# The wide world of Wnts

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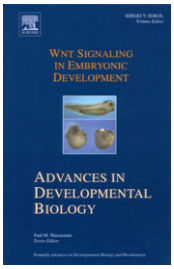


## Wnt Signaling in Embryonic Development

**Edited by Sergei Y. Sokol**

Elsevier (2007) 264 pages
ISBN 978-0-444-52874-2
£99.95/€130/$149.95 (hardback)

Researchers studying the Wnt pathway frequently like to joke that 'Wnts do everything', and that this fact keeps us all in business. Over time, this claim has become less facetious, as the number of known roles for Wnt signaling has grown rapidly. Following on from the first identified functions of Wnts in embryonic tissue patterning and cell proliferation, these signals and their multiple downstream pathways have been implicated in everything from epithelial polarity to synapse formation. The authors of *Wnt Signaling in Embryonic Development*, edited by Sergei Sokol, have attempted to tackle this well characterized and highly important family of molecules and their complex functions. So much new research has been published on Wnt signaling in recent years that this collection of review articles is timely, giving readers an overview of recent findings as well as a more general perspective.

The realization that a relatively small group of extracellular signals can regulate multiple aspects of development throughout the animal kingdom is both advantageous and daunting. On the plus side, it means that a limited set of tools and reagents can be used to perturb signaling in one's organism or tissue of choice, and to analyze the resulting phenotypic effects. The negative side is that understanding the roles of even one of these signals can be challenging; it seems that new functions and components are discovered every day. This can be contrasted with roles of Wnt signaling in cancer, where a few key events, such as proliferation, survival and anchorage-independent growth, receive most of the attention. Because of the vast number of organs and cellular events involved in development, one hope would be to identify common functions for Wnt signaling that can be extrapolated to hypothesis-based experiments in other developmental processes.

This book is presumably aimed at biologists who want to know more about the roles of Wnt signaling in a particular developmental process, and to have a list of tools and phenotypic analyses available to answer a specific question. With this basic information, any researcher can perform gain- or loss-of-function studies in their favorite cell type, and also examine the expression of pathway components and targets. To this end, Dr Sokol has assembled a group of individual reviews from leaders in the field, each focused on a different aspect of Wnt signaling. These authors provide a level of expertise and insight into their respective topics that is difficult to achieve in other formats, and gives the reader confidence that they are receiving the most up-to-date information available.

**This book is akin to an encyclopedia without alphabetization. Most facts that a reader might want to know are in there somewhere, it's just a matter of finding them**

The major weakness of such a compendium is, however, that although the individual chapters are comprehensive and useful, it becomes difficult to synthesize information between them. This is perhaps an unavoidable consequence of the structure of such a book, when each review is essentially independent in focus, although the preface partially helps to tie things together. Because the chapters are also quite divergent in scope, some material is unnecessarily repeated, whereas other findings are missed. A reader might have difficulty knowing where to look for particular information, as some chapters emphasize the signaling pathway itself, whereas others have an organism-centered approach and describe many known roles in a single animal, while the remainder deal specifically with Wnt function in individual tissues.

Two chapters are organized around the best-understood output of Wnt signaling, transcriptional regulation via the 'canonical' or β-catenin pathway. The first by David Parker, Timothy Blaukamp and Ken Cadigan focuses on the biochemical and genetic roles of nuclear components of this pathway throughout animal species, and provides a comprehensive overview of this ever-growing list of molecules. To understand the complexity of this system, one only need view the Wnt homepage schematic generated by Roel Nusse (http://www.stanford.edu/~rnusse/pathways/cell2.html) and view the jumble of factors that occupies the entire nucleus. While covering a lot of ground, this review provides an important reference for anyone interested in Wnt-mediated transcription. By contrast, a chapter by Henrick Korswagen centers specifically on roles of the POP-1 transcription factor in a single organism, *C. elegans*. It provides a more in-depth analysis of a relatively small number of genes and their mutant phenotypes, with useful descriptions of the cellular processes affected. Together, these two chapters provide complimentary overviews of canonical Wnt signaling. Reading both leaves one with a detailed understanding of the mechanism through which Wnts regulate target gene transcription, and examples of the functional outputs of this pathway in a relatively simple model organism.

Another chapter by Jianbow Wang, Leah Etheridge and Anthony Wynshaw-Boris, also covers roles for Wnt signaling in an entire (and much more complex) organism, the mouse. This is obviously an enormously broad topic, including multiple tissue types and different signaling outputs. Considering this, the authors have done a heroic job in summarizing a large volume of literature and provide a comprehensive background for readers interested in the range of Wnt activities in a single animal. The work described in this chapter helps illustrate how gene redundancy and pleiotropic effects have frustrated the ability of researchers to study Wnt function using genetic approaches. However, given the space available, it might have been more beneficial to have focused on either a single output or on fewer tissue types, but in greater depth. Some of the topics discussed here are covered in other chapters, and there is little room for the interpretation of phenotypes, which would help the non-specialist. The chapter ends up being very fact-dense, but is still useful as a general reference for the field.

