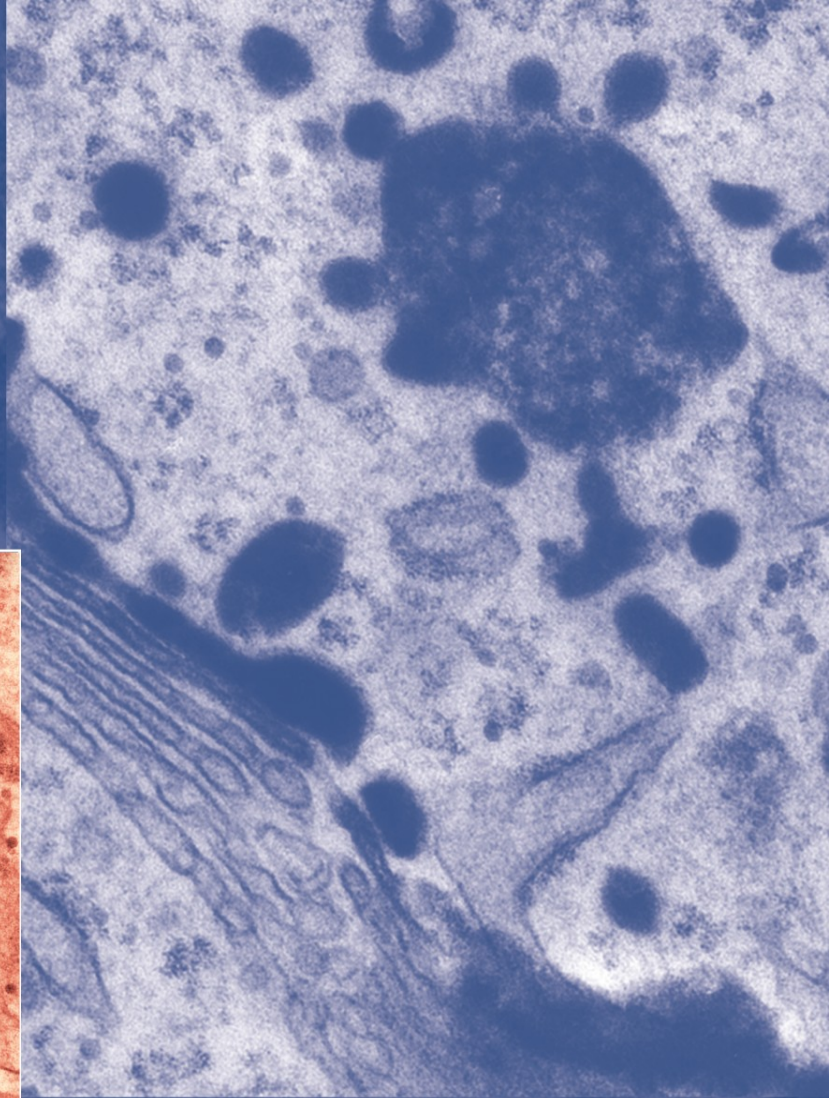
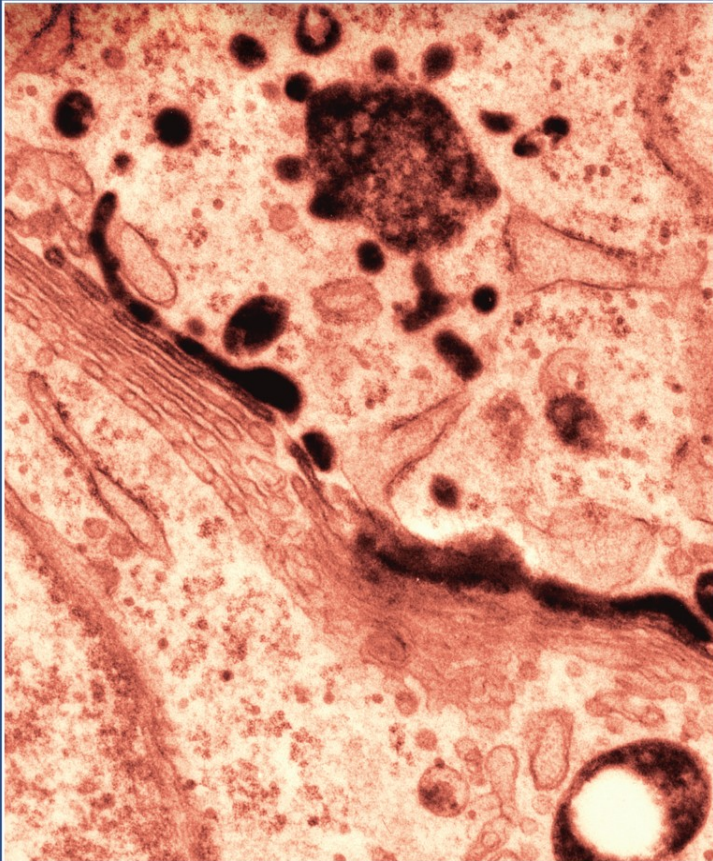


