Principles of Molecular Cardiology

Edited by

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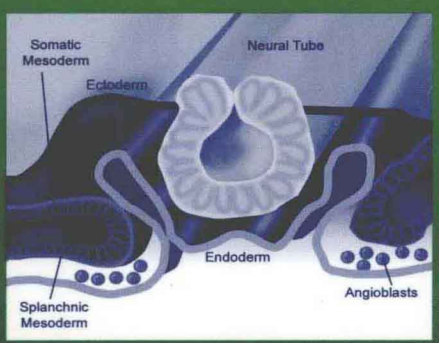

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Principles of Molecular Cardiology

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FOREWORD

Principles of Molecular Cardiology provides a broad and up-to-date treatment of the molecular biology of cardiovascular diseases. This is a timely volume given the impact of cardiovascular diseases in our society and the numerous advances in understanding cardiovascular disease that have followed the molecular and genomic revolutions. This book begins with a broad historical overview of the major themes in molecular cardiology: cardiovascular genetics, the molecular biology of the cardiovascular system, genomics, gene therapy, and stems cells and progenitor cells in cardiovascular disease. These chapters provide concise information about how these areas can be used to understand and develop treatments for cardiovascular diseases.

This overview is followed by a discussion of cardiac function and dysfunction. Subjects covered include the molecular and structural events in heart development; the molecular biology of inherited myocardial diseases with a specific focus on hypertrophic cardiomyopathies and muscular dystrophies that affect the heart; the molecular regulation of inotropic function and the events that occur in cardiomyocytes that contribute to progressive systolic dysfunction; the process of inflammation within the heart with emphasis on how adhesion molecules affect this process; and common cardiac defects and the molecular basis for these defects.

The third section of this book focuses on the important topic of coronary artery disease. This section includes excellent chapters addressing the differentiation of the coronary arteries; the evolution of coronary vascular lesions with emphasis on the effects of platelets, smooth muscle cells, and inflammatory cells in this process; the molecular pathways that activate platelets and the pharmacologic actions of antiplatelet drugs; pathophysiologic events that result in myocardial infarction; the development of arterial disease after cardiac transplantation; the scientific basis for thrombolytic therapy; and the molecular basis for restenosis following percutaneous coronary interventions and recently developed new treatment modalities, including radiation therapy.

The section on cardiac arrhythmias is timely given recent progress in understanding the molecular basis and genetics of arrhythmias and sudden death. Topics covered in this section include the molecular biology of the development of the cardiac conduction system, the electrical events that cause sudden death and the development of arrhythmias, emerging new therapies for arrhythmias based on the molecular understanding, and the genetic basis for arrhythmias.

The section on vascular diseases includes state-of-the-art chapters discussing the molecular events that regulate angiogenesis and the potential for angiogenic therapy, the molecular basis for the metabolism and actions of nitric oxide, the role of inflammation in vascular disease, the pathophysiology of pulmonary hypertension and the genetics that influence its development, the molecular and genetic events that cause malformations of the vascular system, and the molecular events involved in thrombosis.

The book concludes with a section on risk factors for cardiovascular disease. These chapters succinctly summarize the molecular basis for lipid metabolism, the molecular biology of aging and its impact on the cardiovascular system, the role of oxidative species in atherosclerosis, the molecular consequences of diabetes on the cardiovascular system, and the molecular determinants of inflammation and its amelioration with proper risk factor modification.

An understanding of these topics is critically important to anyone who wishes to conduct serious research in any of these areas or teach others about them. Moreover, new therapies that develop in these areas will be based on an understanding of the molecular biology and genetics of these cardiovascular problems.

I believe *Principles of Molecular Cardiology* is an outstanding book. Anyone interested in the development, genetics, and pathologies that affect the cardiovascular system will want to have this book available for ready reference.

