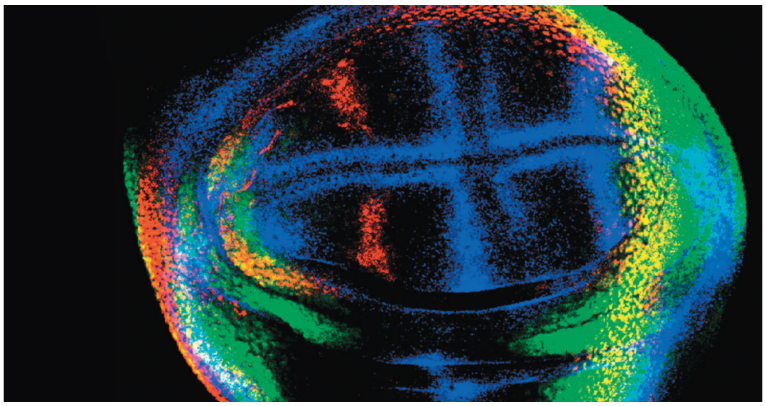

Chapter 18: Regulation of Gene Expression

AP Biology 2013

1

Gene Regulation

- Prokaryotes and eukaryotes alter their gene expression in response to their changing environment
- In multicellular eukaryotes, gene expression regulates development and is responsible for differences in cell types
  - RNA molecules play a role in regulating this

2

Bacteria

- Natural selection favors bacteria that produce only those products needed by the cell
- A cell can regulate the production of enzymes by feedback inhibition or by gene regulation
- In bacteria this is controlled by operons

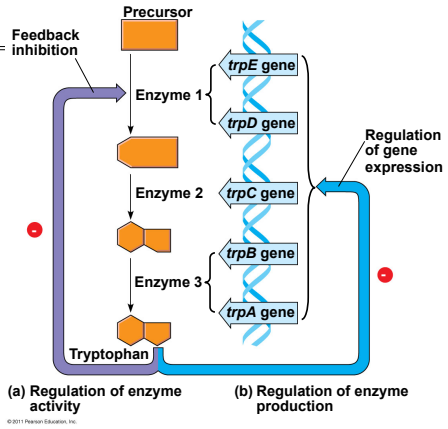

Fig. 18.2

3

Operons

- Cluster of functionally related genes under coordinated control by a single "on-off switch" that includes the operator, promoter, and genes they control
- Regulatory "switch" is a segment of DNA called an **operator** which is usually positioned within the promoter
- Operon can be switched off by a **repressor** protein (works by binding to the operator and blocking RNA polymerase)
  - Repressor is the product of a separate **regulatory gene**
  - Repressor can be in an active or inactive form depending on the presence of other molecules
  - **Corepressor** is a molecule that cooperates with a repressor protein to shut off an operon

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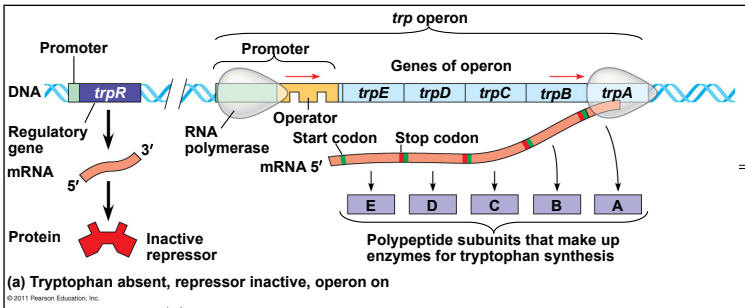
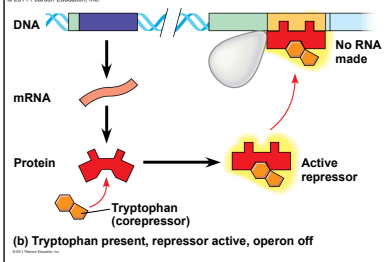


