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ESSENTIAL CONCEPTS IN MOLECULAR PATHOLOGY



Essential Concepts in Molecular Pathology

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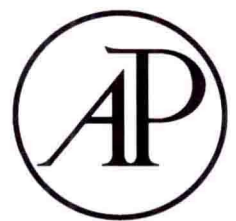
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Dedication

This textbook contains a concise presentation of essential concepts related to the molecular pathogenesis of human disease. Despite the succinct form of this material, this textbook represents the state-of-the-art and contains a wealth of information representing 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 two 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. We dedicate *Essential Concepts in Molecular Pathology* to our colleagues in the field of experimental pathology and to the many pioneers in our field whose work continues to serve as the solid foundation for new discoveries related to human disease. In dedicating this book to our fellow experimental pathologists, we especially recognize the contributions of 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.

We also dedicate *Essential Concepts in Molecular Pathology* to the many people that 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, for providing an unwavering bright spot in our lives, for their unbridled enthusiasm and boundless energy, for giving us a million reasons to take an occasional day off from work just to have fun.

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Preface

Pathology is the scientific study of the nature of disease and its causes, processes, development, and consequences. 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 complimentary 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 upon 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. While 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. Whereas the molecular era of biological science began over 50 years ago, 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, medical residents, allied health students, 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 are not always known or have 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 volume on *Essential Concepts in Molecular Pathology* 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. *Essential Concepts in Molecular Pathology* is an abbreviated version of *Molecular Pathology: The Molecular Basis of Human Disease*, that contains several distinct features. Each chapter focuses on essential concepts related to a specific disease or disease process, rather than providing comprehensive coverage of the topic. Each chapter contains *key concepts*, which capture the essence of the topic covered. In place of long lists of references to the primary literature, each chapter provides a list of *suggested readings*, which include pertinent reviews and/or primary literature references that are deemed to be most important to the reader. This volume is intended to serve as a multi-use textbook that would be appropriate as a classroom teaching tool for medical students, biomedical graduate students, allied health students, advanced undergraduate students, and others. We anticipate that this book will be most useful for teaching students in courses where the full textbook is not needed, but the concepts included are integral

to the course of study. This book might also be useful for students that are enrolled in courses that utilize a traditional pathology textbook as the primary text, but need the complementary concepts related to molecular pathogenesis of disease. Further, this textbook will be valuable for pathology residents and other postdoctoral fellows that desire to advance their understanding of molecular mechanisms of disease beyond what they learned in medical/graduate school, and as a reference book and self-teaching guide for practicing basic scientists and physician scientists that need to understand the molecular concepts, but do not require comprehensive coverage or complete detail. 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 hope that *Essential Concepts in Molecular Pathology* will accomplish its purpose of providing students and researchers with a broad coverage of the essential concepts related to 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

Foreword

Pathology is a *bridging discipline* between basic biological sciences and clinical medicine. Experimental pathologists apply the knowledge and tools developed in basic science disciplines including biochemistry, cell biology, physiology, and molecular biology to understand mechanisms of disease. Clinical pathologists integrate this basic mechanistic understanding of disease with clinical, anatomic, and biochemical information to diagnose disease in individual patients. In the 21st century, this integrated diagnosis of human disease is increasingly based on molecular markers and understanding of disease pathogenesis at the genetic level. This textbook provides fresh insight into the pathogenesis and treatment of disease based on the new discipline of molecular pathology.

Biomedical, clinical, and translational research is conducted by *interdisciplinary teams*. Team members classically have a primary knowledge base and tools in one discipline; however, they must also have the breadth of knowledge and curiosity to incorporate insights from other disciplines to understand, diagnose, and treat human disease. *Essential Concepts in Molecular Pathology* will provide students with a basic foundation in this discipline that will enable them to participate in emerging interdisciplinary research and its clinical applications in the future. For example, molecular pathologists work together with geneticists and ethicists in genetic screening of inherited diseases such as cystic fibrosis. Future research teams including diagnostic pathologists, microbiologists, and biomedical engineers will develop inexpensive, portable devices to diagnose emerging infectious diseases.

Pathologists are also leaders in a new medical paradigm in the 21st century—the practice and application of *personalized medicine* using individual patterns of

gene and protein expression. This new diagnostic paradigm relies on bioinformatics and systems biology using genomic and proteomic technologies. *Personalized medicine* promises more accurate diagnosis of complex diseases and individualized therapeutic approaches that are currently being developed for breast, lung, and colon cancers. The practice of medicine in the 21st century will also require new insights into basic mechanisms of disease. In the post-genomic era, molecular pathologists are exploring epigenetic alterations associated with disease that are based on heritable changes in DNA and chromatin organization in the absence of DNA mutations. Molecular pathologists are collaborating with epidemiologists to identify molecular biomarkers reflecting prior environmental exposures or susceptibility to development of future disease. Biostatisticians and systems biologists will collaborate with pharmacologists and pathologists to develop novel therapeutic approaches for human disease. The ultimate goal of these diverse interdisciplinary teams is disease prevention through early recognition of disease susceptibility using molecular biomarkers with potential for early intervention to prevent neurodegenerative diseases, cancer, type 2 diabetes, and cardiovascular disease.

Welcome to the team!

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We would like to thank the individuals that 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 65 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. We appreciate their willingness to contribute once again to a project that we found worthy. We especially thank the contributors to this volume that were willing to work with us for the first time. 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 that co-authored chapters with us for this textbook. There is no substitute for an excellent co-author 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.

We would also like to thank the many people that work for *Academic Press* and *Elsevier* that made this project possible. Many of these people we have not met and do not know, but we appreciate their efforts to bring this textbook to its completed form. Special thanks goes to three key people that made significant contributions to this project on the publishing side,

and proved to be exceptionally competent and capable. Ms. Mara Conner (*Academic Press*, San Diego, CA) embraced the concept of this textbook when our ideas were not yet fully developed and encouraged us to pursue this 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. We thank her for providing excellent oversight (and for displaying optimistic patience) during the construction and editing of the textbook. Ms. Megan Wickline (*Academic Press*, San Diego, CA) provided excellent support to us throughout this project. As we interacted with our contributing authors, collected and edited manuscripts, and through production of the textbook, Megan 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. Christie Jozwiak (*Elsevier*, Burlington, MA) directed the production of the textbook. She 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. Throughout the production process, Christie gave a tremendous amount of time and energy to the smallest of details. We thank her for her direct involvement with the production and also for directing her excellent production team. This was our second major project working with Mara, Megan, and Christie. It was a pleasure to work with them on this book. We hope that they enjoyed it as much as we did, and we look forward to working with them again soon.

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