margit pavelka, jürgen roth
functional ultrastructure
atlas of tissue biology and pathology



margit pavelka, jürgen roth
functional ultrastructure
atlas of tissue biology and pathology

Margit Pavelka
Jürgen Roth

Functional Ultrastructure

An Atlas of Tissue Biology and Pathology

SpringerWienNewYork

Prof. Dr. med. Margit Pavelka
Medizinische Universität Wien, Zentrum für Anatomie und Zellbiologie
Institut für Histologie und Embryologie, Abteilung für Zellbiologie und Ultrastrukturforschung, Vienna, Austria
(margit.pavelka@meduniwien.ac.at)

Prof. Dr. med. Dr. sc. Dr. h. c. Jürgen Roth
Universität Zürich, Abteilung für Zell- und Molekularpathologie, Zurich, Switzerland
(juergen.roth@usz.ch)

This work is subject to copyright.

All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machines or similar means, and storage in data banks.

Product Liability: The publisher can give no guarantee for all the information contained in this book. This does also refer to information about drug dosage and application thereof. In every individual case the respective user must check its accuracy by consulting other pharmaceutical literature. The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

© 2005 Springer-Verlag/Wien
Printed in Austria

SpringerWienNewYork is part of Springer Science + Business Media
springeronline.com

Typesetting and Printing: Holzhausen Druck und Medien GmbH, 1140 Wien, Austria

Printed on acid-free and chlorine-free bleached paper
SPIN: 10732308

With 157 Figures

Library of Congress Control Number: 2004106811

ISBN 3-211-83564-4 SpringerWienNewYork

This book is dedicated to

Michaela and Ernst

Verena, Raphael, Julia and David

FOREWORD

The period between 1950 and 1980 were the golden years of transmission electron microscopy and produced a plethora of new information on the structure of cells that was coupled to and followed by biochemical and functional studies. TEM was king and each micrograph of a new object produced new information that led to new insights on cell and tissue organization and their functions. The quality of data represented by the images of cells and tissues had been perfected to a very high level by the great microscopists of the era including Palade, Porter, Fawcett, Sjostrand, Rhodin and many others. At present, the images that we see in leading journals for the most part do not reach the same technical level and are not prepared with the same attention to detail as in the golden era of TEM nor do not have the same information content and sheer beauty.

This Atlas by Jürgen Roth and Margit Pavelka is a major exception, as it presents electron micrographs whose image quality and information content is uncompromised and unsurpassed. It has been prepared with great care and attention to detail. It depicts the beautiful diversity of specialized cell types such as those of the exocrine pancreas, intestinal epithelium, sperm and neuron, for example. It reminds the reader that although each cell has the usual complement of organelles their organization is quite different and distinctive and is recognizable to the trained eye. It reminds the cell biologist, biochemist, molecular biologist and pathologist alike, who all too frequently work on cultured cells that lack differentiated features, of the diversity of cells in mammals and how their structure and organization reflect their functions. Thus this atlas provides unique insights on how the architecture of cells, tissues and cell organelles mirror their functions.

It also provides unique insights into how pathological processes affect cell organization.