Fig. 18.3



- *E. coli* synthesizes the amino acid tryptophan
- *Trp* operon is on by default
- When tryptophan is present, it binds to the *trp* repressor protein which turns the operon off (acts as a corepressor)

Ex. *Trp* Operon

5

Repressible and Inducible Operons

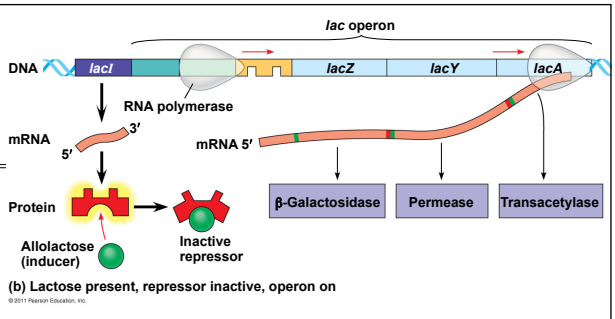
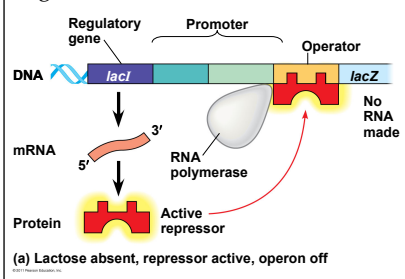


Fig. 18.4



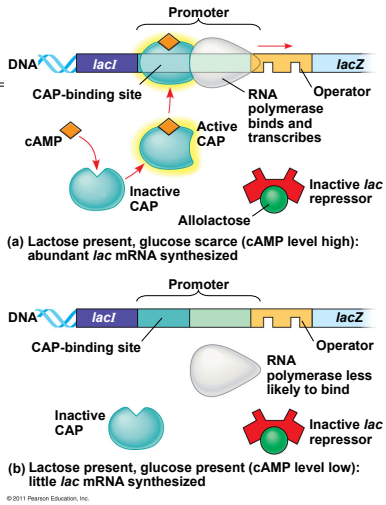
- Repressible operon is usually on (binding of a repressor shuts it off)
  - Ex. *trp* operon
- Inducible operon is usually off (binding of an **inducer** inactivates the repressor and turns on transcription)
  - Ex. *lac* operon - contains genes that code for enzymes used in hydrolysis and metabolism of lactose

6

Positive Gene Regulation

- Positive control caused by a stimulatory protein called an **activator** of transcription (ex. catabolite activator protein - CAP)
  - When glucose is scarce, CAP is activated by binding with cyclic AMP (cAMP)
  - Activated CAP attaches to the promoter of the *lac* operon and increases the affinity of RNA polymerase (accelerating transcription)
  - When glucose levels increase, CAP detaches from the *lac* operon and transcription returns to a normal rate
  - CAP helps regulate other operons that encode enzymes used in catabolic pathways

Fig. 18.5

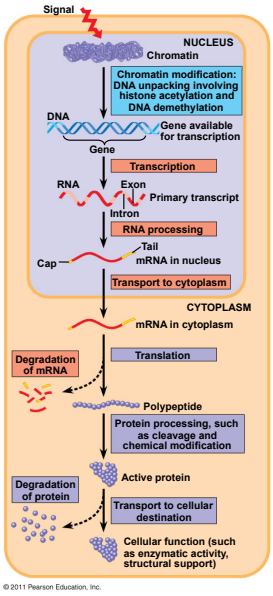


7

Eukaryote Gene Expression

- All organisms must regulate which genes are expressed at any given time
- In multicellular organisms, regulation of gene expression is essential for cell specialization
- Since almost all cells in an organism are genetically identical, differences between cell types result from differential gene expression (expression of different genes by cells with the same genome)
- Abnormalities in gene expression can lead to diseases including cancer
- Gene expression is regulated at many stages

