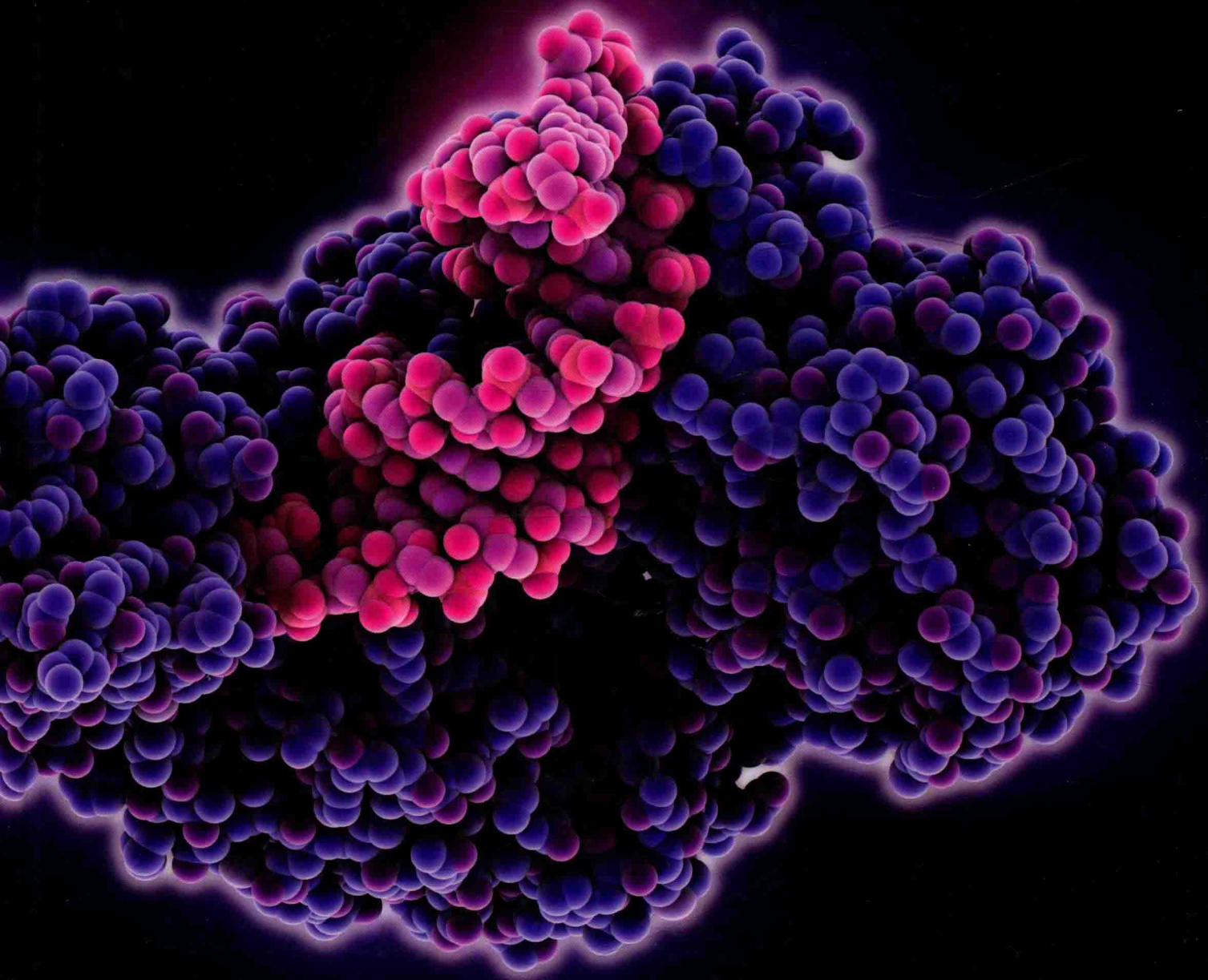
LEWIN'S GENES XII



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LEWIN'S GENES XII

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DEDICATION

To Benjamin Lewin, for setting the bar high.

To my mother, Ellen Baker, for raising me with a love of science; to the memory of my stepfather, Barry Kiefer, for convincing me science would stay fun; to my wife, Susannah Morgan, for decades of love and support; and to my young sons, Rhys and Frey, clearly budding young scientists ("I have a hypopesis"). Finally, to the memory of my Ph.D. mentor Dr. Marietta Dunaway, a great inspiration who set my feet on the exciting path of chromatin biology.