Two chapters focus on cellular functions of Wnt signaling, each with examples from different tissues and organisms. Gretchen Dollar and Sergei Sokol describe how Wnts control cellular polarity, including such well-studied events as apical-basal polarization, planar cell polarity, cell movement and asymmetric division. Each topic is introduced with sufficient background information, followed by genetic and biochemical evidence of Wnt pathway functions in the process. The common themes aid a reader in drawing parallels with their favorite system, and allow predictions for how Wnts might act in unstudied cell types. Almut Köhler, Alexandra Schambony and Doris Wedlich focus specifically on cell migration, using examples from mouse gastrulation, the nervous system, and formation of eye and heart fields. Similarities appear between single-cell and tissue-level migratory regulation, and classical embryological models, such as *Xenopus* gastrulation, are juxtaposed with newer topics, providing a comprehensive overview. Although it is not surprising that non-canonical Wnt signaling can affect cell migration in a variety of systems, this chapter also leaves the reader with the important idea that canonical signaling can regulate migration at the level of gene expression.

Finally, two chapters discuss Wnt signaling functions in specific tissue types. Elizabeth Heeg-Truesdell and Carole LaBonne review multiple stages of neural crest development, providing evidence for regulation by Wnts at each step from crest induction to cellular differentiation. This chapter creates perhaps the clearest overview of how a single class of extracellular signals, through multiple downstream pathways, are used reiteratively throughout the development of one cell type. This is a fundamental concept in developmental biology, as is the idea that Wnts are likely to act in concert with other signals at all these steps. Néstor Masckauchán and Jan Kitajewski focus on Wnt pathways in angiogenesis, which is a relatively new direction of research that has uncovered known and novel members of the signaling cascade using genetic approaches. Most of the initial work has centered on diseases of the retinal vasculature, which have provided a good model for ligand and receptor activity in the growth and regression of vessels. These findings have led to the search for additional functions for Wnt signaling in angiogenesis, with obvious clinical implications. Together, these chapters illustrate the forward movement in the field towards translational research using Wnt pathway modulation to treat developmental disorders and disease.

With all the data accumulated from hundreds of studies, one purpose of these chapters is to help separate the wheat from the chaff. A good chapter should not only summarize the data, but also act as a filter through the expertise of the author to help interpret the current state of the field. Is a finding significant, or is it a one-off observation? How do we interpret studies with directly contradictory conclusions? Some of the chapters are more successful at addressing these questions, offering interpretations of discrepancies in the literature and suggesting general themes. In other chapters, every finding is presented with equal weight, leaving it up to the reader to judge their importance. However, it is nice to see more-recent research directions represented in this book, such as angiogenesis and cell polarity, even if the significance of some of these studies is less clear at this point.

Overall, this book is akin to an encyclopedia without alphabetization. Most facts that a reader might want to know are in there somewhere, it's just a matter of finding them (although the index is helpful). Because of this, one might be better served by reading through the entire volume, rather than searching for specific information in individual chapters. Editors of review compilations are limited by their ability to recruit authors with expertise, and Dr Sokol has brought together a first-rate group, possibly at the expense of a more-standardized selection of topics. The perfect book would have both.

# Through the eye of a book… on the eye

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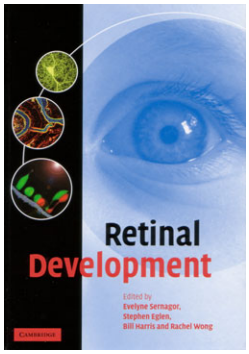



## Retinal Development

**Edited by Evelyne Sernagor, Stephen Eglen, Bill Harris and Rachel Wong**

Cambridge University Press (2006) 383 pages
ISBN 10: 0-521-83798-7
£75/$130 (hardback)

The retina is perhaps our most intricate and well-studied sensory structure. It receives visual information from the outside world and interprets this information as color, shape and movement, and then transmits it to visual centers in the brain in the form of coded impulses. The embryonic and early postnatal retina has long been a rich setting for studying the basics of neural development – from cell genesis through axon guidance, synaptic interactions and the role of activity in the innervation of targets – perhaps more so than any other model sensory system. However, until now, a reference resource in the form of a review collection that guides the reader through the state-of-the-art approaches for studying retinal development has not been available. Especially daunting for the developmental biologist is the recent outpouring of molecular, genetic, functional and structural data on the mature and diseased retina that have been published in a wide range of vision and neuroscience journals. Finding information on the developing eye, or information that bridges basic findings on retinal development to retinal disease, is not an easy task. As such, the book *Retinal Development* is especially welcome and is also a delightful read.

The editors of this fine collection of articles aim to tell the story of how the retina develops and to make this information accessible to developmental biologists, as well as to those interested in the causes of retinal disease. Although by now a little out of date, as is true of most books that are a collection of articles (most references are from 2004 and earlier), the volume serves as a ready reference to themes in retinal development, and points the way to topics now in the current literature. This book bears the stamp of the editors, all distinguished vision scientists who have worked on the developing retina from functional (Evelyne Sernagor and Stephen Eglen) and cell and molecular (Bill Harris and Rachel Wong) viewpoints, and bears

their characteristically clear and articulate style. The summaries, prose and style of the book are rich and consistent, and the index detailed. The editors must have taken to task their authors and guided them with a firm hand as each chapter has the same informative format; each has a developmental component, and brings the topic of a chapter back to the morphological and molecular beginnings of a particular cell type or developmental phase. Each chapter also brings to the fore a broad view of a particular topic, and not simply the purview or opinions of its authors.