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PREFACE

In recent years, molecular studies have had a major impact on cardiovascular clinical practice and outcomes. The rationale for drug therapies for treating cardiovascular diseases such as heart failure has been based primarily on data derived from basic science investigations. The Human Genome Project has implications for biology and mankind that are unparalleled, in part because having such an abundance of information on the inner workings of humans is unprecedented. Our understanding of genetic links to cardiovascular diseases has increased dramatically, helping redefine the etiology and diagnostic criteria for numerous conditions and leading to new, individualized treatments.

Principles of Molecular Cardiology was undertaken to explore the latest developments in molecular cardiology research. In this text, we review the complex process of heart development, explain the molecular bases of cardiovascular diseases, describe the application of research advances in clinical treatment, and provide a historical perspective for important areas within this discipline. This book is intended for researchers, clinicians, students, and healthcare professionals who want to keep abreast of current findings in molecular cardiology research. The authors, all leading specialists, provide a unique perspective of what the future in molecular research holds for their respective fields.

Genetics research and advances in gene therapy are recurring themes throughout this text. Certain genetic mutations are clearly associated with severe cardiovascular disease, and new disease-causing mutations are being identified with increasing frequency. Some researchers estimate that there are probably only 200–300 genes that provide susceptibility for the 20 diseases that account for 80% of all deaths globally. Given the genetic and physical maps of the human genome and the technology of high-throughput nucleotide sequencing, it is conceivable that all human genes that contribute to the genetic risk of major cardiovascular diseases will be known within the next decade.

In the field of vascular biology, the number of genes that have been cloned and linked to vascular wall disease is growing exponentially. Because of their association with cardiovascular function, genes encoding the proteins endothelin-1—a potent vasoactive hormone—and the angiotensin receptor have proven to be attractive sites for pharmacologic intervention, but it is clear that the genes identified today will be the therapeutic targets of tomorrow. In addition, gain-of-function and loss-of-function mice, created through genetic manipulations, have provided enormous insights into such processes as lipid metabolism and the function of cardiac- and vascular wall-specific genes.

Although studies using mouse models have been a major tool to push the field of molecular cardiology forward, advances in human genetics have contributed significantly to the understanding of inherited cardiac diseases such as long QT syndrome and hypertrophic obstructive cardiomyopathy. Although advances have been made in understanding the pathophysiologic and genetic bases of cardiac arrhythmias, current treatment options are still inadequate, prompting a search for genetic strategies to treat these conditions.

Research in the complex area of atherosclerosis continues. Despite the great strides made in recent years, many of the processes involved in atherosclerosis remain poorly characterized. Studies of atherosclerosis in humans are limited by the complexity of the cellular and molecular mechanisms that contribute to the process and the long time course of disease development. There is also significant variability seen in pathogenetic mechanisms. In this text, the authors discuss the latest developments in understanding the pathogenesis of atherosclerosis—its manifestations (coronary artery disease, acute coronary syndromes) and its underlying mechanisms (oxidative stress and inflammation).

Platelets play a central role in the pathogenesis of atherosclerosis. Therefore, platelet inhibition has proven to be a logical therapeutic strategy for acute and chronic treatment of atherosclerosis and its clinical sequelae. The need for efficient inhibition of platelet function is even more evident in the situation of a vascular injury associated with angioplasty. Strategies for inhibiting platelet function are discussed in this text. There are many different potential ways to inhibit platelet activation, and several receptors are considered promising

therapeutic targets, including the thrombin receptor and the TXA_2 receptor.

Restenosis following percutaneous coronary interventions remains a serious problem. Because of the number of molecular targets available for targeting the cell cycle in antirestenosis therapy, gene therapy is a second clinical approach for inhibiting small muscle cell proliferation. Although results from antirestenotic gene therapy trials in humans have not been published, results from animal models are promising. A second antirestenotic gene therapy that affects the cell cycle makes use of the overexpression of cell cycle inhibitory molecules. Experimental data support the use of gene therapy as a cell cycle inhibitor; however, the application of gene therapy to clinical medicine will depend not only on the ability of cell cycle arrest to block restenosis in clinical settings, but also on the demonstration of acceptable safety profiles.

