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Preface

# Lysosomes

Lysosomes were discovered by Chistian de Duve in 1955 more or less by serendipity. De Duve was primarily interested in elucidating the hepatic actions of insulin. He had prepared subcellular fractions enriched in acid phosphatase and noticed that the activity in this fraction reproducibly increased after it was left in the refrigerator for some days. He considered this phenomenon as sufficiently odd to investigate its molecular basis. His curiosity led to the insight that the enzyme was present within membrane limited particles which ruptured and released the enzyme after aging in the refrigerator. Christian de Duve succeeded to separate these particles from mitochondria and microsomes and he realized that they contain besides acid phosphatase several other hydrolases. This led him to suggest that these newly discovered particles constitute a degradative compartment of general function. Therefore he termed these particles lysosomes. This discovery earned him the Nobel Prize in 1974.

At the time of this discovery, the MD Gery Hers worked with De Duve. Hers was interested in disorders of metabolism such as glycogen storage diseases. He noticed that, in one of the glycogen storage disease – Pompe disease – an acid glucosidase was deficient. Because of his tight connections to De Duve, he immediately realized that this hydrolase must be lysosomal. This led him to consider Pompe diseases a lysosomal disease and he suggested the more general concept of inborn lysosomal diseases. This led to a rapid extension of the field and within a few years after Hers publication many lysosomal hydrolases were identified and other disorders were classified as lysosomal storage diseases. By 1980, receptor-mediated endocytosis was recognized to be of central importance for the lysosomal pathway. Experiments performed by Elizabeth Neufeld with fibroblasts of patients suffering from mucopolysaccharidosis set the stage for the identification of mannose-6-phosphate as an important posttranslational modification for delivery of soluble lysosomal enzymes to lysosomes and the identification of mannose-6-phosphate receptors as essential components for lysosomal sorting. At the same time, these experiments also provided the rationale for enzyme replacement therapies, which since then have been clinically established for some of the lysosomal storage diseases. Cloning of genes of lysosomal proteins dominated research in the 1990s. Many genes of lysosomal enzymes were cloned and characterized and mutations causing the respective diseases were identified. Molecular biology led to the identification of sorting and transport signals in lysosomal membrane proteins and a better understanding of the mechanisms of endocytic sorting and delivery of compounds to the lysosome was achieved.

Already in the 1970s, Roscoe Brady had promoted the concept of enzyme replacement therapy in lysosomal storage diseases, which finally led to the clinical application in Gaucher disease in which this therapeutic approach is highly successful. The success of enzyme replacement in Gaucher disease was the basis for the extension of this approach to other lysosomal diseases. This prompted the industrial production of lysosomal enzymes for clinical application in various lysosomal disorders. Besides this protein-based treatment, small molecule-based therapies are also under development. This include substrate reduction therapies in which the synthesis of the accumulating compound is inhibited and molecular chaperone therapies in which the delivery of mutant lysosomal enzymes to lysosomes is improved. The availability of mouse models for many diseases enabled research on experimental therapies such as gene therapy or stem cell-based therapies. Whereas for a few diseases gene therapy is in the late preclinical stages and trials in humans will be performed soon, currently the first patients with tripeptidyl peptidase I-deficiency underwent the first AAV-mediated therapeutic trial.

The following review series updates on several aspects of lysosomal biology mentioned in this brief historical overview. Thus, in the last years, many details of the cellular routes delivering compounds to lysosomes have been revealed. The sorting of resident soluble and transmembrane lysosomal proteins from the biosynthetic route or the plasma membrane to the lysosomes is the focus of the contribution of T. Braulke and J.S. Bonifacino. Endocytosis is one of the major routes delivering proteins, lipids, and other compounds for lysosomal degradation. Advances in our understanding of this route with particular emphasis on proteins are reviewed by P.R. Pryor and J. P. Luzio. Autophagy is essential to cells and provides a pathway by which intracellular material is delivered to the lysosome. The importance of this pathway is highlighted by the contribution of E.-L. Eskelinen and P. Saftig. Taking lipids as an example, the contribution of H. Schulze, T. Kolter, and K. Sandhoff reviews how degradation of compounds occurs after delivery to the lysosome.

Much has been learned from studies on the vacuole as the lysosomal equivalent of yeast. As for other cellular processes, the power of generating yeast mutants has led to the identification of important cellular players in lysosomal biology as summarized by S.C. Li and P.M. Kane. Proteomics has been proven to identify as yet unknown mannose 6-phosphate-containing lysosomal proteins and has been applied selectively to the lysosomal membrane. Several interesting proteins, which were newly recognized through this methodology, are in the focus of the contribution of T. Lübke, P. Lobel, and D.E. Sleat. In contrast to the “classical” soluble lysosomal hydrolases, the knowledge about the function of lysosomal membrane proteins is lagging somewhat behind but has made considerable progress in recent years as outlined in the contribution of B. Gasnier and colleagues. Research on lysosomal function has always been fueled by the existence of more than 50 different genetically and clinically defined lysosomal storage diseases. Our understanding of how storage material actually elicits its detrimental effects and its

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contribution to the pathogenesis of these disorders is only in its early stages and will be a major research area in the next years. A number of processes, such as the cellular effects of storage material, however, have already been identified and are reviewed by A. Ballabio and V. Gieselmann. In addition, secondary accumulation of non-degraded material may contribute to the pathogenesis of lysosomal storage diseases and is reviewed by S.U. Walkley and M.T. Vanier. Neuronal Ceroid Lipofuscinoses comprise a group of diseases, which are genetically heterogeneous but share common clinical features. These disorders are the most frequent cause of neurodegeneration in children. The lysosomal implications in these diseases have only been appreciated in recent years as reviewed by A. Jalanko and T. Braulke. For the non-expert, it is frequently surprising that lysosomal storage can also be due to the deficiency of proteins, which are not primarily lysosomal. These defects are covered in the review of T. Dierks and coauthors. Lysosomes do play a pathogenic role not only in the respective storage disorders, but also in more frequent diseases. As an example, T. Kierkegaard and M. Jaattela review the function of lysosomes in cancer.

About 20-30 years ago, lysosomal storage diseases have been considered as untreatable. This has changed considerably in particular in the last decade. For some diseases, treatment is now clinically established. Many other therapeutic approaches are either in the early experimental stages, preclinical development or in already in clinical trials. The available therapeutic options are discussed in the contribution of F.M. Platt and R.H. Lachmann.

This issue of BBA Molecular Cell Research highlights advances in lysosomal research in recent years. The expanding area of research on lysosomes makes it difficult to cover every aspect with a limited number of reviews. Thus, reviews on lysosome-related organelles and on the role of lysosomes in infectious diseases for example were exempted because they have been covered by various excellent reviews published just recently.

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Dr. Thomas Braulke is a professor of biochemistry at the University Medical Center Hamburg-Eppendorf. He received his doctorate in neurochemistry at the University of Leipzig in 1980, and was trained as a post-doctoral fellow and group leader in the laboratory of Dr. Kurt von Figura at the University in Münster and in Göttingen until 1999 when he moved to Hamburg. His research focuses on the biogenesis of lysosomes and pathogenic mechanisms of lysosomal storage diseases, and the mitochondrial disorder glutaric aciduria type 1.