—Jocelyn Krebs

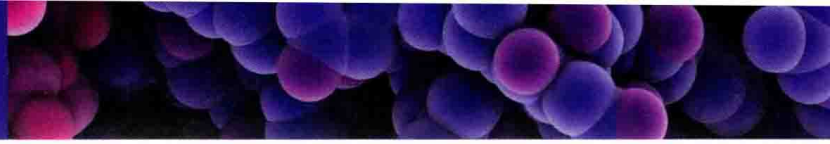
To my family: my wife, Suzanne, whose patience, understanding, and confidence in me are amazing; my children, Andy, Hyla, and Gary, who have taught me so much about using the computer; and my grandchildren, Seth and Elena, whose smiles and giggles inspire me. And to the memory of my mentor and dear friend, Lee A. Snyder, whose professionalism, guidance, and insight demonstrated the skills necessary to be a scientist and teacher. I have tried to live up to his expectations. This is for you, Doc.

—Elliott Goldstein

To my family: my wife, Lori, who reminds me what's really important in life; my children, Jennifer, Andrew, and Sarah, who fill me with great pride and joy; and my parents, Sandra and David, who inspired the love of learning in me.

—Stephen Kilpatrick

PREFACE



Of the diverse ways to study the living world, molecular biology has been most remarkable in the speed and breadth of its expansion. New data are acquired daily, and new insights into well-studied processes come on a scale measured in weeks or months rather than years. It's difficult to believe that the first complete organismal genome sequence was obtained a little over 20 years ago. The structure and function of genes and genomes and their associated cellular processes are sometimes elegantly and deceptively simple but frequently amazingly complex, and no single book can do justice to the realities and diversities of natural genetic systems.

This book is aimed at advanced students in molecular genetics and molecular biology. In order to provide the most current understanding of the rapidly changing subjects in molecular biology, we have enlisted leading scientists to provide revisions and content updates in their individual fields of expertise. Their expert knowledge has been incorporated throughout the text. Much of the revision and reorganization of this edition follows that of the third edition of *Lewin's Essential GENES*, but there are many updates and features that are new to this book. This edition follows a logical flow of topics; in particular, discussion of chromatin organization and nucleosome structure precedes the discussion of eukaryotic transcription, because chromosome organization is critical to all DNA transactions in the cell, and current research in the field of transcriptional regulation is heavily biased toward the study of the role of chromatin in this process. Many new figures are included in this book, some reflecting new developments in the field, particularly in the topics of chromatin structure and function, epigenetics, and regulation by noncoding RNA and microRNAs in eukaryotes.

This book is organized into four parts. **Part I (Genes and Chromosomes)** comprises Chapters 1 through 8. Chapter 1 serves as an introduction to the structure and function of DNA and contains basic coverage of DNA replication and gene expression. Chapter 2 provides information on molecular laboratory techniques. Chapter 3 introduces the interrupted structures of eukaryotic genes, and Chapters 4 through 6 discuss genome structure and evolution. Chapters 7 and 8 discuss the structure of eukaryotic chromosomes.

Part II (DNA Replication, Repair, and Recombination) comprises Chapters 9 through 16. Chapters 9 through 12 provide detailed discussions of DNA replication in plasmids, viruses, and prokaryotic and eukaryotic cells. Chapters 13 through 16 cover recombination and its roles in DNA repair and the human immune system, with Chapter 14 discussing DNA repair pathways in detail and Chapter 15 focusing on different types of transposable elements.

Part III (Transcription and Posttranscriptional Mechanisms) includes Chapters 17 through 23. Chapters 17 and 18 provide more in-depth coverage of bacterial and eukaryotic transcription. Chapters 19 through 21 are concerned with RNA, discussing messenger RNA, RNA stability and localization, RNA processing, and the catalytic roles of RNA. Chapters 22 and 23 discuss translation and the genetic code.

Part IV (Gene Regulation) comprises Chapters 24 through 30. In Chapter 24, the regulation of bacterial gene expression via operons is discussed. Chapter 25 covers the regulation of expression of genes during phage development as they infect bacterial cells. Chapters 26 through 28 cover eukaryotic gene regulation, including epigenetic modifications. Finally, Chapters 29 and 30 cover RNA-based control of gene expression in prokaryotes and eukaryotes.

