The *magnum opus* of a tough scientist

The Regulatory Genome: Gene Regulatory Networks in Development and Evolution

By Eric H Davidson

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Reviewed by Nori Satoh

Five years after the publication of his third monograph, *Genomic Regulatory Systems*, Eric H. Davidson, one of the true pioneers in the realm of developmental genomics, has published another monograph, entitled *The Regulatory Genome*. Based on recent dramatic advances, the book aims to deliver a profound synthesis of the structure of gene regulatory networks and their roles in embryological development and the evolution of bilateral animals. With persuasive descriptions of *cis*-regulatory modules and their networks in relation to the genomic control of animal development, the author has constructed a new paradigm of embryology, evolutionary biology, genomics and systems biology.

One of the most spectacular phenomena in biology is the emergence of diverse animal shapes through embryogenesis, each shape being species-specific and having adapted over a long evolutionary history. The cellular and molecular mechanisms underlying this phenomenon have long been a hot topic of biological studies. The recent sequencing of the genomes of various animals has also revealed the immense complexity of this phenomenon. A key challenge is to coordinate knowledge obtained from studies at different levels to create a new and integrative understanding of developmental genomics.

From beginning to end, the author emphasizes the significant role of *cis*-regulatory modules of transcription factors and their structural and functional basis for regulation of genes responsible for development. Two fundamental processes govern embryogenesis of animals: control of gene expression via transcription factors, and signaling systems between cells. Davidson downplays the significance of signaling systems because signaling cannot achieve its aim, in many cases, if the signal cannot be read out as transcriptional control of target genes. Recent studies have also demonstrated a significant role of microRNAs in development. Again, however, Davidson downplays the potential role of microRNAs in development because microRNAs function mainly in the later phases of embryogenesis, not at the earlier stages responsible for the establishment of the basic body plan.

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In this book, Davidson has created several new terms, each having a precise definition. Most important are 'subcircuits' (small sets of genes and *cis*-regulatory elements functionally linked to execute a given developmental job), 'input and output linkages' (*cis*-regulatory controls on network subcircuits that either switch them on or repress them), 'plug-ins' (common subcircuits that are used for many different developmental functions), 'differentiation gene regulatory batteries' (sets of genes that respond to a common set of cell type–specific regulators with the functional and structural properties of that cell type) and 'kernels' (conserved subcircuits consisting of regulatory genes). Using these terms and the techniques of computational biology, he explains how we can understand the mystery of development—how a single cell, under precise spatiotemporal control, becomes an organism with a complex and functionally well-designed body plan.

The book begins with an introduction of his idea of the regulatory genome or the regulatory apparatus encoded in the genome. In the second chapter, he explains in detail *cis*-regulatory modules and the structural and functional basis of regulatory logic. Here the author emphasizes that comparison of genome sequences of different animals (or species) is helpful to identify highly conserved *cis*-regulatory modules. After a brief explanation in chapter 3 of animal development as a process of regulatory state specification, Davidson argues persuasively that *cis*-regulatory modules act as networks and that the gene regulatory networks are the key to understanding embryonic development (chapter 4) and evolutionary construction of various animal forms (chapter 5). It is also emphasized that computational and systems biological approaches are essential to create the networks. Every step of his logic is presented with examples to explain his idea, with beautiful, well-designed color figures. His concept of the significant roles of gene regulatory networks in development and evolution can be clearly understood using the aforementioned key terms. Namely, animal embryogenesis seems to be established by a complex combination of input and output linkages, plug-ins and differentiation gene regulatory batteries, usually in this order. The diversity of animal forms may be explained in terms of core kernels, alteration in deployment of plug-ins, input and output linkages and differentiation gene regulatory batteries. This order is important for understanding animal evolution at the level of phylum, class, order and family, respectively.

Davidson's previous book was a representation of the author's crude and rather fragmented idea of gene regulatory networks in animal development. The present book expands on this idea and should be read by all researchers, at least in the fields of embryology, evolutionary biology and genome sciences. The book is subtitled *Gene Regulatory Networks in Development and Evolution*, which describes more precisely what is presented here. However, the title *The Regulatory Genome* might reflect the author's ambition to bring developmental genomics into a new era by emphasizing the significance of the gene regulatory networks. Therefore, I strongly recommend this book to young scientists with multidisciplinary talents, who will advance the author's idea of the regulatory genome into its next phase, a voyage into the sea of genome complexity.

Finally, reading this book is a pleasure, as it allows us to touch the incredible spirit of a very tough scientist. Davidson has developed his idea of the gene regulatory network in development and evolution for more than 35 years and has raised it finally to the level of a real paradigm.