The field of developmental biology of the cardiovascular system has also accelerated during the past decade. New developments in the study of blood vessel development and a strong clinical interest in therapeutic angiogenesis have led to greater understanding of the molecular biology of the assembly of cardiovascular structures, and many of these ideas are being translated to clinical practice to treat obstructive vascular disease.

Despite these advances and promising new discoveries, cardiovascular disease remains the leading cause of death in the United States. The aging of the population will undoubtedly be a factor in the increasing incidence of coronary artery disease, heart failure, and stroke. Of the more than 64 million Americans with one or more types of cardiovascular disease, more than 25 million are estimated to be age 65 and older (*Heart Disease and Stroke Statistics—2004 Update*, American Heart Association). For reasons not entirely clear, there is also an increased prevalence of obesity and type 2 diabetes—the major cardiovascular risk factors—in this country. Related complications—hypertension, hyperlipidemia, and atherosclerotic vascular disease—also have increased.

In the next decade, new tools will be applied to the study of cardiovascular disease and function. These instruments will include DNA microarrays, proteomic approaches, comparative DNA analysis, and markers of human genetic variation. The innovative use of these new and powerful tools hold promise to accelerate the pace of discovery in cardiovascular medicine.

There is an untapped potential for molecular and cellular biology to lead to substantial new discoveries in the near future. These discoveries will only be achieved with intensive and focused research. We hope this text will provide a foundation of knowledge and inspiration for investigators to continue the progress in this crucial field of research. As clinicians and scientists, the advancements in molecular cardiology over the preceding decade have inspired the editors in the laboratory and at the bedside, and we are grateful to our colleagues for moving the field so rapidly during this time.

We would like to thank the many individuals who contributed to the success of this book. We especially commend all our authors for devoting their time, energy, and scholarship to preparing these chapters—we asked for the best from our contributors, and we got it. We also thank the following editors who assisted in preparation of the text. Rebecca Bartow, PhD, was primary manuscript editor, and Jennifer King, PhD, also edited and reviewed many chapters; their contributions to this project can be appreciated whenever consistency and cogency are detected in this book. Angela Rego, BBA, coordinated manuscripts, handled correspondence between physician editors and authors, and served as adjutant general for all aspects of this project. Rebecca Teaff, MA, coordinated the editing process and reviewed manuscripts, for which the editors extend their gratitude. Carolyn Kruse, BS, DC, served as a manuscript editor. Kakky Baugher, BA, Erin Allingham, BA, Elizabeth Schramm, BA, and Kelly Scarlett assisted in manuscript review and formatting, as well as verifying references. Katie O'Brien, MA, and Angela Rego, BBA, assisted in preparation of graphics for the text. We would also like to thank Craig Adams of Humana Press for his enthusiastic support in ushering this book through the publication process.

We also extend our appreciation to our colleagues, collaborators, trainees, and laboratory members, including Nageswara Madamanchi, Yaxu Wu, and Holly McDonough, who inspired our desire to tackle this project. We dedicate this book to the memory of Edgar Haber. Dr. Haber trained many of the contributors to this project and influenced all of them. His family—his wife Carol, his sons Eben, Justin, and Graham, and his sister Ruth—shared him with us, for which we are grateful.

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I Overview

1 Cardiovascular Genetics

Christopher Semsarian, MBBS, PhD and Christine Seidman, MD

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INTRODUCTION

When the double helical structure of DNA was first proposed in 1953 by Watson and Crick in a two-page *Nature* article *(1)*, no one could have predicted the tremendous impact this discovery would have in establishing the study of human genetic diseases. This discovery was an important landmark in the development of the field of cardiovascular genetics. In the last 30 years, several technological advances have fueled a surge in cardiovascular genetic research. Such advances include the understanding of biochemical components of DNA, the development of cloning techniques and DNA sequencing, the amplification of DNA by polymerase chain reaction (PCR), the identification of restriction enzymes (the molecular biologist's "scalpel") for handling small pieces of DNA, and the undertaking of the Human Genome Project *(2)*. Today, cardiovascular genetics is characterized by the integration of high-technology laboratory studies and clinical medicine. Within the last decade, cardiovascular genetics has redefined the etiology and diagnostic criteria for numerous diseases and has led to the development of new, individualized treatment for cardiovascular diseases.

