ANATOMY OF GENE REGULATION

A Three-Dimensional Structural Analysis

Determination of three-dimensional structures has revealed astonishing snapshots of molecules in action. No longer simple line drawings on a page, molecular structures can now be viewed in full-figured glory, often in color and even with interactive possibilities.

Anatomy of Gene Regulation is the first book to present the parts and processes of gene regulation at the three-dimensional level. Vivid structures of nucleic acids and their companion proteins are revealed in full-color, three-dimensional form. Beginning with a general introduction to three-dimensional structures, the book looks at the organization of the genome, the structure of DNA, DNA replication and transcription, splicing, protein synthesis, and ultimate protein death. The text discusses genetics and structural mechanics throughout. The concise and unique synthesis of information offers insight into gene regulation and into the development of methods to interfere with regulation at diseased states.

This textbook is appropriate for both undergraduate and graduate students in genetics, molecular biology, structural biology, and biochemistry courses.

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To my daughters
Isidora and Sol

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Preface

What is in the structure? It is, of course, quality!

The determination of the three-dimensional (3-D) structure of DNA in 1953 heralded the beginning of molecular biology. At the same time, we saw one of the first examples of how the 3-D structure of a biomolecule reveals its function. The 3-D structure of DNA immediately suggested how the genetic information is passed to the progeny. Eventually, the discovery of DNA structure led to the understanding of how genetic information accounts for the final product, which is protein synthesis. For the past 40 years, research in molecular biology has led to the identification of a cascade in gene regulation from its packing into chromosomes to transcription, splicing, modifications, protein synthesis, and, finally, the death of proteins. Eventually, knowledge of the mechanisms involved in these events led to manipulation of genes, recombinant DNA, and cloning technology, all of which helped us grasp the function of genes and their role in the study of differentiation, development, and diseases.

As the major players at all the different levels of gene regulation were discovered, it became apparent that the final mechanisms will be best revealed when we can observe the action of enzymes and genes at the 3-D level. Information gathered by biochemical and molecular experiments could identify the function of an enzyme, say the role of DNA polymerase in replication or the role of helicase in unwinding DNA. However, only by observing the process at the 3-D level can we visualize and fathom the mechanism by which the enzyme possesses such activity. In fact, we can visualize enzyme action not only at the molecular level but also at the atomic level.

All this was possible because of the development of technology to determine the 3-D structure of biological molecules. In this sense, molecular biology has given rise to atomic biology where interactions between

biomolecules and mechanisms can be resolved at the atomic level. These techniques have become better over the years and undoubtedly will become even better. So far, the determination of 3-D structures has revealed astonishing snapshots of molecules in action and has made secrets known. We are able now to virtually study the anatomy of molecular events.

In this book, I present the story of gene regulation with emphasis at the 3-D level, thus the title "Anatomy of Gene Regulation." Like surgeons (molecular surgeons), we can now open the nucleus and other organelles and, with extraordinary glasses, see the mechanisms unfolding at the atomic level. I have elected to begin our discussion with the packing (organization) of DNA in the nucleus and then to explore DNA replication, transcription, and splicing, followed by RNA modification. Next, we will follow the path of mRNA to the cytoplasm and its decoding during protein synthesis. The final chapter will consider the birth and death of proteins, which is the end of the regulation process.

Why did I undertake such a task? Even though I am not a structural biologist, I have been teaching molecular biology for nearly 15 years. Throughout my teaching career, I realized that most of the molecular biology textbooks were incredibly massive, full of more information than can be covered in one semester. Furthermore, textbooks in different disciplines overlap considerably. Most textbooks on microbiology, genetics, molecular or cellular biology, and even developmental biology contain chapters on the basic aspects of gene regulation. Students, therefore, are exposed to the same contents thoughout their education. I believe that, at least in the study of molecular biology, some changes are warranted. Consequently, I slowly started incorporating the 3-D aspects. I soon realized that my course was becoming more unique and exciting to the students. Finally, I decided that a molecular biology course that emphasized 3-D aspects must be beneficial to both undergraduate and graduate students. Determining the 3-D structure of a mechanism is the ultimate level that we should go to if we are to understand the mechanism. Therefore, all disciplines dealing with cellular and molecular events will eventually need to study them at the 3-D level.

Producing this text was very challenging. For every structure presented in the book, I read the corresponding paper(s) very carefully and extracted only the information that would produce a sequence that flows well and is accurate. Therefore, my book is by design short and concise. It focuses on the 3-D aspects of gene regulation only. However, it does not leave out information pertinent to molecular biology when structures are not involved. I intend to focus on the 3-D aspects of gene regulation and not to overwhelm the reader with details that can be found in many other general textbooks and courses. Each chapter is preceded by a section, which I call primer. This section outlines the general plan of the sequence that I follow

in the chapter. It should help keep the reader focused on the main aim of the text.

Even a book on 3-D structures can be overwhelming. For example, the structure of many different DNA polymerases must be solved. Likewise, we must know the 3-D structure of numerous transcriptional factors. Obviously, reporting all of them in a book would be tedious for the reader. Therefore, I have filtered the information and concentrated on a series of structures that best represent the desired style of the book and its aim, which is to acquaint the readers with the 3-D aspects of gene regulation. At the same time, I have tried not to compromise quality and accuracy. The structures are presented in different ways using different models. This technique is deliberate because some aspects of a 3-D structure are better depicted by one model than by others.

Such a synthesis has not been attempted before, so I am sure that there will be supporters and critics. I do count on both to provide me with valuable comments on this project so that can improve it in the future.

Finally, I am grateful to numerous colleagues who have furnished me with the figures that are included in the book. Without their help and co-operation, my book would have been impossible to produce. The reference list is not extensive and is concentrated mainly on the papers that deal with the 3-D structures. General references on standard molecular biology can be found in several excellent textbooks, which are cited in the reference section.

CREDITS

Several databases, which have cataloged available three-dimensional structures of proteins, were a big help. Throughout the book numerous images have been used from these databases. These databases follow:

Berman, H. M., Olson, W. K., Beveridge, D. L., Westbrook, J., Gelbin, A., Demesy, T., Hsieh, S-H., Srinivasan, A. R., and Schneider, B. (1992). The nucleic acid database: A comprehensive relational database of three-dimensional structures of nucleic acids (NDB). *Biophys. J.* 63: 751–9. http://ndbserver.rutgers.edu/NDB/NDBATLAS/

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