TGF- β signalling unfolds

The TGF- β family

Edited by Rik Derynck and Kohei Miyazono

Cold Spring Harbor Monograph Series, 2008, \$135/£91

Reviewed by Stefano Piccolo

Research on TGF- β began thirty years ago, when it was first described as a secreted factor that induced a reversible, 'transformed' phenotype in cultured fibroblasts. From these pioneering efforts, research on TGF- β has grown into a large field, with more than 40,000 publications to date. For the many of us who find this amount of information overwhelming, *The TGF- β family*, edited by Rik Derynck and Kohei Miyazono, comes as a very welcome guide.

The book is a comprehensive review of the whole TGF- β family (including Activin and BMP ligands), nicely integrating a description of the biological effects with an in-depth definition of the molecular aspects of the signalling cascade. The first two chapters provide a critical basic introduction of TGF- β signalling, raising key questions and themes that are discussed in greater detail in subsequent chapters; for example, how can a simple transduction cascade regulate a bewildering diversity of cellular responses? What is the effect of the 'context' of the target cell, namely, of their genetic make-up and environment? How can specificity be attained at the level of the promoters regulated by this pathway? The remaining thirty-one chapters of the book are grouped into four sections: *Cell Biology*; *Signaling*; *Differentiation, Development, Physiology*; *Cancer and Disease*.

Signaling, the second section of the book, goes to the heart of the mechanisms that regulate the pathway. On the surface, the TGF- β cascade seems straightforward: Smads transcription factors transduce the signal from the receptors to the nucleus. However, this simplicity contrasts sharply with the complexity of the biological effects of TGF- β . The book covers this critical aspect very well, detailing the multiple layers of regulation that impinge on the core components of the pathway. For example, two chapters are dedicated to the extracellular regulation of TGF- β ligands by soluble antagonists and by other factors affecting their availability.

TGF- β are morphogens and, as such, quantitative aspects of the signal they generate, such as its strength and duration, are as crucial as the signal itself. The book sheds light on this enigmatic issue by presenting the comprehensive set of regulatory modifications and co-factors that affect receptor activity and trafficking, as well as the connections between the

post-translational modifications of Smads and their nucleo-cytoplasmic shuttling or transcriptional activities. As thoroughly discussed, this complexity is in part attained by extensive feedback loops and by the cross-talk between the TGF- β and BMP pathways with other signalling cascades. Smads interact with multiple transcription factors, but the specific relevance of these events is difficult to capture from the bulk of the available literature. The authors successfully draw the attention of the reader to the most critical transcriptional complexes that cooperate to achieve target gene regulation by Smads.

Another welcome strength of the book is the recognition that many of the principles that shape our understanding of the pathway have come from studying model organisms. The third section deals with the role of TGF- β and BMP in embryonic development and clearly exposes how the genetic dissection of the pathway in mouse and *Drosophila melanogaster* early embryos is essential to build and refine the framework of these pathways. The *Xenopus* embryo has been equally invaluable; I was pleased to see clearly outlined some of the most direct and reliable bioassays in the TGF- β field that can be performed in this system. These assays still serve as powerful tools to identify new components of the pathway. In general, a notable feature of the book is that aspects of TGF- β biology so far dispersed in the specialized literature are now reviewed in a precise and balanced manner. This is particularly useful for anyone beginning to work in these fields: examples are the chapters on TGF- β in stem cells, or in skeletal and haematopoietic cells.

The last section of the book covers the wide range of topics related to the role of TGF- β in cancer and disease. TGF- β has emerged as one of the most potent inhibitors of cell proliferation, through direct effects on target cells or, indirectly, by regulating the microenvironment. The book offers a useful list of the genetic evidence in mouse and humans that link mutations in components of the cascade to cancer initiation and progression. The book also attempts to explain the paradoxical duality of TGF- β in cancer, acting as a tumour suppressor in normal cells and early tumours, but as a promoter of malignancy in advanced stages of the disease. The latter responses depend on autocrine and paracrine effects of TGF- β on tumour cells and on its cross-talk with the microenvironment, which ultimately leads to epithelial-mesenchymal transition, cell movement, immune suppression and metastasis. The sophisticated nature of TGF- β signalling and its pleiotropic functions in cancer present not only a challenge but also an opportunity to develop new strategies for therapeutic intervention. From this perspective, the book captures and summarizes the most recent trends in therapeutic approaches based on the knowledge of the mechanism of action of TGF- β .

In summary, I found *The TGF- β family* a great book. Tables and illustrations will surely prove useful in guiding the reader through complex problems and the book can be certainly recommended for teaching purposes. The clarity and comprehensiveness of the monograph, the eminence of the editors and authors, and the extensive bibliography at the end of each chapter make this book a 'must-have' reference for established investigators and clinicians and for newcomers attracted to TGF- β from various fields.

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