

2nd edition



Enhanced
**DIGITAL
VERSION**
Included.
Details inside.

Molecular Pathology

The Molecular Basis of Human Disease



Edited by
William B. Coleman
Gregory J. Tsongalis



Molecular Pathology

The Molecular Basis of Human Disease

SECOND EDITION

Editors

William B. Coleman

Gregory J. Tsongalis



ACADEMIC PRESS

An imprint of Elsevier

Table of Contents

Cover image

Title page

Copyright

Dedication

List of Contributors

Preface

Acknowledgments

Chapter 1. Molecular Mechanisms of Cell Death

Introduction

Modes of Cell Death

Structural Features of Necrosis and Apoptosis

Cellular and Molecular Mechanisms Underlying Necrotic Cell Death

Pathways to Apoptosis

Mitochondria

Nucleus

Endoplasmic Reticulum

Lysosomes

Shared Pathways to Necrosis and Apoptosis

Programmed Necrosis

Concluding Remark

Chapter 2. Acute and Chronic Inflammation Induces Disease Pathogenesis

Introduction

Leukocyte Adhesion, Migration, and Activation

Acute Inflammation and Disease Pathogenesis

Pattern Recognition Receptors and Inflammatory Responses

Chronic Inflammation and Acquired Immune Responses

Tissue Remodeling During Acute and Chronic Inflammatory Disease

Chapter 3. Infection and Host Response

Introduction

Microbes and Hosts—Balance of Power?

The Structure of the Immune Response

Regulation of Immunity

Pathogen Strategies

Staphylococcus aureus: The Extracellular Battleground

Mycobacterium tuberculosis and the Macrophage

Herpes Simplex Virus: Taking Over

The African Trypanosome and Antibody Diversity: Dueling Genomes

HIV: The Immune Guerilla

Perspectives

Chapter 4. Neoplasia

Introduction

Cancer Statistics and Epidemiology

Classification of Neoplastic Diseases

Characteristics of Benign and Malignant Neoplasms

Clinical Aspects of Neoplasia

Chapter 5. Basic Concepts in Human Molecular Genetics

Introduction

Molecular Structure of DNA, DNA Transcription, and Protein Translation

Molecular Pathology and DNA Repair Mechanisms

Modes of Inheritance

Central Dogma and Rationale for Genetic Testing

Allelic Heterogeneity and Choice of Analytical Methodology

Conclusion

Chapter 6. The Human Genome: Understanding Human Disease in the Post-Genomic Era

Introduction

Structure and Organization of the Human Genome

Overview of the Human Genome Project

Impact of the Human Genome Project on the Identification of Disease-Related Genes

Sources of Variation in the Human Genome

Types of Genetic Diseases

Genetic Diseases and Cancer

Perspectives

Chapter 7. The Human Transcriptome: Implications for Understanding, Diagnosing, and Treating Human Disease

Introduction

Gene Expression Profiling—Early Attempts to Search for Candidate Genes Involved in Normal Physiological Processes and Pathogenesis

Preparation of Target RNA From Biological and Clinical Specimens

Transcriptome Analysis Based on Microarrays—Technical Aspects

Transcriptome Analysis Based on RNA Sequencing—Technical Aspects

Bioinformatics I—Basic Processing of Microarray and RNA-seq Data

Bioinformatics II—Exploration and Statistical Evaluation of Transcriptomics Data

Repositories for Transcriptome Data

Transcriptome Analysis—Applications in Basic Research and Translational Medicine

Perspectives

Chapter 8. The Human Epigenome—Implications for the Understanding of Human Disease

Introduction

Epigenetic Regulation of the Genome

Genomic Imprinting

Cancer Epigenetics

Human Disorders Associated With Epigenetics

Environment and the Epigenome

Chapter 9. Clinical Proteomics and Molecular Pathology

Understanding Cancer at the Molecular Level: An Evolving Frontier

Microdissection Technology Brings Molecular Analysis to the Tissue Level

Serum Proteomics: An Emerging Landscape for Early-Stage Cancer Detection

Chapter 10. Integrative Systems Biology

Introduction

Data Generation

Data Integration

Modeling Systems

Implications for Understanding Disease

Discussion

Chapter 11. Pathology: The Clinical Description of Human Disease

Introduction

Terms, Definitions, and Concepts

A Brief History of Approaches to Disease

Current Practice of Pathology

The Future of Diagnostic Pathology

Conclusion

Chapter 12. Understanding Molecular Pathogenesis: The Biological Basis of Human Disease and Implications for Improved Treatment of Human Disease