For instructors who prefer to order topics with the essentials of DNA replication and gene expression followed by more advanced topics, the following chapter sequence is suggested:

Introduction: Chapter 1
Gene and Genome Structure: Chapters 4–6
DNA Replication: Chapters 9–12
Transcription: Chapters 17–20
Translation: Chapters 22–23
Regulation of Gene Expression: Chapters 7–8 and 24–30

Other chapters can be covered at the instructor's discretion.

THE STUDENT EXPERIENCE

This edition contains several features to help students learn as they read:

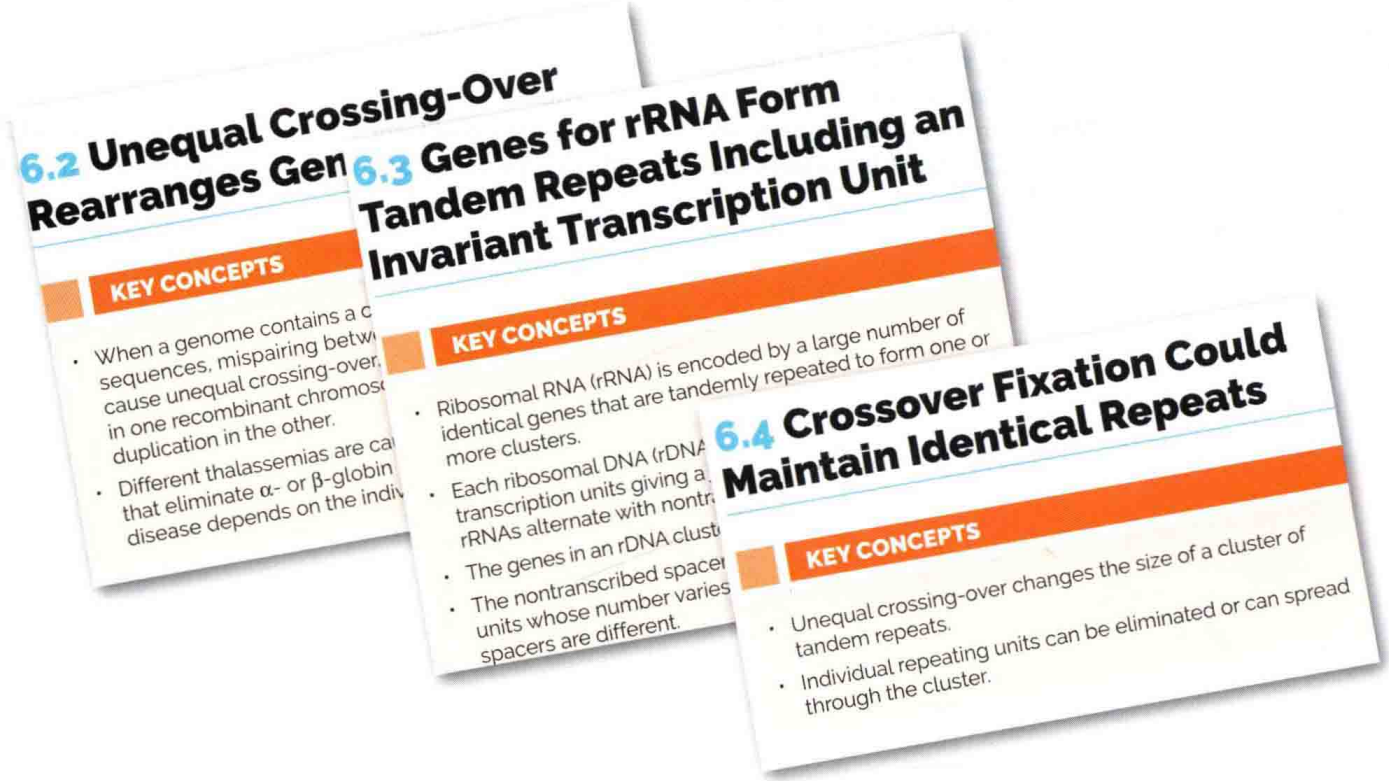
- Each chapter begins with a **Chapter Outline** that clearly lays out the framework of the chapter and helps students plan their reading and study.