The book begins with several chapters on 'how a patch of ectoderm becomes committed to become the complex sensory structure that the retina is'. The most remarkable of these, the first chapter by Michael Zuber and Harris, is on the formation of the eye field in the early embryo. Retinal neurons must then be generated and must migrate and become organized into layers, as described in the chapters by David Rapaport and by Leanne Godinho and Brian Link, which highlight how these events differ from those of the more widely studied cortical neurons. A refreshing aspect of the book is that it moves effortlessly up and down the phylogenetic scale, from zebrafish models to primates, and from early eye development through to more traditionally covered topics, such as retinal mosaics (by Eglen and Lucia Galli-Resta), programmed cell death (Rafael Linden and Ben Reese) and optic nerve formation (David Sretavan). As discussed below, these excellent chapters are capped off by considerations of the role of early neural activity in synaptogenesis (Sernagor) and in the onset of light responses (Sernagor and Leo Chalupa).

Far from being a dull review of what is known on these topics, the chapters in this book offer a blend of information on many different aspects of a given cell type or process that would be difficult to parse from a search in PubMed. A favorite chapter of mine is by Michalis Agathocleous and Harris on cell determination – how the different cell classes are formed and to what extent cell cycle progression affects this process. Vital nuggets of information are offered in these comparative reviews; for example, in the chapter by Jennie Close and Tom Reh, which emphasizes that the ciliary margin zone of frogs and fish is a continual source of progenitors or stem cells. As one who has searched for information about this specialized rim of the retina, I found a single figure and page packed with information on this structure that was enlightening. Likewise, fascinating information on the mosaic organization of the retina can be found in the chapter by Eglen and Galli-Resta, and in the chapters by James Fadool and John Dowling and by Jeff Mumm and Christian Lohmann, on how cells and their dendrites are 'tiled' during early development.

A second goal of the editors was to highlight how the incredibly rapid development of techniques drives discovery, and, as is the case with imaging, how this progress can reveal detail never achieved before about developmental processes and cell organization. Several chapters describe studies that have been fuelled by advances in imaging of the retina in transgenic fish and mice, in which specific classes of cells have been labeled with fluorescent markers, an advance over the capricious Golgi method. Agathocleous and Harris discuss the monitoring of the activities of living, twitching neurons, and of retinal precursors that divide, migrate and visibly turn on a specification gene. Mumm and Lohmann chronicle the laying down of dendritic fields in the plane of the retina and the refinement of the lamination of dendritic arbors in the vertical plane of intrinsic retinal cells during retinal development. Always magical to witness, these studies are much needed if we are to understand how such neural circuitry arises in all its complexity.

**The editors of this fine collection of articles aim to tell the story of how the retina develops and to make this information accessible to developmental biologists and to those interested in retinal disease**

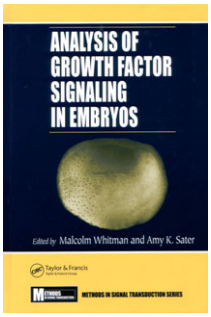
During later development, even before the eyes open, intrinsic electrical activity is generated in retinal neurons and spreads across the retinal sheet. There is much debate about how this activity is generated, from which cells, and about which processes might require it. Also under debate is how this activity might direct the formation of the eye-specific connections of the long axons of retinal ganglion cells with their targets. A couple of chapters help to explain the context for, and the findings that contribute to, this debate. For example, the chapter by Sernagor describes how to make sense of electrophysiological recordings from dozens of retinal cells and how to interpret synaptogenesis, whereas a companion chapter by Sernagor and Chalupa explains how to distinguish between retinal waves and the earliest light responses in the retina, and discusses how the plasticity of retinal ganglion cells is due to these modes of activities.

Some chapters, such as the one on glial cells in the retina, are wonderfully detailed. The chapter by Kathleen Zahs and Manuel Esguerra reviews everything you might want to know about the development, cell relationships and physiology of the Mueller glia, which, like the Bergmann glia of the cerebellum, remain radial throughout adulthood. Meanwhile, the chapter by Close and Reh outlines the developmental potential of radial glia, which can act as neural progenitors, and of retinal pigment epithelial cells, which can not only regenerate, but differentiate into new tissue containing the proper types and organization of retinal cells. These chapters are essential reading for those interested in stem cells.

Will clinical researchers working on the developmental origins of glaucoma or on adult macular degeneration refer to this volume? Most likely, yes. They should find David Sretavan's chapter on the developmental and molecular aspects of optic nerve formation of interest; the optic nerve is the primary site of damage in glaucoma, secondarily causing retrograde damage and the death of retinal ganglion cells. The chapter by Fadool and Dowling is of clinical relevance as it lays out the advantages of zebrafish as a model genetic system for identifying candidate disease genes through large-scale mutagenesis screens for factors that affect retinal cell development. Seth Blackshaw's chapter describes his herculean efforts at gene discovery in the retina. He points out the plusses and minuses of the different gene profiling techniques, and lists some of the developmentally relevant and cell-specific genes that have been identified. The chapters by Rachael Pearson on neurotrophins and neurotransmitters, and by Linden and Reese on cell death, describe growth factors that delay apoptosis in genetically determined retinal dystrophies. Some of these themes are hidden in chapters with basic science-sounding titles.

