

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 microenvironment (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 dysregulation 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 extracellular 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 hematopoietic 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.

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