DNA Replication

CHAPTER OUTLINE

11.1 Introduction
11.2 DNA Polymerases Are the Enzymes That Make DNA
11.3 DNA Polymerases Have Various Nuclease Activities
11.4 DNA Polymerases Control the Fidelity of Replication
11.5 DNA Polymerases Have a Common Structure
11.6 The Two New DNA Strands Have Different Modes of Synthesis
11.7 Replication Requires a Helicase and a Single-Stranded Binding Protein
11.8 Priming Is Required to Start DNA Synthesis
11.9 Coordinating Synthesis of the Lagging and Leading Strands
11.10 DNA Polymerase Holoenzyme Consists of Subcomplexes
11.11 The Clamp Controls Association of Core Enzyme with DNA
11.12 Okazaki Fragments Are Linked by Ligase
11.13 Separate Eukaryotic DNA Polymerases Undertake Initiation and Elongation
11.14 Lesion Bypass Requires Polymerase Replacement
11.15 Termination of Replication

- Each section is summarized with a bulleted list of **Key Concepts** to assist students with distilling the focus of each section.



6.2 Unequal Crossing-Over Rearranges Gen

KEY CONCEPTS

- When a genome contains a c
sequences, mispairing betw
cause unequal crossing-over,
in one recombinant chromos
duplication in the other.
- Different thalassemias are ca
that eliminate α- or β-globin
disease depends on the indiv

6.3 Genes for rRNA Form Tandem Repeats Including an Invariant Transcription Unit

KEY CONCEPTS

- Ribosomal RNA (rRNA) is encoded by a large number of identical genes that are tandemly repeated to form one or more clusters.
- Each ribosomal DNA (rDNA
transcription units giving a
rRNAs alternate with nontr
- The genes in an rDNA clust
- The nontranscribed spacer
units whose number varies
spacers are different.

6.4 Crossover Fixation Could Maintain Identical Repeats

KEY CONCEPTS

- Unequal crossing-over changes the size of a cluster of tandem repeats.
- Individual repeating units can be eliminated or can spread through the cluster.

- *GENES XII* includes the high-quality **illustrations and photographs** that instructors and students have come to expect in this classic title.

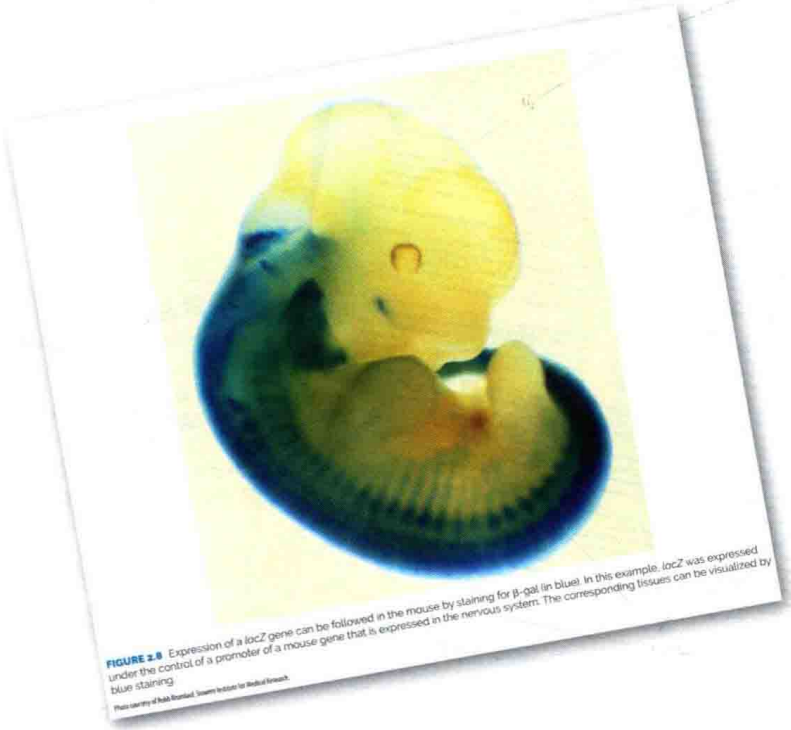


FIGURE 2.8 Expression of a *lacZ* gene can be followed in the mouse by staining for β-gal (in blue). In this example, *lacZ* was expressed under the control of a promoter of a mouse gene that is expressed in the nervous system. The corresponding tissues can be visualized by blue staining.