Although this book is aimed at the specialist, it will make good reading for graduate students and postdocs who are starting out on a project on the retina or visual system. My recommendation is: keep an eye out for it for your lab.

# What can embryos teach us about communication?

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## Analysis of Growth Factor Signaling in Embryos

**Edited by Malcolm Whitman and Amy K. Sater**

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ISBN 0-8493-3165-X
£92 (hardcover)

Multicellular organisms coordinate their growth, development and homeostasis through cell-cell communication mediated by a relatively small number of extracellular signaling molecules, often referred to as growth factors. Nowadays, it is difficult to open a new volume of a developmental biology journal and not find at least one article describing the role of growth factor signaling in a developmental event. It is safe to expect that most developmental decisions involve growth factor signaling. For this reason, it is no longer sufficient to show that a growth factor is involved in a developmental event. Instead, current and future growth factor signaling research should focus on how growth factors mediate such varied effects on cells during development, growth and homeostasis. In other words, why does a particular growth factor mediate a mitogenic response in one cell, but a survival effect in another, or a migratory effect in another, or a change in fate in yet another. Thus, in my view, the exciting current and future work being done in the broad field of growth factor signaling involves investigating how growth factor signaling is modulated in space and time, and how cells interpret the signals appropriately and in a coordinated fashion. This level of understanding is essential for us to truly understand not only how growth factor signaling coordinates development, but also how and why failures in this coordination result in disease states, such as cancer and congenital abnormalities.

Historically, much effort has gone into investigating growth factor signaling in tissue culture assays. However, it is difficult to imagine that a deep understanding of the details of growth factor signal modulation and interpretation can be achieved by studying them in cell lines, in particular when addressing multicellular and even multi-tissue processes, such as morphogenesis. When tackling these difficult questions, it is embryos that have much to teach us, as they provide a more physiological, in vivo context in which to investigate the complexities of growth factor signaling. The question is: how does one tease out the secrets of the intricacies of growth factor signaling from embryos? The book, *Analysis of Growth Factor Signaling in Embryos*, edited by Malcolm Whitman and Amy Sater, aims to provide the theoretical and technical framework to investigate how growth factor signaling is modulated and coordinated in embryos. The book is divided into four sections: (1) Signals and Pathways; (2) Ionic Signals; (3) Transcriptional Regulation of Target Genes; and (4) Emerging Strategies for the Analysis of Signaling in Development.

**I found the book very useful and I am happy to have a copy in my office. However, I cannot say that the book is wholly inclusive**

The first section of the book contains seven chapters, devoted to what could be most conventionally described as growth factor signaling in embryos. It covers a chapter (Chapter 1) on the study of canonical Wnt signaling by Wilson K. Clements and David Kimelman; a chapter (Chapter 2) on non-canonical Wnt signaling by Michael Kühl and Randall T. Moon; and a chapter (Chapter 6) on Wnt signaling through Rho-family members by Raymond Habas and Xi He. Thus, Wnt signaling is very well covered in the book. There is only one chapter devoted to the study of TGFβ signaling (Chapter 3). This chapter, written by Shailaja Sopory and Jan L. Christian, is devoted to the analysis of proprotein processing during the activation of TGFβ ligands. This chapter is interesting, but I would have expected at least another chapter on the modulation of TGFβ-family signaling by extracellular inhibitors (such as noggin and chordin during BMP signaling), or perhaps one on the regulation of Smad activity by the Nodal/BMP pathways in conjunction with other pathways. There is no chapter devoted to general receptor tyrosine kinase (RTK) signaling (such as FGF, PDGF, EGF, Ephrin, neurotrophins), which I think is lacking. However, there is a very good overview (Chapter 4) on the analysis of MAP kinase pathways in embryos, written by Amy K. Sater and Heithem M. El-Hodiri. There is also a comprehensive overview of retinoic acid signaling (Chapter 5) by Malcolm Maden. Malcolm Whitman's chapter (Chapter 7) is devoted to the use of phosphospecific antibodies to query the activation state of signal transduction pathways in embryos, either by western blots or in situ, using whole-mount immunohistochemistry.

The second section only has two chapters: one devoted to calcium signaling by Diane C. Slusarski (Chapter 8) and the other devoted to biophysical or electric fields by Dany S. Adams and Michael Levin (Chapter 9). These chapters would not be commonly thought of as fitting neatly under the growth factor signaling umbrella, but I am very pleased that they were included. Growth factor signaling can obviously lead to a calcium response, but so can other events, such as fertilization. However, there is no doubt that embryos are ideal systems in which to study the complexities, roles and regulation of calcium signaling in an in vivo context. The chapter on biophysical signals by Adams and Levin is, without question, the most significant chapter in the book. For one, it covers 85 pages, although admittedly, 29 pages are devoted to appendices and 17 pages to references. But perhaps the most useful aspect of this chapter is to force those of us who tend to ignore electric fields or biophysical forces in biology to take note and to open our eyes, as there are signaling mechanisms in development beyond those mediated by conventional growth factors.