This information is vital to current work in which the emphasis is on integrating approaches from proteomics, molecular biology, molecular imaging and physiology, and pathology to understand cell functions and derangements in disease. In this current era, there is a growing tendency to substitute modern light microscopic techniques for electron microscopy because it is less technically demanding and is more readily available to researchers. This atlas reminds us that the information obtained by electron microscopy is invaluable and has no substitute. The increased insights obtained are comparable to the superior resolution (1000 x greater) obtained by the two methods. In fact this atlas reminds us that these two approaches are complementary, and neither one can substitute for the other.

Careful perusal of the images in this atlas makes one realize how many details are visible that go beyond those already known as far as even normal cell architecture is concerned. There is still a gold mine to be discovered for those wishing to put forth the effort. When it comes to cellular pathology in particular the surface has barely been scratched.

It can be anticipated that this atlas may stimulate readers to undertake further ultrastructural studies coupled with functional studies on both normal and diseased cells to harvest the detailed insights this will provide. In the age of harvesting the “cell genome and proteome”, we should also not forget to pay attention to harvesting the cell “struaturome”. This atlas provides the reader with the opportunity to get started.

La Jolla, August 2004

Marilyn G. Farquhar

PREFACE

The present-day exciting era of genomics and proteomics, which provided new and revolutionary insights into the life of cells, has also led to a renewed interest and special appreciation of ultrastructure research. For the understanding of the functions of cells and tissues, it is mandatory to precisely know the structure of their macromolecular and supramolecular assemblies and essential to identify their sites of action with high resolution as well as to explore their dynamics in the life of cells and their organisation in higher systems. It is the today's top challenge and priority of all ultramicroscopic methods to visualise functional processes in cells and tissues in their correlation with subcellular organelles and their ultrastructurally recognizable domains. Major progress has become possible through the refinement of existing preparation techniques and the development of new ones as well as the development of new types of microscopes. Among others, high pressure cryofixation and cryoelectron microscopy applied for high resolution 3D structural analysis of isolated macromolecular complexes, electron tomography and 3D reconstruction of the inner architectures of cells, low temperature embedding resins and cryoultramicrotomy in combination with immunogold labelling and hybridisation techniques and atomic force microscopes have become fully integrated into the range of methods used in modern molecular cell biology.

Our principal aim in compiling this atlas was to provide the reader with first-hand information about the major role ultrastructure research continues to play in the various fields of cell and tissue biology and pathology. We hope it will be useful for investigators, both beginners and experienced researchers, not only of biology and medicine but also of molecular biology and biochemistry as an aid and guide for the evaluation and interpretation of electron micrographs. The plates of electron micrographs of this atlas illustrate the

use of both classical and present-day electron microscopy in the study of normal and diseased cells and tissues. They are accompanied by brief explanatory texts, schemes and diagrams and selected classical as well as recent publications and key reviews for further reading. For those readers who want to up-date the references, a most useful on-line service is provided by Pubmed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db>).

The first part of the atlas deals with the cell and its various constituents, cell-cell contacts and cell-matrix interactions. Here we aimed to be as complete as possible in the documentation of the various structures and their function in the context of molecular cell biology. In addition we included representative examples of characteristic organelle changes under various experimental conditions and under conditions of disease. The second part exemplifies principles of tissue organisation and is supplemented with selected examples of ultrastructural tissue pathologies. Here, we aimed not on completeness but particular emphasis was placed on morpho-functional aspects in order to demonstrate that the ultrastructure of cells and tissues mirrors their main tasks and reflects specific functions.

We hope that this atlas is not looked upon as a mere collection of striking electron microscopic pictures. Each of the electron micrographs is intended to convey a specific message related to the properties, functions, or pathologies of the tissues and cells shown. Last but not least we would like to hear from our readers and use these suggestions (mail to: juergen.roth@usz.ch and margit.pavelka@meduniwien.ac.at) to improve future editions.

