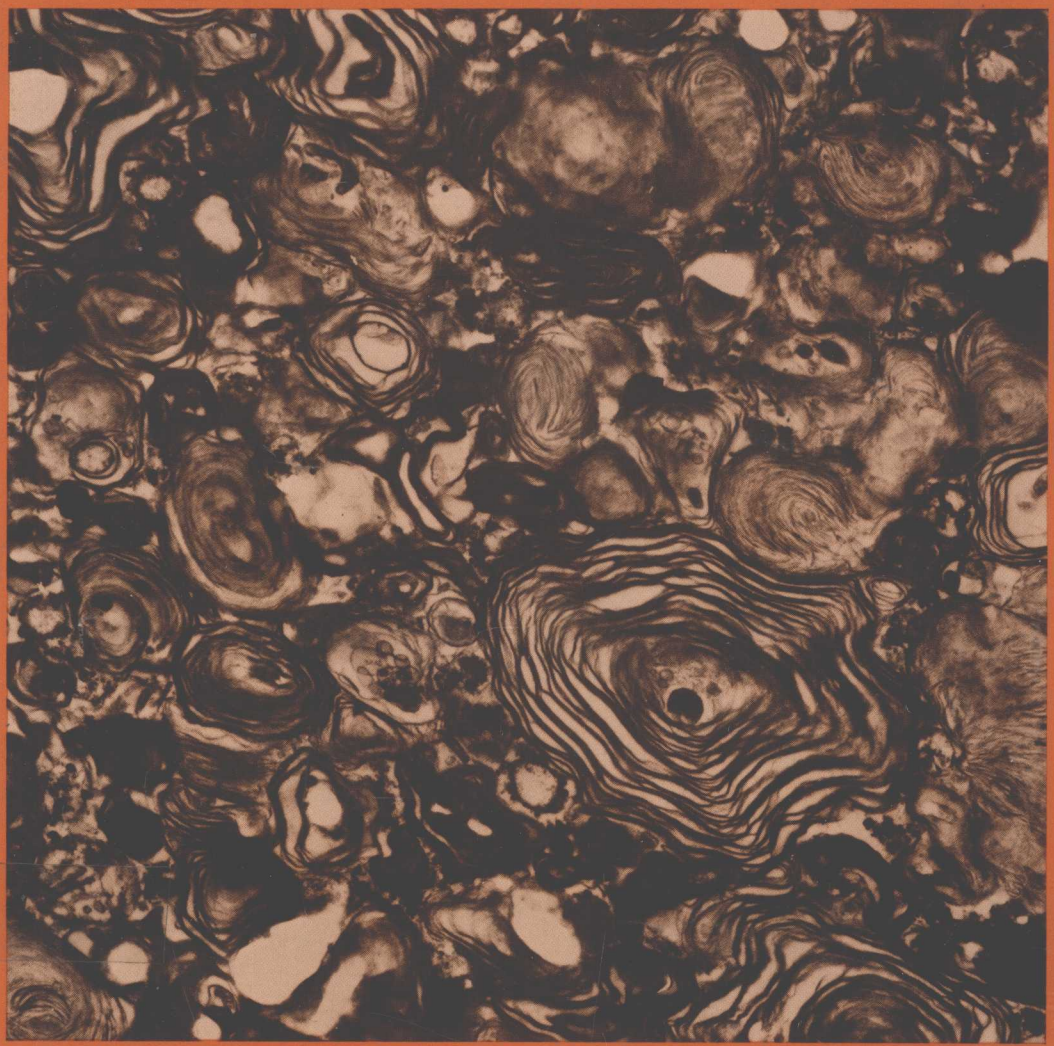
Lysosomes & Lysosomal Storage Diseases

Editors John W. Callahan • J. Alexander Lowden



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Lysosomes and Lysosomal Storage Diseases

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Preface

In 1955 Christian de Duve coined the term *lysosome,* meaning lytic particles, for membrane-bound organelles containing five acid hydrolases that he and his colleagues had been studying for several years. Those five enzymes have barely been mentioned in this volume because only one is inactive in a recognized storage disease. In 1955, none of the storage disorders described in these chapters was known to result from a defect in an acid hydrolase. Today, twenty-five years later, a wealth of knowledge about the molecular biology of the lysosome has accumulated, much of it uncovered by investigations of the many genetic perturbations of the enzymes located in this fascinating organelle. Many questions remain unanswered, however, and this volume is directed toward those problems.

In the presence of a specific lysosomal enzyme deficiency, the activity of some hydrolases is markedly elevated while that of others is within normal limits. How are the enzymes programmed to become part of the lysosomal apparatus? If all lysosomal hydrolases were synthesized and parcelled in unison, one would expect that the activities of all of them would rise and fall to the same degree. This does not appear to happen, and one tantalizing hypothesis presumes the existence of clones of primary lysosomes each containing a defined array of lytic enzymes. Each clonal population could be separately programmed and targeted. The concept also presupposes receptor domains in the endoplasmic reticulum that act as templates for organelle formation.

In this book we have attempted to bring together studies on the molecular biology of the lysosome and its enzymes with reports on several of the genetic defects in the activity of these enzymes. The first part of the volume discusses genetic and metabolic regulation of lysosomal activity, aspects of complex carbohydrate biosynthesis and recognition, processing and compartmentalization of lysosomal hydrolases. This background serves as a foundation for discussion of the structure and function of a variety of lysosomal hydrolases involved in the catabolism of sphingolipids, glycoproteins, and glycosaminoglycans.