Introduction

Hepatitis C Virus Infection

Summary

Acute Myeloid Leukemia

Summary

Cystic Fibrosis

Summary

Chapter 13. Integration of Molecular and Cellular Pathogenesis: A Bioinformatics Approach

Introduction

Overview of Bioinformatics

Database Resources

Data Analysis

The Future of Bioinformatics

Chapter 14. Molecular Basis of Cardiovascular Disease

Introduction

General Molecular Principles of Cardiovascular Diseases

The Cells of Cardiovascular Organs

Atherosclerosis

Ischemic Heart Disease

Aneurysms

Vasculitis

Valvular Heart Disease

Cardiomyopathies

Lymphatic Circulation

Chapter 15. Molecular Basis of Hemostatic and Thrombotic Diseases

Introduction and Overview of Coagulation

Disorders of Soluble Clotting Factors

Disorders of Fibrinolysis

Disorders of Platelet Number or Function

The Thrombophilias

Chapter 16. Molecular Basis of Lymphoid and Myeloid Diseases

Introduction

Development of the Blood and Lymphoid Organs

Myeloid Disorders

Lymphocyte Disorders

Outlook for the Treatment of Leukemia

Chapter 17. Molecular Basis of Diseases of Immunity

Introduction

The Normal Immune System

Major Syndromes

The Hygiene Hypothesis

Chapter 18. Molecular Basis of Pulmonary Disease

Introduction

Neoplastic Lung and Pleural Diseases

Nonneoplastic Lung Disease

Interstitial Lung Diseases

Surfactant Dysfunction Diseases

Pulmonary Vascular Diseases

Chapter 19. Molecular Basis of Diseases of the Gastrointestinal Tract

Introduction

Gastric Cancer

Colorectal Cancer

Chapter 20. Molecular Basis of Liver Disease

Molecular Basis of Liver Development

Molecular Basis of Metabolic Zonation in the Liver

Molecular Basis of Liver Regeneration
Liver Stem Cells in Liver Health and Disease
Molecular Basis of Hepatocyte Death
Molecular Basis of Nonalcoholic Fatty Liver Disease
Molecular Basis of Alcoholic Liver Disease
Molecular Basis of Hepatic Fibrosis and Cirrhosis
Molecular Basis of Hepatic Tumors

Chapter 21. Molecular Basis of Diseases of the Exocrine Pancreas

Introduction
Acute Pancreatitis
Inflammation: Cause and Consequence of Acinar Cell Damage
Chronic and Hereditary Pancreatitis
Summary

Chapter 22. Molecular Basis of Diseases of the Endocrine System

Introduction
The Pituitary Gland
The Thyroid Gland
The Parathyroid Gland
The Adrenal Gland
Puberty

Chapter 23. Molecular Basis of Gynecologic Diseases

Introduction
Benign and Malignant Tumors of the Female Reproductive Tract
Disorders Related to Pregnancy

Chapter 24. Molecular Basis of Kidney Disease

Introduction
Clinical Manifestations
Diagnosis of Renal Disease

Specific Glomerular and Tubular Diseases

Tubulointerstitial Fibrosis

Conclusions

Chapter 25. Molecular Pathogenesis of Prostate Cancer

Introduction

Incidence and Etiology of Prostate Cancer

Genetic Contributions to Prostate Cancer Risk

Somatic Alterations in Gene Expression

Epigenetics

Advances in Mouse Models of Prostate Cancer

Conclusion

Chapter 26. Molecular Biology of Breast Cancer

Introduction

Histopathological Classification

Biomarkers

Gene Expression Profiling

Massively Parallel Sequencing

Conclusions

Chapter 27. Molecular Basis of Skin Disease

Introduction

Skin Diseases and Their Impact

Molecular Basis of Healthy Skin

Skin Development and Maintenance Provide New Insight Into the Molecular Mechanisms of Disease