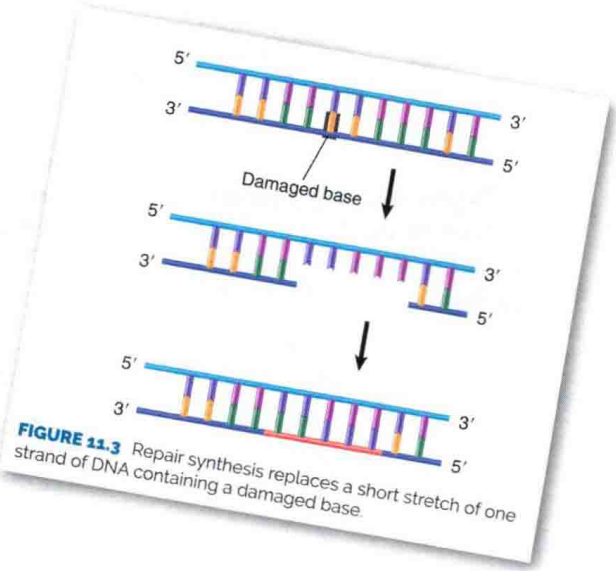


FIGURE 11.3 Repair synthesis replaces a short stretch of one strand of DNA containing a damaged base.

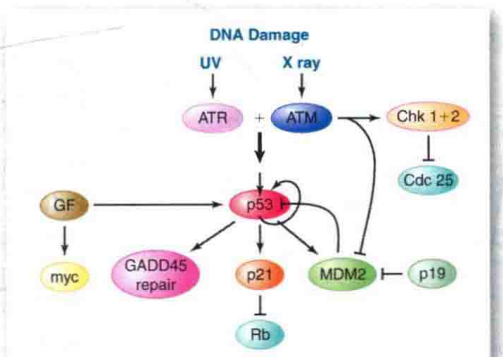


FIGURE 9.16 DNA damage pathway. p53 is activated by DNA damage. Activated p53 halts the cell cycle through Rb and stimulates DNA repair. p53 is regulated by a complex set of activators and inhibitors.

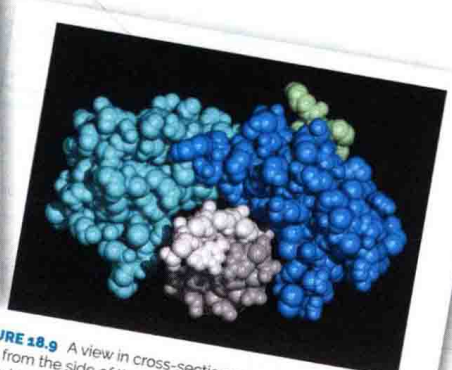


FIGURE 18.9 A view in cross-section shows that TBP surrounds DNA from the side of the narrow groove. TBP consists of two related (40% identical) conserved domains, which are shown in light and dark blue. The N-terminal region varies extensively and is shown in green. The two strands of the DNA double helix are in light and dark gray.

Photo courtesy of Stephen K. Burley.

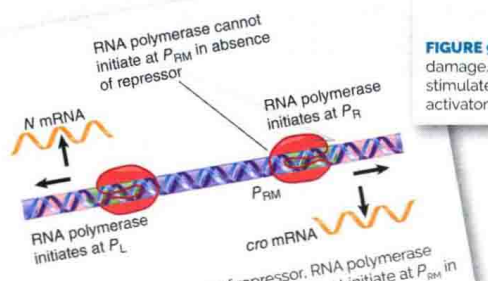


FIGURE 25.16 In the absence of repressor, RNA polymerase initiates at the left and right promoters. It cannot initiate at P_{RM} in the absence of repressor.

- **Key Terms** are highlighted in bold type in the text and compiled in the **Glossary** at the end of the book.

GLOSSARY

10-nm fiber A linear array of nucleosomes generated by unfolding from the natural condition of chromatin.

-10 element The consensus sequence centered about 10 bp before the start point of a bacterial gene. It is involved in melting DNA during the initiation reaction.

14-3-3 adaptors A family of seven evolutionarily conserved and highly homologous adaptors that form homo- or heterodimers and/or tetramers and that bind a multitude of protein and DNA ligands through either the amphipathic groove or the outer surface. They regulate diverse cell homeostasis events, such as signal transduction, survival, cell cycle progression, and DNA replication, as well as cell differentiation processes, such as class switch recombination (CSR).