Understanding the structural and kinetic properties of the hydrolases and identification of the genetic defects in storage diseases allows the investigation of genetic heterogeneity, carrier screening programs, and development of strategies for treatment such as enzyme replacement. The order in which these subjects are discussed follows from the molecular aspects of lysosomes and hydrolases to the applied clinical area of enzyme replacement. The authors of the chapters were chosen because of their special expertise and outstanding contributions to the current state of knowledge. Not only do portions of the subject matter present new unreported data but the text provides a framework for many chal-

lenging new ideas which presently lack a firm foundation of experimental data.

In a volume of this size one cannot cover the vast field of knowledge about the lysosome and its related storage diseases. We have attempted to highlight important areas where new developments have taken place in recent months. The volume will be of value to research scientists in the area of biochemistry, genetics, and neurochemistry as well as to physicians in pediatrics, neurology, and internal medicine.

The Editors

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LIST OF ENZYMES AND ENZYME COMMISSION NUMBERS

Enzyme	*E. C. Number*
Acid lipase (triacyl glycerol lipase)	EC.3.1.1.3
Acid phosphatase	EC.3.1.3.2
APS kinase	EC.2.7.1.25
APS phosphohydrolase	EC.3.1.3.30
APS sulfohydrolase	EC.3.6.2.2
APS sulfotransferase	EC.2.8.2.5
ATP sulfurylase	EC.2.7.7.4
Arylsulfatase	EC.3.1.6.1
α-L-Fucosidase	EC.3.2.1.51
α-galactosidase	EC.3.2.1.22
α-L-Iduronidase	EC.3.2.1.76
α-Mannosidase	EC.3.2.1.24
α-Neuraminidase	EC.3.2.1.18
β-galactosidase	EC.3.2.1.23
β-glucuronidase	EC.3.2.1.31
β-N-acetylhexosaminidase	EC.3.2.1.52
galactosylceramide β-galactosidase	EC.3.2.1.46
galactosylceramide 3-SO_4 sulfatase	EC.3.1.6.8
glucosylceramide β-glucosidase	EC.3.2.1.45
Sphingomyelinase	EC.3.1.4.12
Sulfoglucosamine sulfamidase (sulfamatase)	EC.3.10.1.1

LIST OF ABBREVIATIONS

Ac Ph	Acid phosphatase
α-L-Fuc	α-L-fucosidase
α-Gal	α-galactosidase
α-Gal NAc	α-N-acetylgalactosaminidase
α-Glc	α-glucosidase
α-Glc NAc	α-N-acetylglucosaminidase
α-IdoU	α-Iduronidase
α-Man	α-Mannosidase
α-Neur	α-Neuraminidase
APS	Adenosine phosphosulfate
ASA	Arylsulfatase A
ASB	Arylsulfatase B
ATP	Adenosine triphosphate
β-Gal	β-galactosidase
β-Glc	β-glucosidase
β-GlcU	β-Glucuronidase
β-Hex	β-Hexosaminidase
β-Xyl	β-Xylosidase
CDH	Lactosylceramide
C4S	Chondroitin 4 sulfate
DS	dermatan sulfate
4-MU-β-gal	4-methylumbelliferyl-β-D-galactopyranoside
4-MU-β-glc	4-methylumbelliferyl-β-D-glucopyranoside
4-MU-β-glcNAc	4-methylumbelliferyl-2-acetamido-2-deoxy-β-D-glucopyranoside
4-MU-SO_4	4-methylumbelliferylsulfate
4-MU-β-Xyl	4-methylumbelliferyl-β-D-xyloside
Gal-cer	Galactosylceramide (galactocerebroside)
Gal-cer β-gal	Galactosylceramide β-galactosidase
GalNAc-4-SO_4 Sulf	N-acetylgalactosamine 4-sulfate sulfatase
Gal-3-SO_4 Sulf	Galactose 3-sulfate sulfatase
Gal-6-SO_4 Sulf	Galactose 6-sulfate sulfatase
Gb_3Cer	Globotriaosylceramide (trihexosylceramide)
Gb_4Cer	Globotetraosylceramide (globoside)
GDla,GDlb	disialogangliosides
Glc-cer	Glucosylceramide (gluco-cerebroside)
Glc-cer β-glc	Glucosylceramide β-glucosidase
GlcNAc-6-SO_4	N-acetylglucosamine 6-sulfate
GlcNAc-6-SO_4 Sulf	N-acetylglucosamine 6-sulfate sulfatase
G_{M1}, G_{M2}, G_{M3}	Monosialogangliosides
GlcUA	Glucuronic acid
HS	Heparan sulfate
IdoUA	Iduronic acid
IdoU SO_4 Sulf	Iduronic acid 2-sulfate sulfatase
KS	Keratan sulfate
MPS	Mucopolysaccharides
NANA	N-acetylneuraminic acid

$NC\text{-}SO_4$	Nitrocatechol sulfate
PAPS	Phosphoadenosine phosphosulfate
Sulf	Sulfatase (s)
Sulfamatase	Sulfoglucosamine sulfamidase
TLC	Thin layer chromatography

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