Fig. 18.6

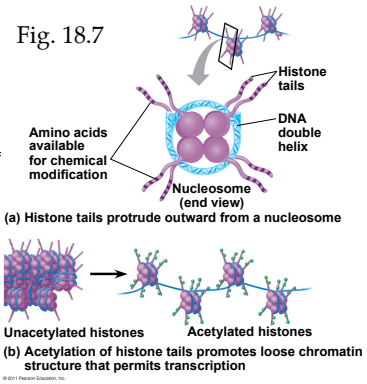


8

Regulation of Chromatin Structure

- Genes with highly packed heterochromatin are usually not expressed
- Chemical modifications to histones and DNA of chromatin influence both chromatin structure and gene expression
  - Histone acetylation - acetyl groups are attached to positively charged lysines in histone tails which loosens chromatin structure (promoting transcription)

Fig. 18.7



- Adding methyl groups (methylation) condenses chromatin
- If phosphate groups are added to the methylated amino acid, the chromatin is loosened.

9

DNA Methylation

- Adding methyl groups to certain bases in DNA is associated with reduced transcription in some species
- DNA methylation can cause long-term inactivation of genes in cellular differentiation
- In genomic imprinting, methylation regulates expression of either the maternal or paternal alleles of certain genes at the start of development

10

Epigenetic Inheritance

- Although chromatin modifications do not alter DNA sequences, they can be passed on to future generations **of cells**
- Inheritance of traits transmitted by mechanisms not directly involving the nucleotide sequence is called **epigenetic inheritance**

11

Organization of a Typical Eukaryotic Gene

- Most eukaryotic genes are associated with multiple **control elements** (segments of noncoding DNA that serve as binding sites for transcription factors that regulate transcription)

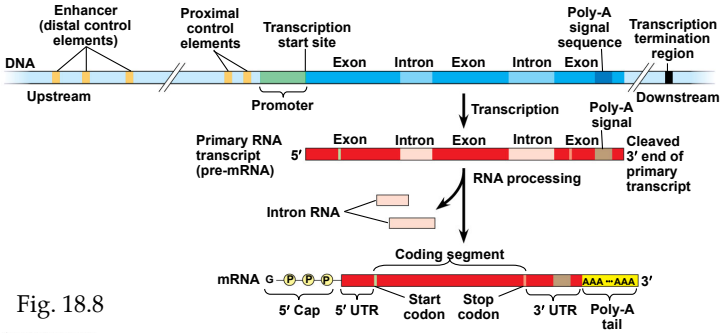
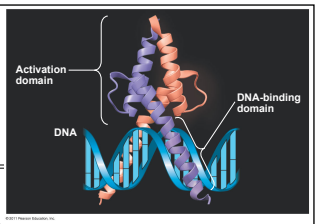


Fig. 18.8

12

Transcription Factors



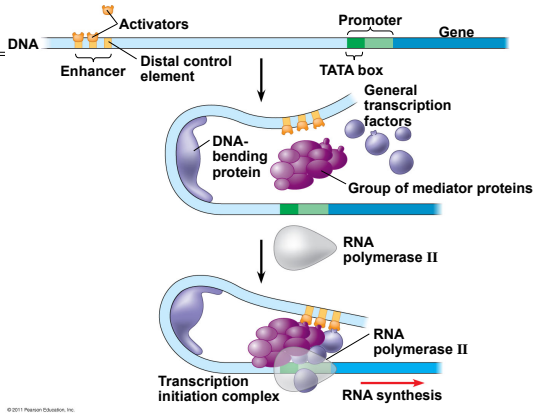
- To initiate transcription, eukaryotic RNA polymerase requires the assistance of proteins called **transcription factors** (essential for transcription of all protein-coding genes)

Fig. 18.9

- Proximal control elements are located close to the promoter. Distal control elements (called **enhancers**) may be far away from a gene or even located in an intron.
- An activator binds to an enhancer and stimulates transcription of a gene. (Activator has two domains - one binds to DNA and second activates transcription)

