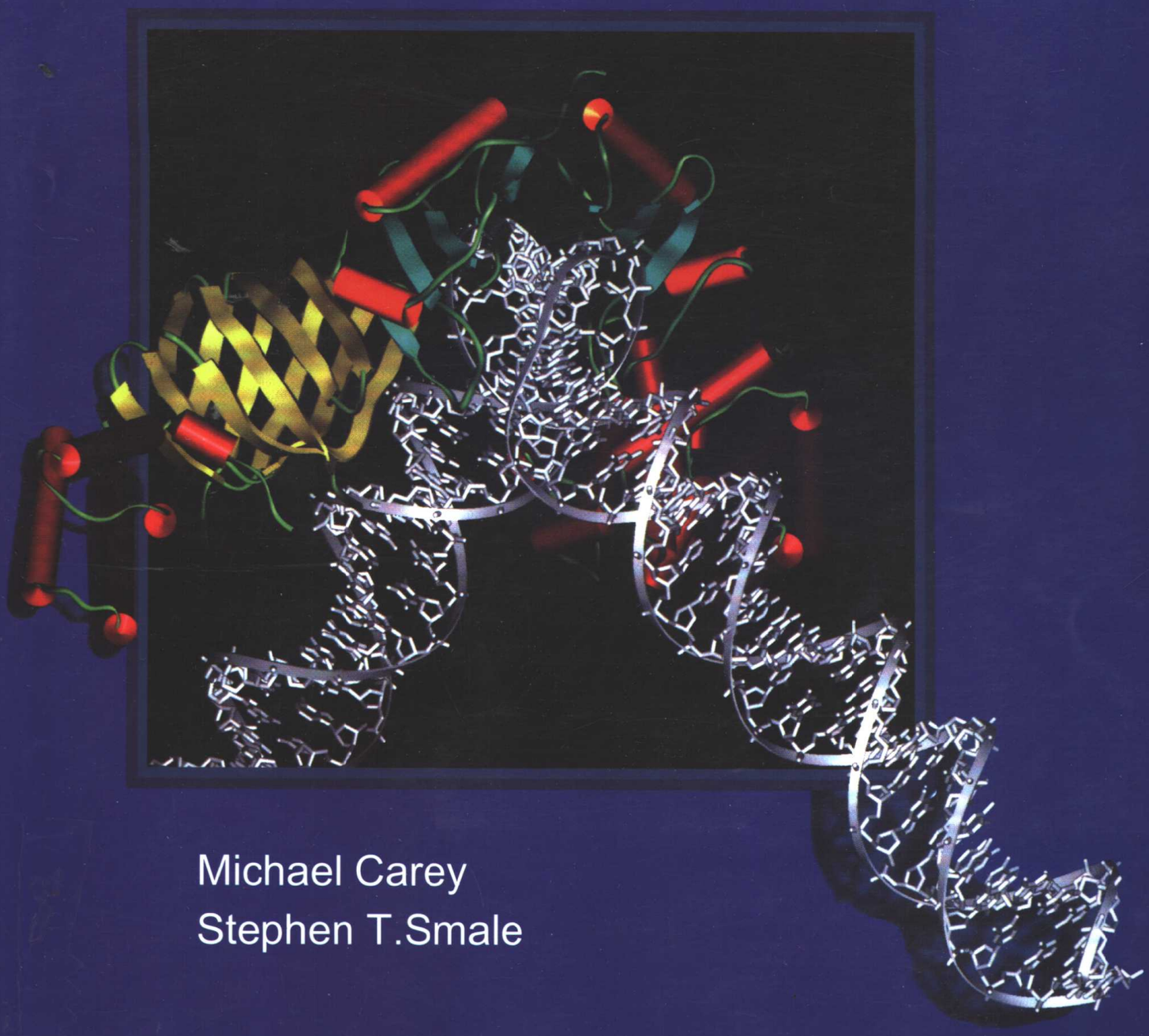
真核生物转录调控

Transcriptional Regulation in Eukaryotes

概念，策略和方法

Concepts, Strategies, and techniques



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CHAPTER 1

A Primer on Transcriptional Regulation in Mammalian Cells

INTRODUCTION

One of the central goals of the gene expression field is understanding how a mammalian organism regulates transcription of approximately 100,000 genes in the proper spatial and temporal patterns. Knowledge of how transcription factors function during this "differential" gene expression can be applied to fundamental issues in the fields of biology and medicine. To decipher these mechanisms, we need to understand the numerous processes influencing transcription and develop technical and strategic approaches for addressing them. This chapter provides an introduction to basic aspects of RNA polymerase II transcription. The goal is to prepare the novice for the issues raised in subsequent chapters and to provide a general overview of the field as of this writing. However, this field is evolving rapidly and the reader is encouraged to consult recent reviews in the literature. *Current Opinion in Cell Biology* and *Current Opinion in Genetics and Development* publish such reviews in the June and April issues, respectively. Some of the topics are quite advanced, although we have cited numerous review articles to allow the novice to explore unfamiliar areas. Almost all of the topics are covered in subsequent chapters and may help clarify concepts discussed briefly in this chapter.

A General Model for Regulation of a Gene

In eukaryotes, DNA is assembled into chromatin, which maintains genes in an inactive state by restricting access to RNA polymerase and its accessory factors. Chromatin is composed of histones, which form a structure called a nucleosome. Histones can be modified posttranslationally to decrease the ability of the nucleosome to inhibit transcription factor binding. Nucleosomes themselves are assembled into higher-order structures with different properties depending on the regulatory context. During the process of development,

genes are turned on and off in a pre-programmed fashion, a process that eventually generates cell specificity. This developmental program is orchestrated by transcription factors, which bind to specific DNA sites near genes they control. A single transcription factor is not dedicated to each regulatory event. Instead, a mechanism called combinatorial control is employed. In combinatorial control, different combinations of ubiquitous and cell-type-specific regulatory proteins are used to turn genes on and off in different regulatory contexts (Britten and Davidson 1969). The ability of an organism to employ small numbers of regulatory proteins to elicit a larger number of regulatory decisions is based on the principles of cooperativity and synergy, issues we discuss later in the chapter.

Activating a Gene

