Methods in ENZYMOLOGY

Volume 426

Integrins

Edited by

David A. Cheresh

VOLUME FOUR TWENTY SIX

METHODS IN ENZYMOLOGY

Integrins

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EDITED BY

DAVID A. CHERESH
Department of Pathology
Moores Cancer Center
University of California
San Diego, La Jolla

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Contributors

Brian D. Adair
Department of Cell Biology, The Scripps Research Institute, La Jolla, California

Alireza Alavi
Department of Pathology, School of Medicine, Moores Cancer Center, University of California at San Diego, La Jolla, California

M. Amin Arnaout
Structural Biology Program, Leukocyte Biology and Inflammation Program, Nephrology Division, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts

Richard K. Assoian
Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Martina Bauer
Max Planck Institute of Biochemistry, Department of Molecular Medicine, Martinsried, Germany

Laurent Bodin
Division of Hematology-Oncology, Department of Medicine, University of California, San Diego, La Jolla, California

David Boettiger
Department of Microbiology, University of Pennsylvania, Philadelphia, Pennsylvania

David A. Calderwood
Department of Pharmacology and Interdepartmental Program in Vascular Biology and Transplantation, Yale University School of Medicine, New Haven, Connecticut

Paola Castagnino
Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Keefe T. Chan
Department of Molecular and Cellular Pharmacology, University of Wisconsin, Madison, Wisconsin

Chun Chen
Lung Biology Center, Department of Medicine, University of California, San Francisco, San Francisco, California

Shu Chien
Departments of Bioengineering and Medicine, Whitaker Institute of Biomedical Engineering, University of California at San Diego, La Jolla, California

Matthew W. Conklin
Department of Pharmacology, University of Wisconsin Medical School, University of Wisconsin–Madison, Madison, Wisconsin

Christa L. Cortesio
Department of Biomolecular Chemistry, University of Wisconsin, Madison, Wisconsin

Lance A. Davidson
Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania

Sumiko Denda
Shiseido Research Center 2, Kanazawa-ku, Yokohama, Japan

Douglas W. DeSimone
Department of Cell Biology, and Morphogenesis and Regenerative Medicine Institute, School of Medicine, University of Virginia, Charlottesville, Virginia

Bette Dzamba
Department of Cell Biology, School of Medicine, University of Virginia, Charlottesville, Virginia

Reinhard Fässler
Max Planck Institute of Biochemistry, Department of Molecular Medicine, Martinsried, Germany

Mark Fuster
Department of Medicine, University of California, San Diego, California

Barbara Garmy-Susini
Moores UCSD Cancer Center, University of California, San Diego, La Jolla, California

Scott Gehler
Department of Pharmacology, University of Wisconsin Medical School, University of Wisconsin–Madison, Madison, Wisconsin

Filippo G. Giancotti
Sloan-Kettering Division, Weill Graduate School of Medical Sciences, Cornell University, New York, New York

Simon L. Goodman
Preclinical Oncology Research, Merck KGaA, Damstadt, Germany

Wenjun Guo
Whitehead Institute for Biomedical Research, Cambridge, Massachusetts

David S. Harburger
Department of Pharmacology and Interdepartmental Program in Vascular Biology and Transplantation, Yale University School of Medicine, New Haven, Connecticut

Dominik Heckmann
Department of Chemistry, Technical University München, Garching, Germany

B. G. Hoffstrom
Department of Biological Sciences, Columbia University, New York, New York

Anna Huttenlocher
Departments of Pediatrics and Molecular and Cellular Pharmacology, University of Wisconsin, Madison, Wisconsin

Hisashi Kato
Division of Hematology-Oncology, Department of Medicine, University of California, San Diego, La Jolla, California

Patricia J. Keely
Department of Pharmacology, University of Wisconsin Medical School, University of Wisconsin–Madison, Madison, Wisconsin

Horst Kessler
Department of Chemistry, Technical University München, Garching, Germany

Eric A. Klein
Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Devashish Kothapalli
Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Yatish Lad
Department of Pharmacology and Interdepartmental Program in Vascular Biology and Transplantation, Yale University School of Medicine, New Haven, Connecticut

Shaohua Li
Department of Surgery, Robert Wood Johnson Medical School, New Brunswick, New Jersey

Milan Makale
Moores UCSD Cancer Center, University of California, San Diego, La Jolla, California

Denise K. Marciano
Department of Medicine, Division of Nephrology and Neuroscience Program, Department of Physiology and Howard Hughes Medical Institute, University of California, San Francisco, San Francisco, California

Eloi Montanez
Max Planck Institute of Biochemistry, Department of Molecular Medicine, Martinsried, Germany

Aleksandra Piwko-Czuchra
Max Planck Institute of Biochemistry, Department of Molecular Medicine, Martinsried, Germany

Suzanne M. Ponik
Department of Pharmacology, University of Wisconsin Medical School, University of Wisconsin–Madison, Madison, Wisconsin

Nicolas Prévost
Division of Hematology–Oncology, Department of Medicine, University of California, San Diego, La Jolla, California

Paolo P. Provenzano
Department of Pharmacology, University of Wisconsin Medical School, University of Wisconsin–Madison, Madison, Wisconsin

Yuliya Pylayeva
Cell Biology Program, Memorial Sloan-Kettering Cancer Center, and Sloan-Kettering Division, Weill Graduate School of Medical Sciences, Cornell University, New York, New York

Louis F. Reichardt
Department of Physiology, Neuroscience Program, Howard Hughes Medical Institute, University of California, San Francisco, San Francisco, California

Sanford J. Shattil
Division of Hematology–Oncology, Department of Medicine, University of California, San Diego, La Jolla, California

Dean Sheppard
Lung Biology Center, Department of Medicine, University of California, San Francisco, San Francisco, California