Molecular Pathology of Mendelian Genetic Skin Disorders

Molecular Pathology of Common Inflammatory Skin Diseases

Skin Proteins as Targets for Inherited and Acquired Disorders

Molecular Pathology of Skin Cancer

Molecular Diagnosis of Skin Disease

New Molecular Mechanisms and Novel Therapies

Chapter 28. Molecular Basis of Bone Diseases

Introduction

Molecular Basis of Bone Modeling and Remodeling

Molecular Basis of Bone Disease Associated With Bone Matrix

Molecular Basis of Bone Disease Associated With Bone Resorption

Molecular Basis of Metabolic Bone Disease

Molecular Basis of Bone Infection and Inflammation

Molecular Basis of Bone Cancer

Molecular Basis of Bone Metastasis

Chapter 29. Molecular Basis of Diseases of the Nervous System

Anatomy of the Central Nervous System

Neurodevelopmental Disorders

Neurological Injury: Stroke, Neurodegeneration, and Toxicants

Neoplasia

Disorders of Myelin

Chapter 30. Molecular Diagnosis of Human Disease

Introduction

Regulatory Agencies and CLIA

Quality Assurance, Quality Control, and External Proficiency Testing

Method Validation

Clinical Utility

Molecular Laboratory Subspecialties

Chapter 31. Molecular Assessment of Human Diseases in the Clinical Laboratory

Introduction

Molecular Pathology Techniques

Clinical Applications

Emerging Technologies

Chapter 32. Pharmacogenomics and Personalized Medicine in the Treatment of Human Diseases

Introduction

Historical Perspective

Genotyping Technologies

PGx and Drug Metabolism

Drug–Drug Interactions

PGx and Drug Transporters

PGx and Drug Targets

PGx Applied to Oncology

Targeted Therapies in Oncology

Challenges Encountered

Conclusion

Index

Copyright

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Copyright © 2018 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

ISBN: 978-0-12-802761-5

For information on all Academic Press publications visit our website at
<https://www.elsevier.com/books-and-journals>



Publisher: Mica Haley

Acquisition Editor: Tari Broderick

Editorial Project Manager: Jennifer Horigan

Production Project Manager: Anusha Sambamoorthy

Cover Designer: Christian Bilbow

Typeset by TNQ Books and Journals

Dedication

The wealth of information contained in this textbook represents the culmination of innumerable small successes that emerged from the ceaseless pursuit of new knowledge by countless experimental pathologists working around the world on all aspects of human disease. Their ingenuity and hard work have dramatically advanced the field of molecular pathology over time and in particular in the last three decades. This book is a tribute to the dedication, diligence, and perseverance of the individuals who have contributed to the advancement of our understanding of the molecular basis of human disease, especially the graduate students, laboratory technicians, and postdoctoral fellows, whose efforts are so frequently taken for granted, whose accomplishments are so often unrecognized, and whose contributions are so quickly forgotten.

The second edition of *Molecular Pathology: The Molecular Basis of Human Disease* is dedicated to the memory of Oliver Smithies, DPhil, Weatherspoon Eminent Distinguished Professor of Pathology and Laboratory Medicine at the University of North Carolina School of Medicine (Chapel Hill, NC) who passed away on January 10, 2017 at the age of 91 years. Dr. Smithies was a cherished colleague to everyone at UNC and renowned for his gentle character, generous spirit, infectious curiosity, and passion for science. He was a friend to all and eager to help others succeed. Dr. Smithies was also a giant in the field of genetics who made numerous seminal discoveries over the course of his lifelong career (over 70 years at the bench). In 2007, he was a corecipient of the Nobel Prize for Physiology or Medicine for his contributions to the development of techniques for homologous recombination, which enable genetic modification of mammalian cells. These techniques provide the methodological foundation for engineered (transgenic and knockout) animal models of disease, which have been so valuable in the study of human diseases. Despite his tremendous accomplishments, status in the

field, and numerous awards and honors, Dr. Smithies was unpretentious and approachable. We are proud to have known him for many years and for the example he provided for us and so many others as a distinguished and accomplished experimental pathologist and a genuinely good person. Even though he is gone, Dr. Smithies continues to inspire generations of scientists who were fortunate enough to have known him to do their best work.

