Dipeptidyl peptidase IV
ERT	Enzyme replacement therapy
FD	Fabry disease
GAA	α-glucosidase
GBA	β-glucosidase
Gb3	Globotriaosylceramide
GD	Gaucher disease
GLA	α-galactosidase A
GT	Gene therapy
HSC	Hematopoietic stem cell
HSC-GT	Hematopoietic stem cell-Gene therapy
HSCT	Hematopoietic stem cell transplantation
NPC	Niemann-Pick type C disease
M6P	Mannose-6-phosphate
M6PR	Mannose-6-phosphate receptor
LSD	Lysosomal storage disorders
PCT	Pharmacological chaperone therapy
PD	Pompe disease
SRT	Substrate reduction therapy

1. Introduction

Lysosomal storage disorders (LSD) are a heterogeneous group of inborn metabolic diseases. More than 50 LSDs are described [1], which although they occur individually rarely, in total they affect a large number of patients with an incidence of about 1:5000 to 1:7000 live births [2]. All together LSDs are amongst the most common diagnosis of neurodegeneration in children, representing up to 45% of the confirmed cases of neurodegeneration in the UK [3]. Therefore, besides the strongly reduced quality of patients' lives, LSDs are a high economic burden for every health care system.

The different diseases are caused by monogenic mutations affecting only one gene, but in general numerous mutations in the same gene are described, all resulting in the main cellular characteristic of all LSDs, progressive intra-lysosomal accumulation of non-metabolised substrates. As a consequence of substrate accumulation, lysosome-related pathways are impaired, thus affecting the metabolism of the whole cell [4–6]. On the cellular level mutations are often found in soluble lysosomal acid hydrolases, of which 50–60 different enzymes have been identified [7]. The mutations elicit variable effects on the folding, intracellular trafficking and targeting as well as on the function of these proteins. Besides hydrolases, non-enzymatic lysosomal proteins may be affected. Examples are activator proteins (saposins) required for sphingolipid hydrolysis [8], integral membrane proteins, like the lysosome-associated membrane protein-2 (LAMP2) affected in Danon disease [9], protective protein/cathepsin A affected in galactosialidosis [10] or modifier proteins like the Cα-formylglycine-generating enzyme showing reduced activity in post-translational modification of sulphatases thus leading to multiple sulphatase deficiencies [11].

Depending on the affected gene a wide range of substrates may accumulate including; glycosphingolipids, glycosaminoglycans, cholesterol, glycogen, oligosaccharides, peptides and glycoproteins [5]. Accumulation occurs in multiple organs resulting in distinct combinations of visceral, neurological, skeletal, hematologic and ocular manifestations with a phenotypic spectrum that varies in the degree of severity and the age of onset, even within the same disease. The age of onset of LSDs is often related to its severity [12]. While the infantile forms of LSD often present with neurological implications like seizures or dementia and are characterised by a fast progression, the adult forms show a slow progression and often affect peripheral organs inducing symptoms like hepatosplenomegaly and abnormal bone formation [8,12]. The broad clinical manifestations, the different times of onset within each disease and the individual rarity of LSDs together contribute to a diagnostic delay and probably to a high number of undiagnosed or misdiagnosed patients that ultimately hinder appropriate treatment. Recent research has focussed on the underlying mechanisms of LSDs including the effect of lipid accumulations and how they result in an altered membrane trafficking and subsequent contribution to the pathophysiology of LSDs. Although this review concentrates on the impact of membrane trafficking on LSDs, it has to be emphasised that many other factors play essential roles in the manifestation of these disorders. The accumulation of unmetabolised substrates impairs several other functions of the lysosome itself and of other cellular organelles, finally resulting in the LSD's pathology. Bellettato et al. nicely reviewed the pathophysiology of neuropathic LSDs, including impaired autophagy, morphological changes in neurons, neuroinflammation, mitochondrial dysfunction, altered ER and Golgi functions, perturbation of lipid rafts, altered calcium and iron storage as well as an altered cellular homeostasis, all together resulting in neuronal cell death explaining the CNS pathologies [13].

2. Lipids and membranes

2.1. Lipid metabolism

Cellular membranes consist of hundreds of lipid species, which can be categorised into three major lipid classes; sterols, phospholipids and glycolipids, with approximately 5% of genes required to synthesise the extensive repertoire of lipids present in cells indicating the importance of lipid variation to cell homeostasis [14]. Lipids have been shown to play important roles in a wide range of cellular functions, including hormone synthesis, signalling, ion exchange, autophagy, apoptosis, virus entry and replication, extracellular trap formation, antimicrobial functions and in the focus of this review, protein and lipid trafficking [15–19].

In eukaryotic cells, lipids are predominately synthesised in the endoplasmic reticulum (ER). Complex sphingolipids are additionally processed in the Golgi complex, whereby three major enzymes, ceramide galactosyltransferase, glucosylceramide synthase and sphingomyelin synthase generate an enormous diversity of (glycol-)sphingolipids [20]. Additional lipid synthesis has also been suggested to occur in the mitochondria due to the high concentration of lipid biosynthesis-associated enzymes [21]. Once synthesised, lipids are rapidly transported to the Golgi where they undergo sorting. Due to the synthesis of sphingomyelin in the Golgi, it is suggested that this lipid plays a key role in the sorting of other lipids and proteins between different cell organelles and the plasma membrane via lipid rafts [14].

Sphingomyelin consists of three components; a polar phosphorylcholine head group, an amide-linked acyl chain and a sphingoid base. The amide-linked acyl chain has been shown to be

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