Dwayne G. Stupack
Department of Pathology, School of Medicine, Moores Cancer Center, University of California at San Diego, La Jolla, California

Judith A. Varner
Moores UCSD Cancer Center, University of California, San Diego, La Jolla, California

Yingxiao Wang
Department of Bioengineering and Molecular & Integrative Physiology, Neuroscience Program, Center for Biophysics and Computational Biology, Beckman Institute for Advanced Science and Technology, University of Illinois, Urbana-Champaign, Urbana, Illinios

E. A. Wayner
Antibody Development Laboratory, Fred Hutchinson Cancer Research Center, Seattle, Washington

Sara M. Weis
Moores UCSD Cancer Center, University of California, San Diego, La Jolla, California

Jian-Ping Xiong
Structural Biology Program, Leukocyte Biology and Inflammation Program, Nephrology Division, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts

Mark Yeager
Department of Cell Biology, The Scripps Research Institute, and Division of Cardiovascular Diseases, Scripps Clinic, La Jolla, California

Yuval Yung
Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Peter Yurchenco
Department of Pathology, Robert Wood Johnson Medical School, Piscataway, New Jersey

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Preface

Integrins are a family of cell surface receptors that mediate contact between a cell and its surrounding extracellular matrix and microenvironment. Integrins not only regulate cell attachment (Chapter 1), but also act to transmit signals across the plasma membrane (2, 6, 9). They also serve as mechanotransducers (8) that, in turn, influence the cells' cytoskeleton assembly (4), leading to changes in cell migration/invasion (3, 16) and ultimately influencing cell survival (5) and cell cycle control (8). The techniques associated with understanding how cells respond to integrin ligation in two dimensional setting (1) and in three dimensional microenvironments (2, 5) have greatly advanced the field and our basic understanding of biology and disease. As such, integrins have been shown to play a key role in embryonic development (10, 12), immune recognition, tissue homeostasis, and wound repair (13). In addition, integrins have been shown to regulate various pathological conditions such as cancer, inflammation, and cardiovascular disease (6, 12, 13, 18, 21). In fact, integrin mutations or disregulation of integrin function are responsible for diseases associated with defective platelet aggregation and clotting, altered immune function, and altered tissue morphogenesis (6, 12, 18, 21). Integrin ligands (11) are typically found in the extacellular matrix and basement membrane and include proteins such as collagens, fibronectins, and laminins. However, during tissue remodeling, cancer, and angiogenesis (21), some specific integrins expressed on invasive cells recognize provisional matrix proteins including fibronectin, vitronectin, fibrin, and osteopontin, among others. For this reason it is important to have techniques available to understand how integrins function to promote cell adhesion to and invasion of the extracellular matrix (1–4). In some cases, integrins can recognize ligands on the surface of other cells. This is particularly true among hemaptoietic cells, those in the blood stream, and in the lymphatic system (6, 18, 21).

Recently, integrins have been recognized as important drug targets. In fact, there has been considerable effort in establishing technology to design integrin antagonists for use in treating various disease conditions (7, 20). For example, inhibitors (antagonists) of the platelet integrin $\alpha IIb\beta 3$ are used to suppress clot formation in patients with thrombotic disorders (6). Other integrin antagonists suppress immune recognition and thereby regulate inflammatory disease and/or autoimmune diseases such as multiple sclerosis. More recently, clinical trials have established that alpha V integrin antagonists can be used to treat or diagnose human cancer (20, 21). These alpha V

integrin antagonists have been shown to directly suppress tumor growth and invasion and/or suppress the process of tumor angiogenesis. There are three forms of integrin antagonists: antibodies, peptides, and small organic peptidomimetics. Anti-integrin antibodies can directly compete for ligand binding or act as allosteric inhibitors. In general, integrin antibody antagonists tend to be more specific than peptide or peptidomimetic antagonists. The development of specific, function-blocking antibodies to integrins (7) has provided the most important tool for the biologist to understand how integrins function in the context of cells and the intact organism. However, integrin antibodies are generally produced in mice (7) and then subjected to humanization prior to being developed as clinical candidates. The development of integrin inhibitors has been aided by scientific approaches to studying how integrins function on cells (1–6, 8, 18, 21) and how they structurally interact with their ligands (14, 15, 20). In addition, the use of genetic models of mice lacking integrins or expressing mutant integrins have been absolutely critically in understanding the role that integrins play in the intact organism (12, 13, 17, 19). However, in a number of cases integrin knockout mice can have a different phenotypes than what one observes when treating mice with specific integrin antagonists. For example, mice deficient in alpha V integrins can develop with a normal-looking vasculature, yet animals treated with alpha V integrin antagonists show a disrupted angiogenic response (21). This may be due to compensatory changes that occur in response to the genetic knockout or due to molecular redundancy. In either event, it is difficult to compare the phenotypes of wild-type mice treated with integrin antagonists to mice entirely lacking an integrin to begin with.

The integrin field has not only made a significant impact on our understanding of basic cell biology, but it has provided important insight into tissue remodeling in the embryo and the adult. The structural, molecular, and biological techniques have combined to elucidate the role that integrins play in these processes and in the development of a wide array of pathological conditions. The field has now progressed to the point where new therapeutic strategies have been developed or are under development to treat everything from cardiovascular disease to inflammatory disease and cancer. The techniques outlined in this volume provide a complete guide to understanding the structure, function, and biological properties of integrins.

I would like to thank the authors of this volume for agreeing to participate in this project as these individuals, having made many of the key contributions to our understanding of the structure, function, and biology of integrins, represent the leaders in this field. I am particularly grateful to Cindy Minor and Jamey Stegmaier and their project management efforts in making this volume possible.

David A. Cheresh

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