Vienna Zurich, July 2004

*Margit Pavelka
Jürgen Roth*

ACKNOWLEDGEMENTS

Many people were involved in the various aspects of this project and we would like to acknowledge and thank them for their precious time, valuable suggestions and encouragement during the various phases of the evolution of this book. We are greatly indebted to those colleagues who have generously supplied us with exceptional electron micrographs. A number of micrographs from the own archives represent the results of fruitful collaboration with present and past members of our groups and colleagues from abroad and these include (in alphabetical order) Moise Bendayan, Eric G. Berger, Dieter Bitter-Suermann, Daniela Brada, Dennis Brown, Eric Carlemalm, Pierre M. Charest, Paul Debbage, Michel Deschuyteneer, Adolf Ellinger, Jingyu Fan, Richard M. Franklin, Alfred Gangl, Irwin J. Goldstein, Bruno Guhl, Michael Hess, Robert L. Hill, Kristijan Jezernik, Eduard Kellenberger, Reinhard Kofler, Peter M. Lackie, Hans Lassmann, John M. Lucocq, Roberto Montesano, Josef Neumüller, Armando Parodi, James C. Paulson, Hanns Plenck, Christian Schöfer, Robert G. Spiro, Douglas J. Taatjes, Kiyoteru T. Tokuyasu, Monika Vetterlein, Werner Villiger,

Franz Wachtler, Winifred M. Watkins, Klara Weipoltshammer, and Christian Zuber.

The members of our groups and the many colleagues who took their precious time to read the texts and scrutinise the illustrations are gratefully acknowledged for their valuable feedback and suggestions for improvement. Antoinette Schumacher and Monika Vetterlein carefully checked the texts before they went for further polishing to the copy editor Dr. Birte Twisselmann. We also would like to extend our gratitude to Elfriede Scherzer and Beatrix Mallinger for their excellent technical assistance, and to Ulrich Kaindl, Norbert Wey, Stefanie Sulzer and Klaus Schönheinz for their invaluable help in preparing the micrographs and their professional skills in transforming our amateur sketches into artistic schemes and diagrams. A special note of thanks is due to Dir. Rudolf Siegle, Mag. Renate Eichberger and Mag. Wolfgang Dollhäubl and all members of the team at SpringerWienNewYork for their great support and patience during the up and downs of the development of this atlas.

CONTRIBUTORS OF ELECTRON MICROGRAPHS

Dr. Ueli Aebi (Basel)

Dr. Thomas Bächli (Zurich)

Dr. Peter H. Burri (Bern)

Dr. Dusan Cmarko (Lausanne)

Dr. H. Dariush Fahimi (Heidelberg)

Dr. Stanislav Fakan (Lausanne)

Dr. Michael Hess (Innsbruck)

Dr. Ernst B. Hunziker (Bern)

Dr. Françoise Jaunin (Lausanne)

Dr. Kristijan Jezernik (Ljubljana)

Dr. Brigitte Kaissling (Zurich)

Dr. Lars-Inge Larsson (Frederiksberg)

Dr. Hans Lassmann (Vienna)

Dr. Josef Neumüller (Vienna)

Dr. Hanns Plenck jr. (Vienna)

Dr. Charlotte Remé (Zurich)

Dr. Christian Schöfer (Vienna)

Dr. Max Spycher (Zurich)

Dr. Franz Wachtler (Vienna)

Dr. Ewald R. Weibel (Bern)

Dr. Klara Weipoltshammer (Vienna)

Dr. Sadaki Yokota (Yamanashi)

