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Lysosomes as a Central Not Terminal Compartment of Cellular Metabolism

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The lysosomal storage disorders (LSD) are a heterogeneous group of inherited metabolic diseases characterized by tissue deposits of various substrates that are by-products of cellular turnover which are incompletely processed [1]. The biochemical and/or molecular basis for most LSDs have been characterized, and diagnostic confirmation is established, based on demonstration of decreased enzyme activity, excessive metabolite levels in serum or urine and in the case of transport defects or co-factor/activator deficiency identification of the causal gene defect [2].

Although individual LSDs are infrequent to rare, collectively (at 1 in 3,000-5,000 newborn) they account for a significant proportion of inborn errors of metabolism associated with a subacute or chronic course in children and adults [3]. As there can be significant delay in the diagnosis of affected individuals, particularly in the absence of a family history, there has been increasing interest in including certain LSDs in the expanding list of conditions currently screened for in the newborn (NB). Currently, screening for Krabbe disease is undertaken in New York, with hematopoietic stem cells transplantation (using cord blood) recommended in those identified with the infantile form [4].

Orphan drug legislation has fostered the development of pharmacologic therapy for the LSDs [5]. To date, enzyme replacement therapy is available for several LSDs, including Gaucher disease (GD), Fabry disease (FD), Pompe disease and certain mucopolysaccharidosis (MPS); disorders characterized deficiency of distinct enzymes/hydrolases [6]. In addition, substrate reduction therapy is available for GD, wherein the inhibition of precursor synthesis reduces the amount of substrate to within the capacity of the mutant enzyme which retains residual activity [7]. Pharmacologic chaperones, which act as a template for certain misfolded mutant proteins is under investigation for FD and Tay-Sachs disease [8]. Several experimental gene therapy studies have been undertaken in various animal models for particular LSDs. The majority of LSDs are associated with primary central nervous system involvement, and access to pathologic sites with current therapeutic options remains a challenge [9].

There is incomplete knowledge regarding disease mechanisms, which proceed from or are associated with individual LSDs. It is likely there are shared disease pathways, and indeed for several defects of autophagy (a lysosomal-mediated pathway for clearance of long-lived proteins and damaged organelles) have been demonstrated [10]. Interestingly, there is increasing evidence that mechanisms of disease identified in certain LSDs may overlap with that observed in other neurodegenerative disorders; e.g., increased risk for Parkinson disease among patients with GD (acid β-glucosidase deficiency) [11]. Thus, potential insights gained from studies in a rare disease may provide a clue to understand pathogenesis, which may lead to new avenues for therapy. Investigations of disease, particularly in the animal model, are also enabling characterization of the early events, prior to the onset of clinical manifestations. These studies are leading to the identification of biomarkers, which may be useful in screening high-risk populations, and also studies of disease severity [12].

With the increasing availability of therapeutic options, there are efforts to characterize not only the response profile observed in treated patients, but also the natural history. These endeavors are facilitated by disease-specific Registry or Surveillance programs (sponsored by the manufacturer as part of a post-regulatory requirement) [13]. Several reports from these groups have described genotype-phenotype correlations, disease severity scores, and therapeutic outcome which may be used as a benchmark in the management of individual patients [14-16]. A current focus of research is the examination of potential modifiers of disease severity, in as much as patient genotypes have not been shown to be fully predictive of clinical course. In a collaborative study with colleagues at Yale University, we recently reported on a subset of our GD cases (i.e., Ashkenazi and homozygous for the N370S mutation, the most common disease allele) wherein over-expression of *CLN8* was shown to correlate with attenuated disease expression [17]. This observation was unexpected, given recessive mutations of *CLN8* have been identified as the basis for one variant of the neuronal ceroid lipofuscinosis. Anyhow, we are examining the basis of our observations; which may partly implicate abnormalities in sphingolipid signaling and/or metabolism (*NB*, GD is a defect of glycosphingolipid metabolism).

A network of investigators (http://www.lysosomaldiseasenetwork.org/) who have a shared interest in the LSDs has been established, which meets annually to describe recent advances in the field. The network has also been an avenue for collaborative research projects. The pace of discovery in the LSDs and their broad implications requires rapid communications among various investigators at several academic sites, and scientist and clinicians worldwide. Open access to publications serves as a portal to facilitate this process.

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