13

Transcription Factors



- Some act as repressors (inhibiting expression of a gene)
- Some activators and repressors act indirectly by influencing chromatin structure to promote or silence transcription

Fig. 18.10

14

Post-Transcriptional Regulation

- Transcription alone does not account for gene expression
- Regulatory mechanisms can operate at various stages after transcription (allow cell to fine-tune gene expression rapidly in response to environmental changes)
- Alternative RNA Splicing - different mRNA molecules are produced from the same primary transcript (depending on what is treated as exons and introns)
- mRNA Degradation - life-span of mRNA molecule in cytoplasm (eukaryotic mRNA lasts longer than prokaryotic mRNA)

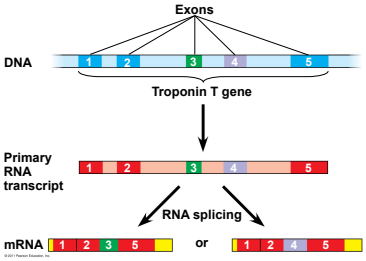


Fig. 18.13

15

Post-Transcriptional Regulation

- Protein processing
- Proteasomes are complexes that bind protein molecules and degrade them

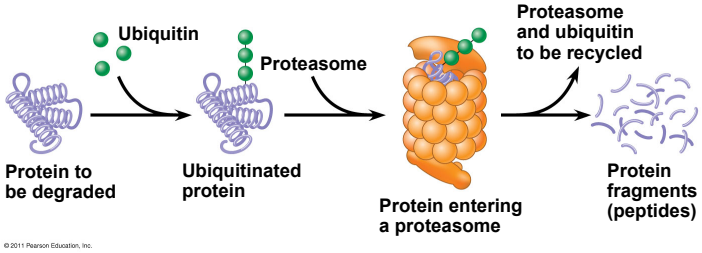


Fig. 18.14

16

Noncoding RNA

- Small fraction of DNA codes for proteins and a very small fraction of non-protein-coding DNA consists of genes for rRNA or tRNA
- Significant amounts of the genome may be transcribed into noncoding RNAs (ncRNAs) which can regulate gene expression at mRNA translation and chromatin configuration
- MicroRNAs (miRNAs) are small single-stranded RNA that can bind to mRNA to degrade or block translation

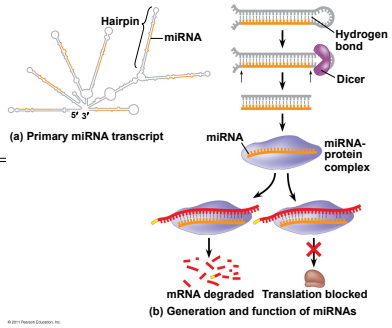


Fig. 18.15

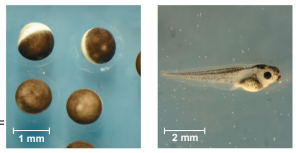
17

Noncoding RNA

- Inhibition of gene expression by RNA molecules is called RNA interference (RNAi)
- RNAi is caused by small interfering RNAs (siRNAs) - siRNAs and miRNAs are similar but form from different RNA precursors
- An increase in the number of miRNAs in a species may have allowed morphological complexity to increase over evolutionary time

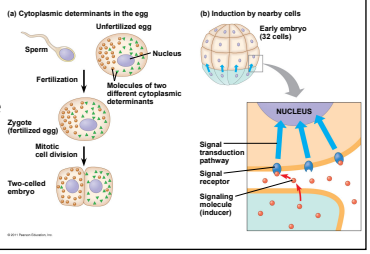
18

Differential Gene Expression



- During embryonic development, a fertilized egg gives rise to many different cell types which are organized into tissues, organs, organ systems, and the whole organism
- Transformation from a zygote to adult results from cell division, cell differentiation, and morphogenesis
  - Cell differentiation - process by which cells become specialized in structure and function
  - Morphogenesis - physical processes that give an organism its shape
  - Cytoplasmic determinants - maternal substances in the egg that influence early development

