# The Cadherin Superfamily

Shintaro T. Suzuki • Shinji Hirano
Editors

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## Key Regulators of Animal Development and Physiology

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# Foreword

Intercellular interactions are prime determinants of the form and function of tissues in all multicellular organisms. It is therefore no wonder that searching for the molecular bases of these interactions has preoccupied developmental and cell biologists for over a half-century. Classical embryological experiments during the 1950s and 1960s by pioneers such as Holtfreter, Moscona, Sperry, and Steinberg led to the idea of selective affinities among cells as a major driving force in morphogenesis. Their compelling hypotheses motivated initial attempts to isolate "adhesion molecules" by the next generation of biochemists, including Glaser, Gottlieb, Lilien, Marchase, Roseman, and Steinberg (Gottlieb and Glaser 1980). Sadly, these forays fared poorly: biochemical methods of the time were inadequate to deal with molecules embedded in membranes and present in small amounts.

Then, suddenly, everything changed. In 1977, Masatoshi Takeichi demonstrated that cells bear two adhesion systems, calcium-dependent and calcium-independent, and that calcium protects the calcium-dependent adhesion molecule from proteolysis (Takeichi 1977). His critical insights suggested a strategy for purifying the adhesion molecules, and within a few years, his group and several others had identified what we now know to be the founding member of the cadherin superfamily, E-cadherin or cdh1. Also in 1977, Edelman's group described the first immunoglobulin superfamily adhesion molecule, N-CAM (Thiery et al. 1977).

These landmark discoveries led to a decade of rapid progress. Takeichi soon identified two additional cadherins (N- and P-) to accompany the original E; Edelman and others identified an additional immunoglobulin superfamily member, Ng-CAM. As molecular biology came of age, their genes were cloned, enabling many additional members to be identified by homology. Other families followed later—for example Eph kinases and ephrins, semaphorins and plexins, Robos and Slits, and leucine-rich repeat proteins. Intercellular binding partners were also identified—for example, the catenins—leading to the realization that proteins initially viewed as merely adhesive are in fact sophisticated signal transducers.

Most important, once key molecules and reagents were in hand, it became possible to return to the organism, an enterprise that began in the 1980s and has

picked up steam ever since. In this regard, the cadherins, to which this book is devoted, have arguably had the greatest impact on our understanding of morphogenesis and physiology. We now know that the mammalian genome encodes over 100 members of the cadherin superfamily, divided into around 10 subfamilies. Their structures and signaling mechanisms vary, but they are united by the presence of extracellular cadherin (EC) domains that mediate adhesion. Together, they have been implicated in processes ranging from gastrulation to tumor invasion to the formation and maintenance of tight and adherens junctions. In the development of the nervous system—my own area of interest—cadherins cast a particularly long shadow, being critical for, among other phenomena, neural crest migration, neurogenesis, neuronal arrangement, axon outgrowth, dendritic patterning, synapse formation, synaptic specificity, and synaptic plasticity. For those of us who believe that genetics provides the best barometer of functional importance, the striking phenotypes of many mouse mutants provides unassailable evidence of the crucial roles that cadherins play.

In this volume, Shintaro T. Suzuki and Shinji Hirano, themselves important contributors to our understanding of cadherins, have assembled an up-to-date summary of our current knowledge about this extraordinary and critically important family of cell surface proteins. The first two chapters give us a broad overview of the history, diversity, and evolution of the cadherin superfamily (Suzuki and Hirano; Hulpiau et al.). The next three chapters (Gumbiner; Shapiro; Tan et al.) discuss the structure of and signaling by the classical cadherins, so-named because they include the original members identified by Takeichi along with their closest relatives. They remain the best-understood subfamily. The chapter by Fujiwara et al. complements these with a thorough review of nectins, a set of adhesion molecules that interact and cooperate with classical cadherins. Five of the subsequent chapters summarize what is known about the other cadherin subfamilies (Chidgey and Garrod; Mah and Weiner; Jontes; Shi et al.; Imai-Okano and Hirano). Finally, four chapters focus on roles in particular tissues and diseases, looking broadly at the involvement of multiple subfamilies (Brayshaw and Price; El-Amraoui and Petit; Albrecht et al.; Hirano and Imai-Okano).

All in all, this book provides the best way, at the moment, for molecular, cell, and developmental biologists to appreciate the current state of knowledge about the cadherins. And the news is good. We are, of course, far from understanding how intercellular interactions shape the organism. Nonetheless, as we approach the 40$^{th}$anniversary of the first description of a cadherin, those of us who stand in Takeichi's shadow can take some satisfaction in the insights that have been gained and the prospects for more to come.

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# Preface

Cadherins were initially identified as $Ca^{2+}$-dependent cell–cell adhesion proteins that were involved in the formation and maintenance of tissue structure after extensive searching for adhesion molecules. Since then, a large number of studies of classical cadherins have been carried out and most of the fundamental questions of classical cadherins have been clarified. Now it is widely accepted that cadherins constitute a large superfamily and are involved in various biological processes not only in the formation and maintenance of tissue architectures but also in diversified signaling processes. However, the research has also revealed many contradictory results and raised new questions. It is clear that the entire field is not so simple as once thought and many unsettled questions remain. Hence, we think it is an appropriate time to publish a book about cadherins in which the current status of cadherin research is reviewed.

The principal aim of this book is to furnish an overview of the entire field of cadherin research and to provide the current basic concept of cadherins for a wide range of readers from beginners to researchers in the field. We invited leading researchers to cover various aspects of the cadherin superfamily including the history of cadherin research, basic properties of classical cadherins as well as non-classical cadherins, cadherin-associated proteins, and the roles of cadherins in health and diseases. In addition, this book presents some contradictory results and important unanswered questions, and the authors propose their working hypotheses or future directions, to inspire future studies, especially by new participants in the field. We hope this book will provide useful information and guidance for all readers.

Finally, we would like to acknowledge all the contributors to this book for their generous acceptance of authorship and their great efforts. In addition, we are grateful to Prof. Joshua Sanes for his kind agreement to write a Foreword to this book at an extremely busy time for him. We also thank Dr. Misato Kochi,

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