2R hypothesis The hypothesis that the early vertebrate genome underwent two rounds of duplication.

3′ untranslated region (UTR) The region in an mRNA between the termination codon and the end of the message.

30-nm fiber A coil of nucleosomes. It is the basic level of organization of nucleosomes in chromatin.

-35 element The consensus sequence centered about 35 bp before the start point of a bacterial gene. It is involved in initial recognition by RNA polymerase.

5′-AGCT-3′ Repeats that occur at a high frequency in Ig switch regions, but not in the genome at large. They are specifically bound by 14-3-3 adaptors and other class switch recombination (CSR) elements. They are important for CSR targeting.

5′ end resection The generation of 3′ overhanging single-stranded regions that occurs via exonucleolytic digestion of the 5′ ends at a double-strand break.

5′ untranslated region (UTR) The region in an mRNA between the start of the message and the first codon.

A complex The second splicing complex; it is formed by the binding of U2 snRNP to the E complex.

A domain The conserved 11-bp sequence of A-T base pairs in the yeast ARS element that comprises the replication origin.

A site The site of the ribosome that an aminoacyl-tRNA enters to base pair with the codon.

Abortive initiation Describes a process in which RNA polymerase starts transcription but terminates before it has left the promoter. It then reinitiates. Several cycles may occur before the elongation stage begins.

Abundance The average number of mRNA molecules per cell.

Abundant mRNA Consists of a small number of individual molecular species, each present in a large number of copies per cell.

Ac (Activator) element An autonomous transposable element in maize.

Acentric fragment A fragment of a chromosome (generated by breakage) that lacks a centromere and is lost at cell division.

Acridines Mutagens that act on DNA to cause the insertion or deletion of a single base pair. They were useful in defining the triplet nature of the genetic code.

Activation-induced (cytidine) deaminase (AID) An enzyme that removes the amino group from the cytidine base in DNA; mediates DNA damage that leads to the initiation of immunoglobulin (Ig) diversification.

Activator A protein that stimulates the expression of a gene, typically by interacting with a promoter to stimulate RNA polymerase. In eukaryotes, the sequence to which it binds in the promoter is called an enhancer.

Activator (Ac) element An autonomous transposable element in maize.

Adaptive (acquired) immunity The response mediated by lymphocytes that are activated by their specific interaction with antigen. The response develops over several days as lymphocytes with antigen specific receptors are stimulated to proliferate and become effector cells. It is responsible for immunological memory.

Addiction system A survival mechanism used by plasmids. The mechanism kills the bacterium upon loss of the plasmid.

Agrocinic plasmids Plasmids that carry genes coding for the synthesis of opines of the agrocinic type. The tumors usually die early.

AID See **activation-induced (cytidine) deaminase**.

Allele One of several alternative forms of a gene occupying a given locus on a chromosome.

Allelic exclusion The expression in any particular lymphocyte of only one allelic coding for the expressed immunoglobulin heavy or light chains. This is caused by feedback from the first immunoglobulin allele to be expressed that prevents activation of the allelic on the other chromosome.

Allolactose A byproduct of β-galactosidase (encoded by LacZ), the true inducer of the lac operon.

Allopolyploidy Polyploidization resulting from hybridization between two different but reproductively compatible species.

Allosteric control The ability of a protein to change its conformation (and therefore activity) at one site as the result of binding a small molecule to a second site located elsewhere on the protein.

Alternative splicing The production of different RNA products from a single product by changes in the usage of splicing junctions.

Alu element One of a set of dispersed, related sequences, each approximately 300 bp long. In the human genome (members of the SINE family). The individual members have Alu cleavage sites at each end.

Amber codon The triplet UAG, one of the three termination codons that end polypeptide translation.

Amplicon The precise, primer-to-primer, double-stranded nucleic acid product of a PCR or RT-PCR reaction.