CONTENTS

THE CELL

Introduction: Structural organisation of a mammalian cell	2
The Nucleus	
Architecture of the cell nucleus	4
Cytochemical detection of ribonucleoproteins	6
Nuclear lamina	6
Detection of sites of DNA replication and of interphase chromosome domains	8
Nucleolus	10
Changes of the nucleolar architecture	12
Detection of sites of RNA synthesis	14
Nuclear pore complexes	16
Nuclear pore complexes: Structural changes as monitored by time-lapse atomic force microscopy	18
Mitosis and cell division	20
Apoptosis	22
Viral inclusions	22
The Cytoplasm: The Secretory System	
Secretory pathway of pancreatic acinar cells	24
Ribosomes, rough endoplasmic reticulum	26
Nuclear envelope and rough endoplasmic reticulum	28
Rough endoplasmic reticulum: Site of protein translocation and initiation of protein <i>N</i> -glycosylation	30
Oligosaccharide trimming, reglucosylation, and protein quality control in the rough endoplasmic reticulum	32
Rough endoplasmic reticulum: Storage site of aggregates of misfolded glycoproteins	34
Russell bodies and aggresomes represent different types of protein inclusion bodies	36
Smooth endoplasmic reticulum	38
Proliferation of the smooth endoplasmic reticulum	40
Pre-Golgi intermediates	42
Pre-Golgi intermediates: Oligosaccharide trimming and protein quality control	44
Golgi apparatus: A main crossroads along secretory pathways	46
Protein secretion visualised by immunoelectron microscopy	48
Protein <i>N</i> -glycosylation: Oligosaccharide trimming in the Golgi apparatus and pre-Golgi intermediates	50
Golgi apparatus: Site of maturation of asparagine-linked oligosaccharides	52
Cell-type-related variations in the topography of Golgi apparatus glycosylation reactions	54
Cell-type-related differences in oligosaccharide structure	56
Topography of biosynthesis of serine/threonine-linked oligosaccharides	58
Golgi apparatus and TGN – Secretion and endocytosis	60
Golgi apparatus, TGN and <i>trans</i> -Golgi-ER	62
Golgi apparatus, TGN and <i>trans</i> -Golgi-ER: Tilt series	64
Brefeldin A-induced disassembly of the Golgi apparatus	66
Brefeldin A-treatment: Tubulation of Golgi apparatus and endosomes	68
Brefeldin A-treatment: Effect on retrograde transport of internalised WGA	70

Brefeldin A-treatment: Transitional ER-elements and pre-Golgi intermediates	72
Heat shock response of the Golgi apparatus	74
Changes of the Golgi apparatus upon ATP-depletion and ATP-replenishment	76
Secretory granules	78
Secretory granule types	80
The Cytoplasm: The Endocytic System	
Receptor-mediated endocytosis via clathrin-coated vesicles and virus endocytosis	82
Endosomes and endocytic pathways	84
Endocytic <i>trans</i> -Golgi network and retrograde traffic into the Golgi apparatus	86
Tubular pericentriolar endosomes	88
Langerhans cells and Birbeck granules: Antigen presenting dendritic cells of the epidermis	90
Caveolae	92
Fluid phase endocytosis and phagocytosis	94
The Cytoplasm: Lysosomes and Lysosomal Disorders	
Lysosomes	96
Lysosomes: Localisation of acid phosphatase, LAMP and polylectosamine	98
I-cell disease	100
Gaucher's disease	102
Fabry's disease	104
G _{M2} gangliosidoses	106
Farber's disease	108
Wolman's disease	110
Glycogenosis type II	112
Cystinosis	112
The Cytoplasm: Autophagocytosis	
Autophagosomes: Organelles for limited self-digestion	114
The Cytoplasm: Mitochondria and Structural Abnormalities	
Mitochondria: Crista- and tubulus-types	116
Abnormalities of mitochondria	118
The Cytoplasm: Peroxisomes and Peroxisomal Diseases	
Peroxisomes: Multitalented organelles	120
Peroxisome biogenesis	122
Peroxisomes: Adaptive changes	124
Peroxisomal diseases	126
The Cytoplasm: Cytosolic Particles	
Glycogen	128
Glycogenosis type I	128
Erythropoietic protoporphyria	130

The Cytoplasm: Cytoskeleton

Cytocentre, centrosome, and microtubules	132
Effects of microtubule disruption	134
Actin filaments	136
Intermediate filaments	138
Mallory bodies	140

The Plasma Membrane and Cell Surface Specialisations

The plasma membrane	142
Cells in culture	144
Brush cell	146
Glycocalyx (cell coat)	148
Glycocalyx: Cell type specificity and domains	150
Glycocalyx changes in tumours	152