Figs. 18.16 & 18.17



19

Sequential Regulation

- Determination commits a cell to its final fate (happens before differentiation)
  - Differentiation is marked by the production of tissue-specific proteins
  - Ex. Myoblasts produce muscle-specific proteins and form skeletal muscle cells
    - *MyoD* is one of several "master regulatory genes" the produce proteins that commit the cell to becoming skeletal muscle
    - MyoD protein is a transcription factor that binds to enhancers of various target genes

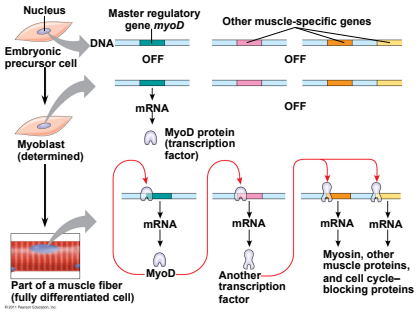


Fig. 18.18

20

Setting Up the Body Plan

- Pattern formation - development of spatial organization of tissues and organs (in animals begins with establishment of major axes)
- Positional information - molecular cues that control pattern formation, tells a cell its location relative to the body axes and to neighboring cells
  - Ex. *Drosophila melanogaster* (fruit fly) - cytoplasmic determinants in the egg determine the axes before fertilization

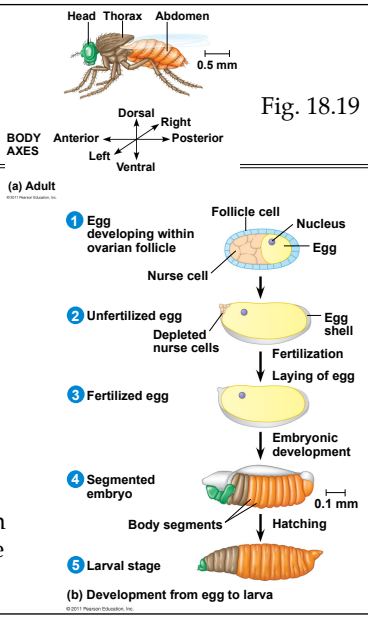
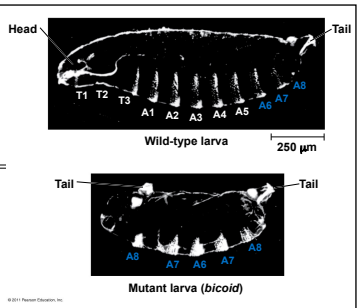


Fig. 18.19

21

Developmental Genes in *Drosophila*

Fig. 18.21



- Homeotic genes - control pattern formation in late embryo, larva, and adult stages
- Embryonic lethals - mutations that cause death during embryogenesis
- Maternal effect genes - encode for cytoplasmic determinants that establish the axes (also called egg-polarity genes)
  - Ex. Bicoid gene - if it is not functional, the fly will lack a front half and have duplicate posterior structures at both ends