The third section contains two chapters, which are devoted to the transcriptional readout of signaling in embryos. Chapter 10, written by Curtis Altmann, describes the use of expression profiling in embryos and Chapter 11, by Daniel R. Buchholz, Bindu Diana Paul and Yun-Bo Shi, describes how to perform chromatin immunoprecipitations

from material isolated from embryos and tadpoles. The final section contains four chapters, which are loosely brought together under the heading 'Emerging Strategies'. Chapter 12, written by Joanne Chan and Thomas M. Roberts, is devoted to the use of chemical compounds to investigate growth factor signaling during embryogenesis. More specifically, the chapter describes how one can use chemical compounds to study vascular development in zebrafish and, conversely, how zebrafish can be used to help identify chemicals with potential value in the treatment of human disease. Perhaps along the same general line, Chapter 14, by Karen J. Liu, Jason E. Gestwicki and Gerald R. Crabtree, describes how one can generate conditional alleles for the protein of your choice, which is activated by small molecules, a very useful technique indeed. Chapter 13, by Karen Symes, provides an overview of how one can study the cellular movements of gastrulation, with the hope of beginning to understand how growth factor signal inputs from many different pathways come together to coordinate a process, which is mind-boggling in its complexity. In the end, we need to start thinking of growth factor signaling in the context of the whole embryo. Each signaling pathway is likely to feed into other pathways, and the responses will sometimes be positive and sometimes negative, and all this has to be coordinated within and between the cells correctly. Clearly, this will turn out to be a very complicated network, which must be modeled so that a deeper understanding can emerge. Thus enters the field of systems biology, and the final chapter of the book, written by Gregory R. Hoffman, Kevin Brown, Adrian Salic and Ethan Lee, which describes how one might start modeling signaling networks in development.

Overall, I found the book very useful and I am happy to have a copy in my office. However, I cannot say that the book is wholly inclusive. There is much that it covers, but there is much that is lacking. For example, the book fails to mention or describe work on Notch signaling, Hedgehog signaling, or on the great plethora of signaling by RTKs. Thus, the book is rather biased in the selection of growth factor signaling that it covers. Another clear bias in the book is in its coverage of experimental organisms, which is mostly of the frog, *Xenopus laevis*. In my laboratory, we use *Xenopus* to investigate growth factor signal modulation, as it provides a powerful system in which to combine large-scale functional genomic screens with biochemistry, cell biology and embryological manipulations. However, I certainly would not say that it is the only useful system in which to study growth factor signaling in embryos. Zebrafish gets a mention in several chapters, but it only features exclusively in one chapter (Chapter 12, entitled 'Chemical Biology in Zebrafish Vascular Development'). Is this enough? I would expect my zebrafish embryology colleagues to be of the view that it is not. Chick embryos are mentioned in Maden's chapter and in Adam and Levin's chapter, but elsewhere they fail to feature at all. Again, my chick embryology colleagues might be disappointed. Invertebrate models, such as *Drosophila*, *C. elegans* and ascidians, are missing altogether. Again, this is an unfortunate failing in the book. However, for what it does contain, the book is very good. I would suggest that every laboratory working on growth factor signaling in *Xenopus* should get one, as should any laboratory planning to work with *Xenopus*.

# On the backroads to cellular asymmetry

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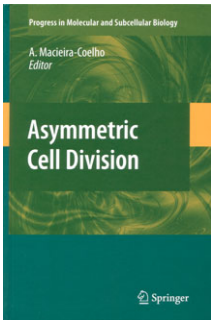


## Asymmetric Cell Division (Progress in Molecular and Subcellular Biology)

**Edited by Alvaro Macieira-Coelho**

Springer-Verlag (2007) 247 pages
ISBN 978-3-540-69160-0
£107.50/€139.95/$189.00 (hardback)

Asymmetric cell division is a process whereby one cell generates two daughter cells that differ in size or developmental potential. Asymmetric cell divisions were first described during the initial, cleavage-like divisions of the zygote, where they contribute to the establishment of the body axes in some organisms. More recently, however, the identification of cell-fate determinants that are segregated asymmetrically in dividing somatic cells has focused the interest of the field on later stages of development. The importance of asymmetric cell divisions for stem cell biology has, in particular, generated a strong interest in the molecular mechanisms that guide this important biological process.

Much of what we know about asymmetric cell division comes from two model organisms: the worm *Caenorhabditis elegans* and the fruitfly *Drosophila melanogaster*. Their study has taught us much of what we know about segregating determinants and the molecules that guide their asymmetric localization during mitosis. The Springer Press book *Asymmetric Cell Division* (in the Progress in Molecular and Subcellular Biology series), edited by Alvaro Macieira-Coelho, wants to go beyond these 'classical' model systems. In a series of reviews, it also includes those model organisms that are less well studied and that are not covered in the standard review literature. It is obvious that this strategy cannot generate a textbook that would be useful for teachers who want to cover asymmetric cell division in their lectures. Nor is the book suitable for students who are confronted with the field for the first time. The book is targeted at scientists working in the field who want to collect information from other model systems, or who are looking for a collection of in-depth reviews that cover some of the latest developments in the field.

The book can be conceptually subdivided into four parts: in the first, a set of reviews describes asymmetric cell division in plants, whereas the second section covers model systems that are less well studied but that are interesting from an evolutionary point of view. This is followed by a third section that covers asymmetric cell divisions in *Drosophila* and in mammalian stem cells in the nervous system and in the ovary, as well as in the human placenta and ovarian surface epithelium. The book concludes with a final part that describes cancer stem cells and the asymmetric segregation of DNA strands, two emerging topics in asymmetric cell division research.