We also dedicate the second edition of *Molecular Pathology: The Molecular Basis of Human Disease* to the many people who have played crucial roles in our successes. We thank our many scientific colleagues, past and present, for their camaraderie, collegiality, and support. We especially thank our scientific mentors for their example of research excellence. We are truly thankful for the positive working relationships and friendships that we have with our faculty colleagues. We also thank our students for teaching us more than we may have taught them. We thank our parents for believing in higher education, for encouragement through the years, and for helping our dreams into reality. We thank our brothers and sisters, and extended families, for the many years of love, friendship, and tolerance. We thank our wives, Monty and Nancy, for their unqualified love, unselfish support of our endeavors, understanding of our work ethic, and appreciation for what we do. Lastly, we give a special thanks to our children, Tess, Sophie, Pete, and Zoe. Their achievements and successes as young adults are a greater source of pride for us than our own accomplishments. As when they were children, we thank them for providing an unwavering bright spot in our lives, for their unbridled enthusiasm and boundless energy, and for giving us a million reasons to take an occasional day off from work just to have fun. Now that they are older, we cherish their friendship and value their companionship.

William B. Coleman

Gregory J. Tsongalis

List of Contributors

Philippe Aftimos, MD, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Hatem A. Azim Jr. MD, PhD, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Sheldon I. Bastacky, MD, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

David O. Beenhouwer, MD

Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, CA, United States

Division of Infectious Diseases, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, United States

Jaideep Behari, MD, PhD, Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh, School of Medicine, Pittsburgh, PA, United States

Joseph R. Biggs, PhD, Department of Pathology and Division of Biological Sciences, University of California San Diego, La Jolla, CA, United States

Sheldon Campbell, MD, PhD, Department of Laboratory Medicine, Yale School of Medicine, VA Connecticut Healthcare System, New Haven, CT, United States

Wai-Yee Chan, PhD, School of Biomedical Sciences, Faculty of Medicine, Lo Kwee-Seong Integrated Biomedical Sciences Building, The Chinese University of Hong Kong, Shatin, Hong Kong SAR

William B. Coleman, PhD, Department of Pathology and Laboratory Medicine, Curriculum in Toxicology, UNC Program in Translational Medicine, UNC Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC, United States

Massimiliano M. Corsi Romanelli, MD, PhD

Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy

U.O.C SMEL-1 Patologia Clinica IRCCS Policlinico San Donato, Milan, Italy

Robin D. Couch, PhD, Department of Chemistry and Biochemistry, George Mason University, Manassas, VA, United States

Justin B. Davis, PhD, Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, VA, United States

Sophie J. Deharvengt, PhD, Laboratory for Clinical Genomics and Advanced Technology (CGAT), Department of Pathology and Laboratory Medicine, Dartmouth Hitchcock Medical Center, Lebanon, NH, United States

Armando J. Del Portillo, MD, PhD, Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, New York, NY, United States

Virginia Espina, PhD, MT(ASCP), Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, VA, United States

Manel Esteller, MD, PhD

Cancer Epigenetics and Biology Program (PEBC), Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Catalonia, Spain

Physiological Sciences Department, School of Medicine and Health Sciences, University of Barcelona (UB), L'Hospitalet, Catalonia, Spain

Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain

Carol F. Farver, MD, Director, Pulmonary Pathology, Vice Chair for Education, Department of Anatomic Pathology, Cleveland Clinic Foundation, Cleveland, OH, United States

Michael D. Feldman, MD, Professor of Pathology, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

Susan L. Fink, MD, PhD, University of Washington, Seattle, WA, United States

Margaret Flanagan, MD, Department of Pathology, Stanford University, Palo Alto, CA, United States