GENETIC BASIS OF CARDIOVASCULAR DISORDERS

A genetic basis has been identified for many cardiovascular disorders (Table 1). Hypertrophic cardiomyopathy, an autosomal dominant disorder, was the first primary cardiomyopathy identified as having a genetic basis and, therefore, has served as a paradigm for the study of genetic cardiovascular disorders. After initial genetic studies in 1989 mapped the gene for familial hypertrophic cardiomyopathy to chromosome 14q1 *(3)*, mutations in the β-myosin heavy chain gene were identified as the cause of hypertrophic cardiomyopathy (Fig. 1A). In the last 10 years, more than 200 mutations in only 10 genes have been identified as causing hypertrophic cardiomyopathy *(5,6)*. Because all 10 genes encode sarcomeric proteins, hypertrophic cardiomyopathy has been redefined as a "disease of the sarcomere." Over the last 5 years, mutations in several genes have been identified as contributing to other cardiovascular diseases (Table 1), including dilated cardiomyopathy *(7–9)*, cardiomyopathies of the right ventricle such as arrhythmogenic right ventricular dysplasia *(10)*, and mitochondrial myopathies *(11)*. In addition, genetic mutations have been linked to arrhythmogenic disorders such as the autosomal dominant (Romano–Ward syndrome) and recessive (Jervell and Lange-Nielsen syndrome) forms of long QT syndrome, and the Brugada syndrome *(12–14)*. These arrhythmogenic disorders have been called "ion channelopathies," because the mutations lie in genes encoding sodium or potassium channel proteins.

Cardiovascular genetics has had an impact on the study of congenital heart diseases and vascular disorders. For example, mutations in the transcription factor TBX5 gene cause Holt–Oram syndrome *(15)*, whereas genetic

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Table 1
The Genetics of Cardiovascular Disorders

Type of disorder	*Pattern of inheritance*	*Locus*	*Gene product*
Arrhythmias			
ARVD	Dominant	1q42	Ryanodine receptor
		2q32	Unknown
		3p23	Unknown
		10p14	Unknown
		14q23-24	Unknown
Brugada syndrome	Dominant	3p21-24	Sodium channel SCN5A
Long QT syndrome	Dominant	3p21-24	Sodium channel SCN5A
		4q25-27	Unknown
		7q35-36	Potassium channel HERG
		11p15.5	Potassium channel KVLQT1
Naxos (ARVD + palmarplantas keratoderma)	Recessive	6p24	Desmoplakin
		17q21	Plakoglobin
Stress-induced ventricular tachycardia	Dominant	1q42	Ryanodine receptor
Cardiomyopathies			
Barth syndrome	X-linked	Xq28	Tafazzin
Dilated	Dominant	1q3	Cardiac troponin T
		2q31	Titin
		14q12	Cardiac β myosin
		15q2	α tropomyosin
		15q14	Cardiac actin
Dilated + conduction disease	Dominant	1p1-q21	Lamin A and C splice variant
		3q22-p25	Unknown
Dilated + muscular dystrophy	Dominant	2q35	Desmin
		6q23	Unknown
	X-lined	Xp21	Dystrophin
Hypertrophic	Dominant	1q3	Cardiac troponin T
		2q31	Titin
		3p	Regulatory light chain
		11p13-q13	Myosin binding protein-C
		12q2	Essential light chain
		14q12	Cardiac β myosin
		15q2	α tropomyosin
		15q14	Cardiac actin
		19q13	Cardiac troponin I
Hypertrophic + conduction disease	Dominant	7q3	γ2 regulatory subunit AMP-activated protein kinase
Congenital			
Alagille syndrome		20q12	Jagged-1 (Notch receptor ligand)
Anomalous pulmonary venous return	Dominant	4q13-q12	Unknown
ASD + atrial aneurysm	Dominant	5p	Unknown
ASD + AV block	Dominant	5q35	Transcription factor NKX2.5

(Continued)