Plants have a particular need for asymmetric cell divisions, as cell migration

or even long-range morphogenetic fields are not available as mechanisms for developmental patterning. The first review by Renze Heidstra focuses on asymmetric cell division in the model plant *Arabidopsis thaliana*. Following an introductory chapter on general features of plant cell division, it covers what we know about asymmetric cell division during the early zygote stages, as well as the postembryonic stem cell divisions that are characteristic of plant meristems. The review finishes with chapters on lateral root development, stomata formation and pollen development, which largely describe the mutants that affect these tissues and the respective gene functions. A second review, by R. M. Ranganath, covers asymmetric cell division in flowering plants. As in the first review, *Arabidopsis* is the main topic, and it is a little unfortunate that the significant redundancy that exists between these two chapters was not avoided by better editorial coordination. As in the first review, both embryogenesis and adult meristem stem cells are covered, but a stronger emphasis is given to gametogenesis and the various asymmetric divisions that occur during male and female gamete formation.

The next two chapters by Thomas Bosch and David Weisblath deal with *Hydra* and the leech *Helobdella robusta*, and cover two of the most exotic models of asymmetric cell division research. Both articles start with a detailed introduction into the evolution of these model organisms and their developmental peculiarities. Needless to say, these reviews have to be descriptive because the work undertaken in these organisms mostly asks whether principles developed in other species can be applied to these organisms as well. Unusually for a review, both chapters contain a large proportion of work by the authors themselves – some even unpublished. However, the authors do a good job in describing how general principles can be derived from following cell biological processes through evolution and, for me, these were certainly two of the more-insightful chapters in the book.

The third part of the book covers more-mainstream model organisms and deals with *Drosophila* and mouse models of germline and neural stem cells, as well as asymmetric cell division in the immune system. In the first review of this section, Pierre Fichelson and Jean-René Huynh describe asymmetric cell division in the *Drosophila* ovarian germline. *Drosophila* germline development is one of the best-understood model systems for stem cell biology and has been extensively covered in many excellent reviews of recent years. Although this review cannot avoid sharing some redundancy with these other papers, the chapter stands out because it specifically covers aspects of intrinsic asymmetry in ovarian stem cells that are usually less emphasized. It finishes with an interesting chapter on asymmetric division during meiosis that integrates work from both vertebrate and invertebrate models.

A second review by Takaki Miyata in this section covers the role of asymmetric cell division during mammalian brain development. This is a controversial topic, and multiple models exist for how progenitor divisions might create both self-renewing and differentiating daughter cells. The review opens by discussing the role of Numb, a segregating determinant that has been identified in *Drosophila*, but whose function in mice remains controversial. It is unfortunate that very recent data that shed important light on this conflict are not included, most likely owing to the lengthy publication process of a book. The remainder of the review draws interesting comparisons between the developing mammalian brain and the *Drosophila* central nervous system. Unlike many other reviews, it emphasizes the differences between the two systems and places particular emphasis on cell culture models and fate regulation by the Notch/Delta system. The review defines a model in which cells enter a 'moratorium' period shortly after division, during which intrinsic differences between daughter cells can still be overridden by external signals.

**I assume that the book will not be consumed as a whole, but that individual scientists will be interested in certain chapters. It is therefore questionable whether the book format is appropriate for such a collection of articles**

Ivana Gaziova and Krishna Moorthi Bhat contribute a review on *Drosophila* embryonic neuroblasts that describes in great detail the terminal and self-renewing asymmetric cell divisions in the *Drosophila* embryonic nervous system. Unlike many of the reviews that exist on this topic, the text does not focus on the machinery for asymmetric cell division, but includes some less well-covered data on particular defined lineage decisions. Among these are results from the authors themselves, as well as data from Gerhard Technau's laboratory suggesting a role for Cyclin E in regulating particular asymmetric divisions. The final review in this part of the book covers asymmetric cell divisions in the human placenta and in stem cells in the fetal ovarian surface epithelium. This is clearly a very specialized review that focuses to a large extent on work by the authors themselves and presents more-original data than review-type summaries. Although interesting for those working in the immediate field, it will probably be hard to grasp for the general reader.

The book finishes with two reviews that cover emerging topics in asymmetric cell division research. In the first, Emmanuel Caussinus and Frank Hirth cover asymmetric cell division in stem cells with a particular focus on cancer stem cell biology. This review focuses almost entirely on results from *Drosophila*, with only a short discussion of cancer stem cells in vertebrates. Since this has been a very active field recently, this focus leaves a sufficient amount of new data unreported. The long delay that occurs between the submission and publication of a book is an inherent problem of this format and one that compromises timeliness; this becomes a particular problem when a book is reviewing a field that is moving rapidly. Recent data on the role of mitotic kinases in tumour suppression, for example, are not included. Nevertheless, the review gives a nice introduction into an emerging field and provides a balanced view.

The final review is by the editor himself. Alvaro Macieira-Coelho covers the asymmetric segregation of DNA in fibroblasts. This topic is certainly somewhat removed from the mainstream, and it is a little unfortunate that the more-recent experiments on asymmetric DNA strand segregation (or the lack thereof) in mammalian stem cells are not included. Again, the review focuses largely on data from the author's laboratory and certainly expresses views that are slightly provocative.