Claudia Fredolini, PhD, SciLifeLab, School of Biotechnology, KTH – Royal Institute of Technology, Solna, Sweden

William K. Funkhouser Jr. MD, PhD, Department of Pathology and Lab Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, United States

Matthias E. Futschik, PhD, School of Biomedical & Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, United Kingdom

Emanuela Galliera, PhD

Department of Biomedical, Surgical and Oral Sciences, Università degli Studi di

Milano, Milan, Italy
IRCCS Galeazzi Orthopedic Institute, Milan, Italy

Avrum I. Gotlieb, MDCM, FRCPC, Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Laboratory Medicine Program, University Health Network, Toronto, ON, Canada

Robert F. Hevner, MD, PhD, Department of Neurological Surgery, Seattle Children's Hospital Research Institute, Seattle, WA, United States

W. Edward Highsmith Jr. PhD, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, United States

Christopher Dirk Keene, MD, PhD, Department of Pathology, University of Washington, Seattle, WA, United States

Nigel S. Key, MD, Department of Medicine, Division of Hematology/Oncology, University of North Carolina, Chapel Hill, NC, United States

Christine M. Koellner, MS, CGC, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, United States

John J. Lemasters, MD, PhD, Departments of Drug Discovery & Pharmaceutical Sciences and Biochemistry & Molecular Biology, Medical University of South Carolina, Charleston, SC, United States

Markus M. Lerch, MD, Department of Internal Medicine A, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany

Lance A. Liotta, PhD, Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, VA, United States

Youhua Liu, PhD, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

Karen H. Lu, MD, Department of Gynecologic Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, United States

Nicholas W. Lukacs, PhD, Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, United States

Alice D. Ma, MD, Department of Medicine, Division of Hematology/Oncology, University of North Carolina, Chapel Hill, NC, United States

Karlyn Martin, MD, Department of Medicine, Division of Hematology/Oncology, University of North Carolina, Chapel Hill, NC, United States

Julia Mayerle, MD, Department of Internal Medicine A, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany

Kara A. Mensink, MS, CGC, Department of Laboratory Medicine and Pathology,

Mayo Clinic, Rochester, MN, United States

Samuel C. Mok, PhD, Department of Gynecologic Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, United States

Satdarshan P.S. Monga, MD, Division of Experimental Pathology, Department of Pathology, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Pittsburgh Liver Research Center, University of Pittsburgh, School of Medicine, Pittsburgh, PA, United States

Thomas J. Montine, MD, PhD, Department of Pathology, Stanford University, Palo Alto, CA, United States

Jason H. Moore, PhD, Division of Informatics, Department of Biostatistics and Epidemiology, Institute for Biomedical Informatics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

Markus Morkel, PhD, Laboratory of Molecular Tumor Pathology and Tumor Systems Biology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Karl Munger, PhD, Department of Developmental, Molecular and Chemical Biology, Tufts University School of Medicine, Boston, MA, United States

Zoltan Nagymanyoki, MD, PhD, Department of Pathology, West Pacific Medical Laboratory, Santa Fe Springs, CA, United States

Robert D. Nerenz, PhD, Assistant Professor of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States

Alan L.-Y. Pang, PhD, TGD Life Company Limited, Hong Kong Science Park, Shatin, Hong Kong SAR

Emanuel Petricoin, PhD, Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, VA, United States

Catherine Ptaschinski, PhD, Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, United States

Reinhold Schäfer, PhD

Charité Comprehensive Cancer Center, Charité – Universitätsmedizin Berlin, Berlin, Germany

German Cancer Consortium (DKTK), German Cancer Research Center, Heidelberg, Germany

Matthias Sandler, MD, Department of Internal Medicine A, Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany

Antonia R. Sepulveda, MD, PhD, Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, New York, NY, United States

Christine Sers, PhD, Laboratory of Molecular Tumor Pathology and Tumor Systems Biology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Lawrence M. Silverman, PhD, Department of Pathology, University of Virginia Health System, Charlottesville, VA, United States

Joshua A. Sonnen, MD, Department of Pathology, University of Utah, Salt Lake City, UT, United States