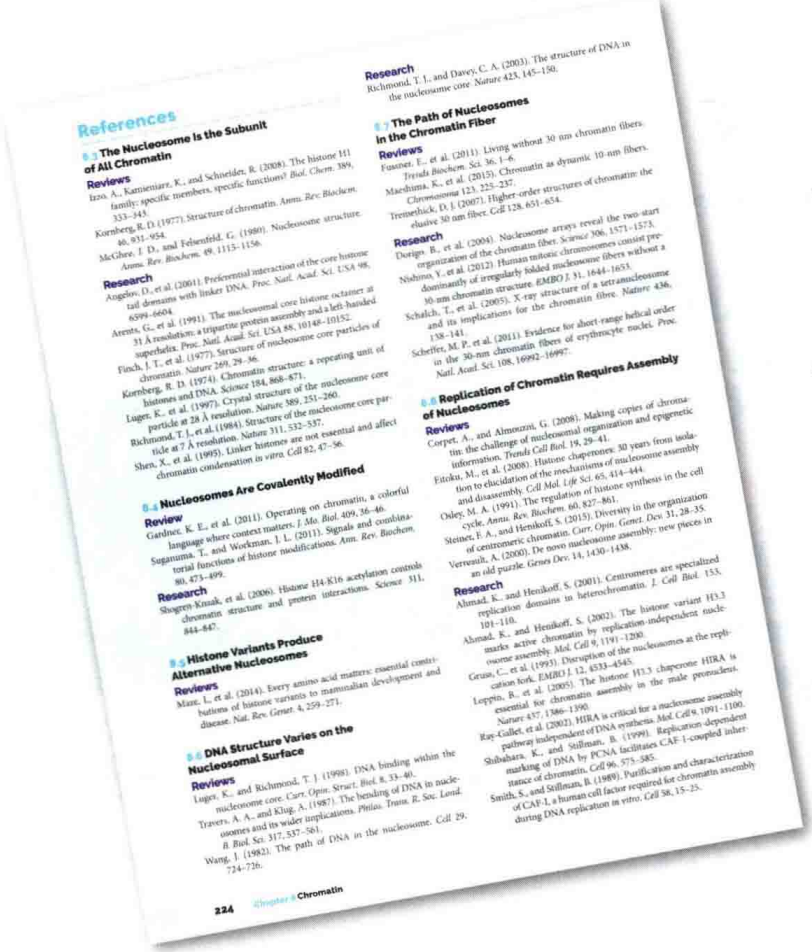
Amyloid fibers Insoluble fibrous protein polymers with a cross β-sheet structure generated by prions or other dysfunctional protein aggregations (such as in Alzheimer's disease).

Annealing The renaturation of a duplex structure from single strands that were obtained by denaturing duplex DNA.

Anti-Sm An autoimmune antiserum that defines the Sm domain that is common to a group of proteins found in snRNPs that are involved in RNA splicing.

Antibody A protein that is produced by B lymphocytes and that binds a particular antigen. Consists of two identical light chains (disulfide bond–linked to two identical heavy chains. They are synthesized in membrane bound and secreted forms. Those produced during an immune response recruit effector functions to help neutralize and eliminate the pathogen.

Glossary 783



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8.3 The Nucleosome Is the Subunit of All Chromatin

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8.7 The Path of Nucleosomes in the Chromatin Fiber

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- Each chapter concludes with an expanded and updated list of **References**, which provides both primary literature and current reviews to supplement and reinforce the chapter content.
- Additional online study tools are available for students and instructors, including practice activities, prepopulated quizzes, and an interactive eBook with **Web Links** to relevant sites, including animations and other media.