Altogether, this is a loose collection of reviews that could have just as well appeared as individual articles in one of the major review journals. It is quite likely, however, that some of the articles would not have survived the stringent review process that is

applied by some of these journals. This is not a book I would have on my bedside (and I would certainly not recommend it to anyone who is not particularly interested in asymmetric cell division). It is probably also not a book that I would buy for my own use. However, it would be appropriate for a biology department's library. Many of us – particularly in the stem cell field – are interested in the mechanisms of asymmetric cell division, and the book is a welcome addition to the more-mainstream articles published by review journals. I personally would find a collection of individual PDFs more useful; such a format could avoid some of the problems of timeliness that are inherent when covering such an active and fast-evolving field. In my view, the field of asymmetric cell division is still too dynamic to be covered by a textbook and, once it is, such a textbook would have to be more basic, more coherent and less opinionated. Scientists or students, however, who work in this field and who have already read some of the mainstream review articles, might find this book a useful addition for understanding the less well-covered areas of asymmetric cell division research.

# An 'all in' account of Smad biology and TGFβ signaling

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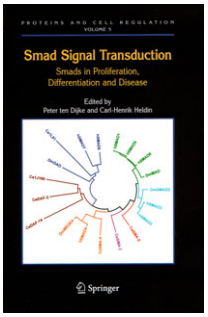


## Smad Signal Transduction: Smads in Proliferation, Differentiation and Disease

**Edited by Peter ten Dijke and Carl-Henrik Heldin**

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The TGFβ signaling system affects many aspects of life, from embryogenesis to congenital and chronic disease, to tissue repair and homeostasis in adult animals. At the cellular level, this all-embracing system regulates cell proliferation and differentiation, survival and apoptosis, migration and intercalation, adhesion, and matrix production and interaction. Developmental biologists want to identify and functionally characterize the many components of the TGFβ system that make cells change their fate and differentiate in embryos and their organs. Altogether, the field has identified many ligand-encoding genes (33 in the human genome), a few receptors (seven type-I and five type-II receptors) and a few receptor-activated Smads (Smads 1, 2, 3, 5, 8), one co-Smad (Smad4) and two inhibitory Smads (Smads 6, 7), many Smad-interacting proteins (SIPs; I stopped counting at 120 two years ago) and still too few direct target genes. With the identification of the Smads as intracellular effector proteins of TGFβ receptor signaling in the mid-90s, the rapid progress and the enormous diversification of the Smad field, as witnessed by the 2,717 hits in a literature database search for Smad at the time of writing this review, time is indeed right to move from the many review articles on Smads to a reasonably comprehensive and accessible text. This text would ideally gather all relevant information on Smads in signal transduction in general and at the crossroads between developmental and cell biology in particular. This is what the book, *Smad Signal Transduction: Smads in Proliferation, Differentiation and Disease*, edited by Peter ten Dijke and Carl-Henrik Heldin, aspires to do, but does not always achieve.

The editors of this book have, however, firmly set themselves an ambitious goal. In 22 chapters (preceded by a preface from the editors) and in 459 pages of text, different researchers in the field cover various fundamental aspects of Smad biology. These include their activities in different processes, their intracellular trafficking, structure-function and evolutionary relationship, post-translational modifications, non-Smad partners, cross-signaling with other systems, novel high-throughput and computational approaches, and their role in disease. Each is a stand-alone chapter, in most cases compiled by one team; about a quarter of the chapters are written by co-authors from different institutes or organizations and, therefore, provide a well-integrated view of a particular aspect of Smad biology. A certain amount of redundancy is present between some chapters, but not to a distracting degree.

In the preface, the editors start by rightly emphasizing the enormously important contributions of *Drosophila* and *Caenorhabditis elegans* genetics to this field, which led to the identification of the *Mad* and *sma* genes, respectively, that encode Smad proteins. This justifies the incorporation into the book of chapters on the molecular evolution of Smad proteins (Chapter 1) and Smad signaling in *C. elegans* (Chapter 2) and *Drosophila* (Chapter 3). The focus in Chapter 1 is on receptor-activated Smads in humans, *Drosophila* and *C. elegans*, and not only provides a table that summarizes Smad nomenclature in different species, but also discusses evolutionary relationships at the level of the Smad domains. The trained zoologist in me missed having an update on the recent progress in *Hydra* and jellyfish (both coelenterates), and in *Ciona* (or any other ascidian as representative of the urochordates). Chapter 2 provides an overview of nematode Smad pathways, and includes interesting views on body size regulation by TGFβ components, including Sno/Ski-like proteins, and a brief discussion of the non-involvement of TGFβ signaling in the control of the dorsal-ventral axis in nematodes, in contrast to *Drosophila* and vertebrates. Chapter 3 incorporates more developmental biology, as it discusses, among other things, how Smads contribute to graded bone morphogenetic protein (BMP) signaling, and how Schnurri and Brinker cooperate in the Smad pathway. It also critically notes that the specificity of the Smad proteins Mad and Smox for BMP and activin receptors, respectively, has never actually been tested in vivo.