To provide a framework for the issues involved in transcription regulation, consider a model for how a typical gene is turned on (Fig. 1.1) and then off again. In a typical gene, a DNA sequence called the core promoter is located immediately adjacent to and upstream of the gene. The core promoter binds RNA polymerase II (Pol II) and its accessory factors ("the general transcription machinery") and directs the Pol II to begin transcribing at the correct start site. In vivo, in the absence of regulatory proteins, the core promoter is generally inactive and fails to interact with the general machinery. A caveat is that some core promoters such as the heat-shock promoter in *Drosophila* and the Cyc-1 promoter in yeast appear to contain partial complements of general factors (i.e., RNA Pol and TATA box-binding protein [TBP], respectively) when inactive, but these factors are insufficient for transcription in the absence of regulatory proteins. Immediately upstream of the core promoter is a regulatory promoter, and farther away either upstream or downstream are enhancer sequences (Fig. 1.1A). Regulatory promoters and enhancers bind proteins called activators, which "turn on" or activate transcription of the gene. Activation generally occurs by recruitment of the general machinery to the core promoter via interactions between the activator bound to promoter DNA and the general machinery in solution. Some activators are ubiquitously expressed, whereas others are restricted to certain cell types, regulating genes necessary for a particular cell's function.

To activate a gene, the chromatin encompassing that gene and its control regions must be altered or "remodeled" to permit transcription. There are different levels of modification needed at different levels and stages of the transcription process. Higher-order chromatin structures comprising networks of attached nucleosomes must be decondensed, specific nucleosomes over gene-specific enhancers and promoters must be made accessible to cell-specific activators, and, finally, nucleosomes within the gene itself must be remodeled to permit passage of the transcribing RNA polymerases (Fig. 1.1B). There are different types of enzymes involved in chromatin remodeling and these must be directed, perhaps by a limited set of activators or other sequence-specific DNA-binding proteins, to the "target" genes. These enzymes fall into two broad classes: ATP-dependent remodeling enzymes and histone acetyltransferases (or simply histone acetylases). Once they bind near a gene, these enzymes remodel the chromatin so that other activators and the general machinery can bind. The mechanisms of remodeling are unclear, but they involve changes in the structure of chromatin and in modification of histones that somehow increase accessibility to transcription factors. Remodeling achieved at a local level affects only the chromatin close to a gene. In some instances, however, a single gene or locus of related genes might spread over 100 kb or more. In these cases, genes might be under control of not simply specific enhancers and regulatory promoters but also of locus control regions

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