Preface

At the request of the American Physiological Society, we have edited this book on *Molecular and Cellular Mechanobiology* as part of the "Perspectives in Physiology" series.

Mechanobiology is a rapidly developing scientific field at the interface of biology, medicine, and engineering that studies how physical forces, cell/tissue mechanics, and their interactions regulate homeostasis in health and pathophysiological changes in disease. Mechanobiology involves the sensing of mechanical cues by cells, the transduction of these cues into molecular signals, and the modulation of gene and protein expression and hence cellular functions. Mechanobiology is distinct from biomechanics in that the latter involves the active application of forces to cells for the elucidation of their physical properties.

This book covers the cutting-edge developments in mechanobiology, with the aim of providing the reader with a clear understanding of this frontier discipline at the molecular and cellular levels, encompassing the mechanosensors, transducers, and genetic and epigenetic regulation, as well as clinical applications.

Part I consists of three chapters on Mechanosensors. Chapter 1 (E.R. Moore and C.R. Jacobs) discusses the primary cilium as a mechanosensor that can modify its structure and composition to tune mechanosensitivity. This chapter presents the experimental studies and computational modeling of the molecular and mechanical bases of mechanosensing and uses animal models to explore cilium-based health complications. Chapter 2 (L.J. Chen, W.L. Wang, and J.J. Chiu) addresses the shear-responsive mechanosensors in the cell membrane, intercellular junctions, cytoplasm, and nucleus of vascular endothelial cells and presents a conceptual framework for understanding their regulation in response to hemodynamic forces in health and disease. Chapter 3 (D.E. Leckband) highlights a new class of force-sensitive cadherin-based adhesion complexes at intercellular junctions and elucidates a new force transduction mechanism that can impact cell mechanics and modulates such cell functions as barrier integrity and cell cycle control.

Part II consists of three chapters on Mechanotransducers. Chapter 4 (Y. Sun, Y. Shao, X. Xue, and J. Fu) presents the emerging roles of YAP/TAZ, which are transcription coactivators in the canonical Hippo signaling pathway, in mechanobiology, addressing the different types of mechanical cues that mediate YAP/TAZ activities and their upstream mechanosensitive molecular machineries. Chapter 5 (C.A. McCulloch) focuses on the role of Rho GTPases in the translation of mechanical and chemical cues into the cellular responses that regulate cell, tissue, and organ structure and function, with special emphasis on their contribution to cell migration and responses to environmental forces. Chapter 6 (V. Swaminathan and C.M. Waterman) illuminates the role of cell adhesion in mechanobiology by using modern microscopy approaches to study integrin-based focal adhesions and discusses how these complex adhesion organelles are built and regulated, as well as the integration of the cell with its environment in mediating physiological functions.

Part III consists of three chapters on Epigenetic and Genetic Regulations in the Nucleus. Chapter 7 (Q. Peng, B. Cheng, S. Lu, S. Chien, and Y. Wang) introduces fluorescence resonance energy transfer (FRET) technologies to visualize in single cells the dynamic epigenetic regulations (particularly histone modifications and DNA methylations) related to mechanobiology in the nucleus, thus enabling the elucidation of functional responses to mechanical environments. Chapter 8 (D. Kelkhoff and T. Downing, S. Li) highlights the potential mechanisms through which mechanotransduction may lead to epigenetic modifications such as DNA methylation and histone methylation and acetylation, and the consequential long-term effects on phenotypic changes, including stem cell differentiation and cell reprogramming. Chapter 9 (J. Irianto, I.L. Ivanovska, J. Swift, and D.E. Discher) discusses the role of lamin in the mechano-responsiveness of nuclei and the signaling pathways that regulate lamin levels and cell fate in response to matrix mechanics and molecular cues. This chapter also discusses the importance of nuclear mechanics in niche anchorage and cell motility in development, hematopoietic differentiation, and cancer invasion. Chapter 10 (Y. Wang, E. Makhija, K. Damodaran, and G.V. Shivashankar) summarizes the physical and chemical connections between ECM and 3D chromosome organization that lead to modular gene regulation, and the role of nucleoskeleton-cytoskeleton linkage in nuclear mechanotransduction and the consequential remodeling of chromatin dynamics, epigenetic landscape, and 3D chromosome organization.

Following the coverage of the basic principles of mechanobiology in the first three parts, Part IV consists of three chapters on the clinical applications of mechanobiology to cardiovascular diseases and cancer. Chapter 11 (A.J. Putnam) focuses on the relationships between mechanical forces and cells of the cardiovascular system (including endothelial cells, smooth muscle cells, and cardiac myocytes), with an emphasis on translating fundamental mechanobiology insights into the control of cell fate for applications in cardiovascular regenerative medicine. Chapter 12 (A. Zhong and C.A. Simmons) reviews the influences of hemodynamic forces in valve development and the roles of shear stress, cyclic strain, and matrix mechanics in regulating the initiation and progression of calcific aortic valve disease, with the goals of identifying therapeutic targets for treating adult valve diseases and guiding the design of living tissue replacement valves. Chapter 13 (L. Fattet and J. Yang) describes how ECM stiffness contributes to tumorigenesis, through different roles on tumor cells or stromal cells, at the primary tumor and at metastatic sites. This chapter also discusses the latest and most promising therapeutic approaches targeting or taking advantage of this newly defined implication of mechanoregulation in cancer progression.

We wish to thank the authors of the 13 chapters for their outstanding contributions that provide state-of-the-art information on this exciting field of molecular and cellular mechanobiology. We also thank Brian Halm of Springer Science for his administrative help in the preparation of this book.

This book has the following unique features:

- An integrative approach across different scales from molecular sensing to mechanotransduction, gene modulation, and physiological regulation of cellular functions, as well as application to pathophysiological states in disease.
- An integration of molecular and cellular physiology with the physics and engineering of biomechanics, thus providing a comprehensive understanding of the roles of physico-chemical microenvironment and intracellular responses in determining cellular function in health and disease.
- An interdisciplinary approach that takes into account the diverse backgrounds of readers. It is written to:

  Help physiologists and biologists interested in mechanobiology, but new to the field, to understand the impact of mechanobiology on physiological regulation in health and disease.

  Help engineers interested in physiology and life sciences, but lacking formal training, to gain insights into the molecular and cellular bases of fundamental biological processes related to engineering mechanics.

  Help clinicians to understand the roles of mechanobiology in the pathogenesis, diagnosis, treatment, and prevention of disease.

This book is suitable for a broad range of readers, including physiologists and other experimental biologists (including cell biologists, biophysicists, pharmacologists, pathologists, and others), bioengineers and other engineers (mechanical engineers, systems engineers, and others), clinical investigators, clinicians (including oncologists, cardiologists, and others), faculty, industry scientists, postdoctoral fellows, and graduate students.

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