Christos Sotiriou, MD, PhD, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Roderick J. Tan, MD, PhD, Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

Gregory J. Tsongalis, PhD

The Audrey and Theodor Geisel School of Medicine at Dartmouth, Hanover, NH, United States

Laboratory for Clinical Genomics and Advanced Technology (CGAT), Department of Pathology and Laboratory Medicine, Dartmouth Hitchcock Medical Center, Lebanon, NH, United States

Vesarat Wessagowit, MD, PhD, The Institute of Dermatology, Rajvithi Phyathai, Bangkok, Thailand

Eli S. Williams, PhD, Department of Pathology, University of Virginia Health System, Charlottesville, VA, United States

Kwong-Kwok Wong, PhD, Department of Gynecologic Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, United States

Dani S. Zander, MD, Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, OH, United States

Dong-Er Zhang, PhD, Department of Pathology and Division of Biological Sciences, University of California San Diego, La Jolla, CA, United States

Weidong Zhou, MD, PhD, Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, VA, United States

Preface

Pathology is the study of disease. The field of pathology emerged from the application of the scientific method to the study of human disease. Thus, pathology as a discipline represents the complementary intersection of medicine and basic science. Early pathologists were typically practicing physicians who described the various diseases that they treated and made observations related to factors that contributed to the development of these diseases. The description of disease evolved over time from gross observation to microscopic inspection of diseased tissues based on the light microscope and more recently to the ultrastructural analysis of disease with the advent of the electron microscope. As hospital-based and community-based registries of disease emerged, the ability of investigators to identify factors that cause disease and assign risk to specific types of exposures expanded to increase our knowledge of the epidemiology of disease. Although descriptive pathology can be dated to the earliest written histories of medicine and the modern practice of diagnostic pathology dates back perhaps 200 years, the elucidation of mechanisms of disease and linkage of disease pathogenesis to specific causative factors emerged more recently from studies in experimental pathology. The field of experimental pathology embodies the conceptual foundation of early pathology—the application of the scientific method to the study of disease—and applies modern investigational tools of cell and molecular biology to advanced animal model systems and studies of human subjects. The molecular era of biological science began over 60 years ago, whereas recent advances in our knowledge of molecular mechanisms of disease have propelled the field of molecular pathology. These advances were facilitated by significant improvements and new developments associated with the techniques and methodologies available to pose questions related to the molecular biology of normal and diseased states affecting cells, tissues, and organisms. Today, molecular pathology encompasses the investigation of the molecular mechanisms of disease and interfaces with translational medicine where new basic science discoveries form the basis for the development of new strategies for disease prevention, new therapeutic approaches and targeted therapies for the treatment of disease, and new diagnostic tools for disease diagnosis and prognostication.

With the remarkable pace of scientific discovery in the field of molecular pathology, basic scientists, clinical scientists, and physicians have a need for a source of information on the current state of the art of our understanding of the molecular basis of human disease. More importantly, the complete and effective training of today's graduate students, medical students, postdoctoral fellows, and others, for careers related to the investigation and treatment of human disease, requires textbooks that have been designed to reflect our current knowledge of the molecular

mechanisms of disease pathogenesis, as well as emerging concepts related to translational medicine. Most pathology textbooks provide information related to diseases and disease processes from the perspective of description (what does it look like and what are its characteristics), risk factors, disease-causing agents, and to some extent, cellular mechanisms. However, most of these textbooks lack in-depth coverage of the molecular mechanisms of disease. The reason for this is primarily historical—most major forms of disease have been known for a long time, but the molecular basis of these diseases is not always known or has been elucidated only very recently. However, with rapid progress over time and improved understanding of the molecular basis of human disease, the need emerged for new textbooks on the topic of molecular pathology, where molecular mechanisms represent the focus.