The next four chapters take the reader on a tour of the role(s) of Smads in different ligand-controlled cellular processes, such as in the arrest or stimulation of cell cycle progression and cell proliferation (Chapter 4), in the stimulation or inhibition of mesenchymal differentiation (Chapter 5), in apoptosis versus survival (Chapter 6), and in epithelial-to-mesenchymal transition (EMT) and vice versa (MET) (Chapter 7). In all of these chapters, the two 'faces' of the TGFβ-Smad system are clearly visible, as its signaling can elicit opposite effects depending on the players and/or the cellular context. For the developmental biologist,

the content of these chapters somehow suffers from the fact that much of the initial work is inherently linked to cell culture. A chapter on the role of TGFβ signaling in hematopoiesis or in heart development (to name but a few) would have been equally welcome. Chapter 5, however, does present a very nice picture of the mechanisms through which BMP-activated Smads promote, and TGFβ-activated Smad3 inhibits, osteoblast differentiation. It then compares this with adipocyte, chondrocyte and myocyte differentiation. Similarly, Chapter 7 gives a coherent and critical view of the role of Smad and non-Smad signaling in EMT/MET, which are studied both in vitro and in vivo. I appreciated very much the compilation in Chapter 8 of the currently available mouse models for studying Smads in development, disease and cancer. The time is indeed ripe to update this list and also the conclusions that can be drawn from conventional and tissue-specific Smad knockouts and double knockouts. However, the conditional mouse models discussed in this chapter are mainly ones in which gene function has been altered or abrogated in adult tissue or in relation to cancer rather than to embryogenesis.

**This is definitely an 'all-in' book ... a must for all of us working in the field of TGFβ signaling and Smad signal transduction**

The book then moves into more cell biological studies of the connection between the endocytic routing of receptors and Smad activation (Chapter 9) and the nuclear import and export of Smads (Chapter 10). Both of these processes contribute to the regulation of Smad availability and/or activity. Endocytosis does not exclusively serve to downregulate ligand-bound receptors, but is also crucial for the spatial and temporal regulation of Smad activation. Depending on the endocytic route taken (the best-studied are clathrin-mediated endocytosis towards early endosomes and the caveolar route to the caveosome), the cell responds differently, at least in cell culture. Unfortunately, the authors of this chapter, Christine Le Roy, Rohit Bose and Jeffrey Wrana, have not included recent findings that BMP receptor complexes not only assemble in different ways, but also that their differential routing can determine Smad versus non-Smad signaling. Recent insights (from the group of Eddy de Robertis) into the role of BMP-Smad linker-domain phosphorylation in the subcellular distribution of Smad proteins will be an appropriate addition to Chapter 10 in a future edition of this book. In addition to receptor endocytosis, the post-translational modification of Smads by phosphorylation (discussed in Chapter 12) and by ubiquitylation and sumoylation (covered in Chapter 13) also regulate Smad activation and functions. These two chapters provide an excellent entry into this rapidly evolving subfield.

Chapter 11, on the structure-function relationship of receptor-activated Smad proteins, is one of the best I have read in the field. It is excellently written and, as you might expect, excellently structured. The content of the chapter is timeless and will be a very important reference text for many of us in the future.

One of the nearly impossible tasks the authors, Kohei Miyazono, Shingo Maeda and Takeshi Imamura, faced was that of giving a comprehensive review of the Smad transcriptional partners. However, they succeeded in doing so in Chapter 14 by structuring this vast amount of information into sections on Smad complex-induced transcriptional activation and repression, respectively, and by their focus on the well-studied players. A concise introduction to the role of chromatin modulation itself would have been useful here, as would a discussion of the function(s) of multi-domain SIPs when they are not bound to Smad(s). The next chapter truly enforces the – sometimes fatalistic – view that TGFβ signaling has really been invented to interfere, or more diplomatically, to cross-signal, with many other signaling systems. How TGFβ signaling integrates with Wnt, Notch, Hedgehog, Jak/Stat, nuclear hormone receptor, NF-κB, HIF1 (hypoxia), p53, PKA and non-receptor kinases, is all compiled here. However, much of this work remains to be put into a physiological context. Similarly, the content of Chapters 15 and 16 (which covers the integration of Smad and MAP kinase pathways) is likely to be subject to rapid change.

The discussion of high-throughput or systems-based approaches for investigating TGFβ signaling comes with important words of caution from Erwin Böttinger and Wenjun Ju, and from Muneesh Tewari and Arvind Rao, the authors of Chapters 17 and 18, respectively. There is no doubt that a Smad protein can act as a true node in a signaling network, but much of this work is still descriptive and without quantitative predictions of system behavior if one of the TGFβ components is removed or downregulated. Finally, the remaining chapters discuss disease, notably the role of inhibitory Smads in human disease (Chapter 19), and the association of altered Smad signaling with carcinogenesis (Chapter 20). This chapter also provides a status report on the use of TGFβ receptor kinase inhibitors for cancer and fibrosis therapy.

This is definitely an 'all-in' book for those interested in or working on TGFβ receptor signal transduction in general and Smad proteins in particular. It will not entirely satisfy the developmental biologist, but it may well have not aimed to do so. However, it is a must for all of us working in the field of TGFβ signaling and Smad signal transduction, and for those of us who are teaching post-graduate courses in signal transduction. An important feature of this book, in this regard, is that many of its figures are available in color on an accompanying website.

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