Thematic review series: Recent advances in the treatment of lysosomal storage diseases

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The identification of the lysosome as a unique cellular organelle by Christian de Duve (1) occurred less than sixty years ago. The importance of his discovery was immediately appreciated when several monogenic diseases arising from the loss of lysosomal enzyme activities were identified. Over fifty lysosomal disorders have subsequently been identified to date. Most of these diseases were linked to lysosomal proteins that were identified by the traditional cell fractionation techniques employed by de Duve. However, with recent advances in proteomics (2) and transcriptomics (3), undoubtedly many new lysosomal storage diseases (LSDs) are likely to be identified.

Among the fifty known LSDs, several are associated with impaired lipid metabolism or of lipid-associated modifications of proteins and so represent an appropriate focus for the *Journal of Lipid Research*. Studies on these lipidoses have led to important advances in biochemistry, cell biology, and medicine. These advances include the delineation of the anabolic and catabolic pathways for sphingolipid metabolism, insights into protein trafficking mechanisms, and the role of the lysosome in autophagy and cell death, to name but a few.

LSDs were among the first group of genetic diseases for which effective therapeutics were developed. Seminal work that delineated the role of mannose containing glycans for protein trafficking (4) and cellular uptake led to the use of mannose terminated β-glucocerebrosidase for the treatment of Gaucher disease type 1 (5). This treatment paradigm, termed enzyme replacement therapy, has been successfully employed in several other LSDs. Both the success and limitations of enzyme replacement therapy have motivated many investigators to explore alternative strategies for treating LSDs. Much of this work is the basis for these reviews. Included in this series are papers on lysosome exocytosis (Samie and Xu), gene therapy (Cheng), chemical inhibitors of lysosomal substrate synthesis and chemical chaperones (Shayman and Larsen), lipid sequestration employing cyclodextrin (Vance and Karten), and heat shock proteins (Kirkegaard). In addition, therapeutic approaches to the synucleinopathies are covered to exemplify how therapeutics for LSDs may eventually be applied to common diseases, including Parkinson's (Sybertz and Krainc). Other diseases that may eventually be targeted in this manner include diabetes mellitus, polycystic kidney disease, systemic lupus erythematosis, and cancer.

Several themes emerge upon a collective reading of these reviews. First, advances in the understanding of lysosomal biology have led to the identification of novel targets for therapeutics. Examples of new "druggable targets" in this series are the regulation of lysosomal exocytosis and use of heat shock proteins as potential targets. Second, novel insights in lysosomal biology have arisen from efforts to more fully understand the mechanisms by which certain drugs act. Recent examples of such insights include β-glucocerebrosidase 2, now appreciated to be the primary target of miglustat, mechanisms of cellular cholesterol egress by β-cyclodextrin, and lysosomal phospholipase A2 as a primary mediator of drug-induced phospholipidosis. Third, the pathogenesis of common diseases may be linked to lysosomal dysfunction or occur secondarily to the accumulation of an uncatabolized substrate in either a lysosomal or nonlysosomal compartment. Thus, the pursuit of effective therapies for the rare LSDs may result in advances in the treatment of common disorders. Fourth, the successful development of therapeutics for LSDs has led to the identification of scientific strategies that can be generalized and applied to the challenge of identifying effective treatments for the thousands of other rare nonlysosomally based diseases. The strategies for targeting orphan diseases, originally championed by biotechnology companies, have more recently been adopted by large pharmaceutical companies as well.

Despite the success in treating a handful of LSDs realized to date, existing therapies have significant limitations with regard to efficacy and untoward effects. More importantly, for most of the LSDs, there remains no available or effective therapy. The unmet medical need represented by these disorders should be heard as a clarion call for biochemists, cell biologists, pharmacologists, geneticists, and clinicians to muster their scientific expertise and creativity in ways that will lead to the discovery of the next generation of therapies. The exciting recent significant insights in lysosomal biology and disease in addition to the novel

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approaches to the treatment of LSDs will undoubtedly provide further motivation for the scientific community in pursuit of this goal.

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