Cell-Cell and Cell-Matrix Contacts

Junctional complex	154
Tight junctions and gap junctions	156
Spot desmosomes	158
Cellular interdigitations	160
Basal labyrinth	162
Basement membrane	164
Glomerular basement membrane	166
Alport's syndrome (hereditary nephritis)	166
Descemet's membrane	168
Skin basement membrane and keratinocyte hemidesmosomes:	
An epithel-connective tissue junctional complex	170
Epidermolysis bullosa simplex	172

PRINCIPLES OF TISSUE ORGANISATION**Secretory Epithelia**

Pancreatic acinus	176
Acinar centre: Acinar and centroacinar cells	178
Pancreatic intercalated duct	180
Submandibular gland	182
Parietal cells of stomach: Secretion of acid	184
Intercalated cells of kidney: Important regulators of acid-base balance	186
Endocrine secretion: Insulin-producing beta cells of islets of Langerhans	188
Impaired insulin processing in human insulinoma	190
Cells of the disseminated endocrine system	192
Liver epithelium	194
Liver epithelium: Bile canaliculi	196
Liver epithelium: Pathway of secretory lipoprotein particles	198
Choroid plexus ependyma	200

Resorptive Epithelia

Small intestine: Absorptive cells	202
Small intestine: Pathway of lipids	204
Renal proximal tubule: A reabsorption plant	206
Parathyroid hormone response of renal proximal tubules	208

Sensory Epithelia

Photoreceptor cells of the retina: Signalling of light	210
Photoreceptor cells of the retina: Light-induced apoptosis	212

Stratified Epithelia

Corneal epithelium	214
Epidermis	216
Differentiation of keratinocytes and formation of the epidermal fluid barrier	218

Epithelia of the Respiratory Tract

The tracheo-bronchial epithelium	220
Ciliary pathology: Immotile cilia syndrome and Kartagener syndrome	222
Alveoli: Gas exchange and host defense	224

Urothelium

Umbrella cell – Surface specialisations	226
Umbrella cell - Fusiform vesicles	228

Endothelia and Glomerulus

Continuous capillary, Weibel-Palade bodies	230
Fenestrated capillary	232
Endothelio-pericyte and endothelio-smooth muscle cell interactions	234
Glomerulus: A specialised device for filtering	236
Pathology of the glomerular filter: Minimal change glomerulopathy and congenital nephrotic syndromes	238
Pathology of the glomerulus: Membranous glomerulonephritis	240
Pathology of the glomerulus: Membranoproliferative glomerulonephritis	242
Pathology of the glomerulus: Chronic allograft glomerulopathy	244

Connective Tissue

Loose connective tissue	246
Fibroblast, fibrocyte, macrophage	248
Collagen und elastic fibres	250
Eosinophilic granulocyte, plasma cell, macrophage, mast cell	252
Dense connective tissue: Collagen bundles in the cornea	254
Bowman's layer	256
Amyloidosis of kidney	258
Amyloid fibrils: Growth as seen by time lapse, atomic force microscopy	260

Cartilage	
Articular cartilage	262
Bone	
Osteoblasts and osteocytes	264
Osteoclast	266
Skeletal Muscle	
Myofibrils and sarcomere	268
Sarcoplasmic reticulum, triad, satellite cell	270
Neuromuscular junction	272
Muscular dystrophies	274
Cardiac Muscle	
Myofibrils, intercalated disk	276
Smooth Muscle	
Smooth muscle cells, synapse á distance	278
CADASIL	280
Nerve Tissue	
Central nervous system: Neuron, glial cells	282
Blood-brain barrier, synapses	284
Unmyelinated nerve fibre	286
Peripheral nerve, connective tissue components	288
Myelinated nerve fibre, myelin	290
Node of Ranvier	292
Axonal degeneration	294
Neuroaxonal dystrophy	296
Neuropathies associated with dysproteinaemias	298
Metachromatic leukodystrophy	300
Neuronal ceroid lipofuscinosis	302
Blood	
Red blood cells and cells of the erythroid lineage	304
Neutrophilic granulocyte	306
Eosinophilic granulocyte	308
Monocyte	310
Lymphocyte	312
Megakaryocyte and thrombocyte	314
Thrombocytes	316
Subject Index	319