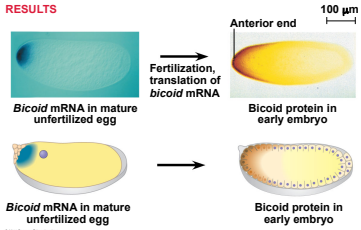


Fig. 18.22

22

Cancer

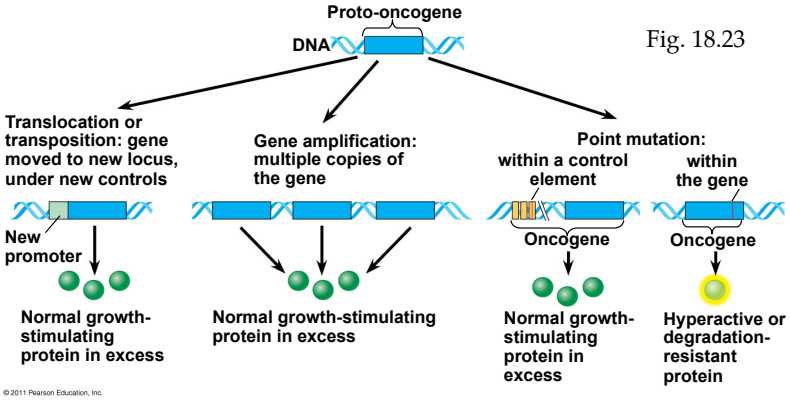
- Gene regulation systems that go wrong in cancer are the same systems involved in embryonic development

- Cancer is caused by mutations in genes that regulate cell growth and division
- Tumor viruses can also cause cancer in animals including humans
- Oncogenes - cancer-causing genes
- Proto-oncogenes - normal cellular genes responsible for normal cell growth and division
- Conversion of a proto-oncogene to an oncogene can lead to abnormal stimulation of the cell cycle
  - Conversion can be caused by movement of DNA near a promoter, amplification of a proto-oncogene, point mutations in the proto-oncogene or its control elements

23

Conversion of a Proto-oncogene

Fig. 18.23



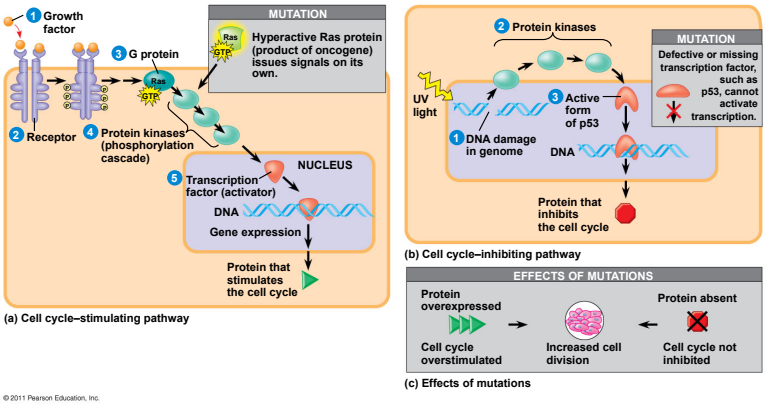
24

Tumor Suppressor Genes

- Help prevent uncontrolled cell growth
- Mutations that decrease production of tumor suppressor genes contribute to cancer onset
- Tumor suppressor proteins repair damaged DNA, control cell adhesion, and inhibit the cell cycle
- Mutations in the *ras* proto-oncogene and *p53* tumor suppressor gene are common in human cancers
  - Mutations in the *ras* gene leads to hyperactive Ras protein and increased cell division
  - p53 prevents a cell from passing on mutations due to DNA damage

25

Proto-oncogenes and Tumor Suppressor Genes

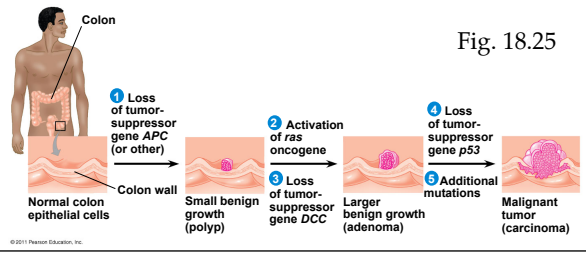


26

Multistep Model of Cancer Development

- Multiple mutations are generally needed for full-fledged cancer (this is why incidence increases with age)
- Usually requires at least one active oncogene and mutations in several tumor-suppressor genes
- Individuals can inherit oncogenes or mutant alleles of tumor suppressor genes

Fig. 18.25



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