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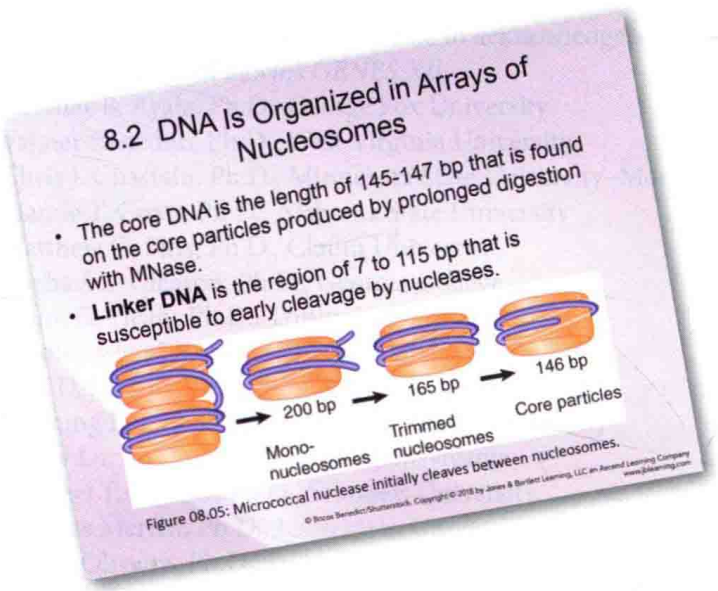
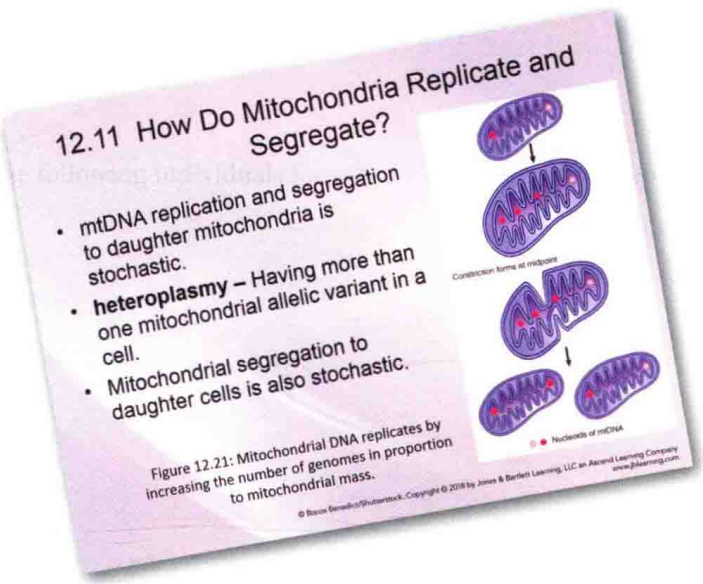
A variety of teaching tools are available via digital download and multiple other formats to assist instructors with preparing for and teaching their courses with *Lewin's GENES XII*:

- The **Lecture Outlines in PowerPoint format** presentation package developed by author Stephen Kilpatrick of the University of Pittsburgh at Johnstown provides outline summaries and relevant images for each chapter of *Lewin's GENES XII*. Instructors with Microsoft PowerPoint software can customize the outlines, art, and order of presentation.





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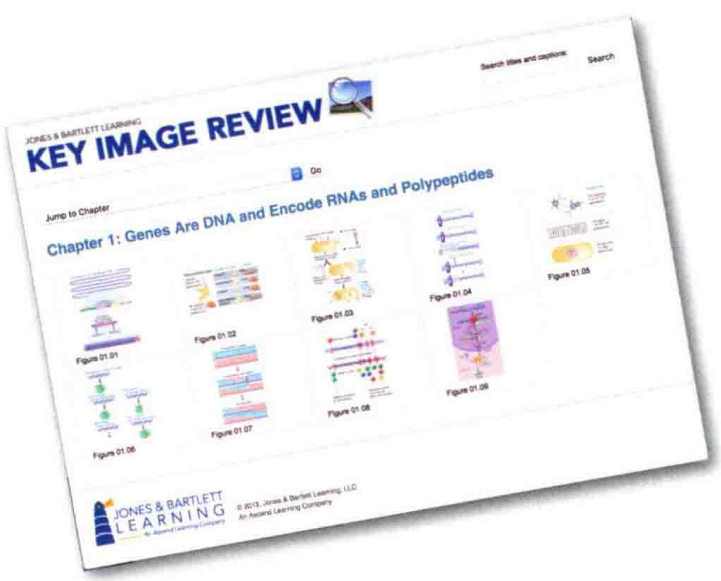

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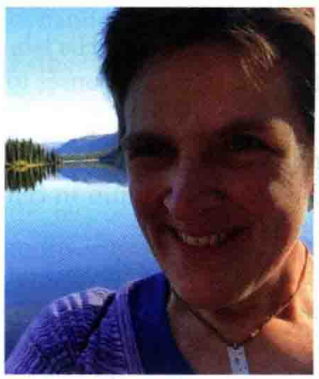

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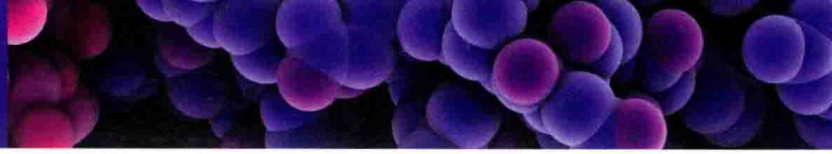

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