In this second edition of *Molecular Pathology: The Molecular Basis of Human Disease*, we have assembled a group of experts to discuss the molecular basis and mechanisms of major human diseases and disease processes, presented in the context of traditional pathology, with implications for translational molecular medicine. This volume is intended to serve as a multiuse textbook that would be appropriate as a classroom teaching tool for medical students, biomedical graduate students, allied health students, and others (such as advanced undergraduates). Furthermore, this textbook will be valuable for pathology residents and other postdoctoral fellows who desire to advance their understanding of molecular mechanisms of disease beyond what they learned in medical/graduate school. In addition, this textbook is useful as a reference book for practicing basic scientists and physician scientists who perform disease-related basic science and translational research, who require a ready information resource on the molecular basis of various human diseases and disease states. To be sure, our understanding of the many causes and molecular mechanisms that govern the development of human diseases is far from complete. Nevertheless, the amount of information related to these molecular mechanisms has increased tremendously in recent years, and areas of thematic and conceptual consensus have emerged. We have made an effort to integrate accepted principles with broader theoretical concepts in an attempt to present a current and comprehensive view of the molecular basis of human disease. We hope that this second edition of *Molecular Pathology: The Molecular Basis of Human Disease* will accomplish its purpose of providing students and researchers with in-depth coverage of the molecular basis of major human diseases in the context of traditional pathology so as to stimulate new research aimed at furthering our understanding of these molecular mechanisms of human disease and advancing the theory and practice of molecular medicine.

William B. Coleman

Gregory J. Tsongalis

Acknowledgments

The editors would like to acknowledge the significant contributions of a number of people to the successful production of the second edition of *Molecular Pathology: The Molecular Basis of Human Disease*.

We would like to thank the individuals who contributed to the content of this volume. The remarkable coverage of the state of the art in the molecular pathology of human disease would not have been possible without the hard work and diligent efforts of the 62 authors of the individual chapters. Many of these contributors are our long-time colleagues, collaborators, and friends, and they have contributed to other projects that we have directed, and we sincerely appreciate their willingness to contribute once again to a project that we found worthy. We especially thank the contributors to this volume who were willing to work with us for the first time. This group also includes some of our long-time friends and colleagues, as well as some new friends. We look forward to working with all of these authors again in the future. Each of these contributors provided us with an excellent treatment of their topic, and we hope that they will be proud of their individual contributions to the textbook. Furthermore, we would like to give a special thanks to our colleagues who coauthored chapters with us for this textbook. There is no substitute for an excellent coauthor when you are juggling the several responsibilities of concurrently editing and contributing to a textbook. Collectively, we can all be proud of this volume, as it is proof that the whole can be greater than the sum of its parts.

Thanks to Ms. Mara Conner (Senior Acquisitions Editor, *Academic Press—Elsevier*) who worked with us on the first edition of this textbook. She embraced the concept of this textbook when our ideas were not yet fully developed and encouraged us to pursue the project. She was receptive to the model for this textbook that we envisioned and worked closely with us to evolve the project into its final form. Without Mara's early support, the first edition of this textbook would not have been so successful and this second edition would not have been possible.

We would also like to thank the many people who work for *Academic Press—Elsevier* that made this project possible. We have not met and do not know many of these people, but we appreciate their efforts to bring this textbook to its completed form. Special thanks goes to three key people who made significant contributions to this project on the publishing side and proved to be exceptionally competent and capable. Ms. Tari Broderick (Senior Acquisitions Editor, *Academic Press—Elsevier*) provided excellent oversight (and optimistic patience) during the construction and editing of this edition of the textbook and has become our valued colleague as we develop new projects. Ms. Lisa Eppich (Editorial Project Manager, *Elsevier*) provided

excellent support to us throughout this project. As we interacted with our contributing authors, collected and edited manuscripts, and began production of the textbook, Lisa assisted us greatly by being a constant reminder of deadlines, helping us with communication with the contributors, and generally providing support for details small and large, all of which proved to be critical. Ms. Anusha Sambamoorthy (Project Manager, *Elsevier*) worked with us closely to ensure the integrity of the content of the textbook as it moved from the edited manuscripts into their final form. We thank her for her direct involvement with the production and also for directing her excellent production team. It was a pleasure to work with Tari, Lisa, and Anusha on this project. We hope that they enjoyed it as much as we did, and we look forward to working with them again soon.

William B. Coleman

Gregory J. Tsongalis