Chapter 18

Control of Gene Expression

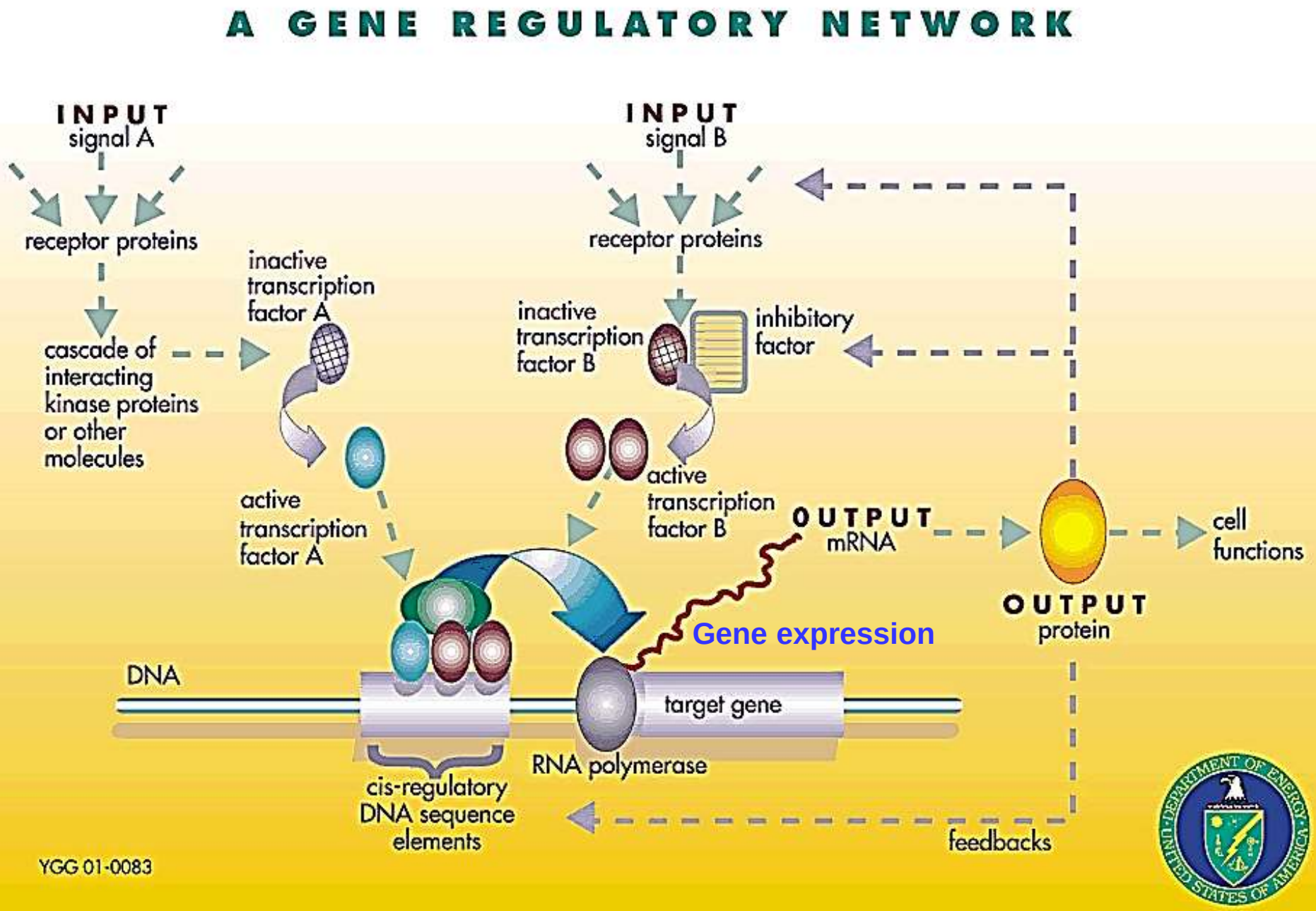
Modified by YJ Chuang at NTHU-DMS

Overview: **Differential Expression of Genes**

- Prokaryotes and eukaryotes alter gene expression in response to their changing environment
- In multi-cellular eukaryotes, gene expression regulates development and is responsible for differences in cell types
- Among other molecules, RNAs play many roles in regulating gene expression in eukaryotes

For example, **microRNA**

Key Concept


A GENE REGULATORY NETWORK
INPUT
signal A
receptor proteins
cascade of interacting kinase proteins or other molecules
inactive transcription factor A
active transcription factor A
INPUT
signal B
receptor proteins
inactive transcription factor B
inhibitory factor
active transcription factor B
OUTPUT
mRNA
OUTPUT
protein
cell functions
Gene expression
DNA
target gene
RNA polymerase
cis-regulatory DNA sequence elements
feedbacks
YGG 01-0083

Concept 18.1: Bacteria often respond to environmental change by regulating transcription

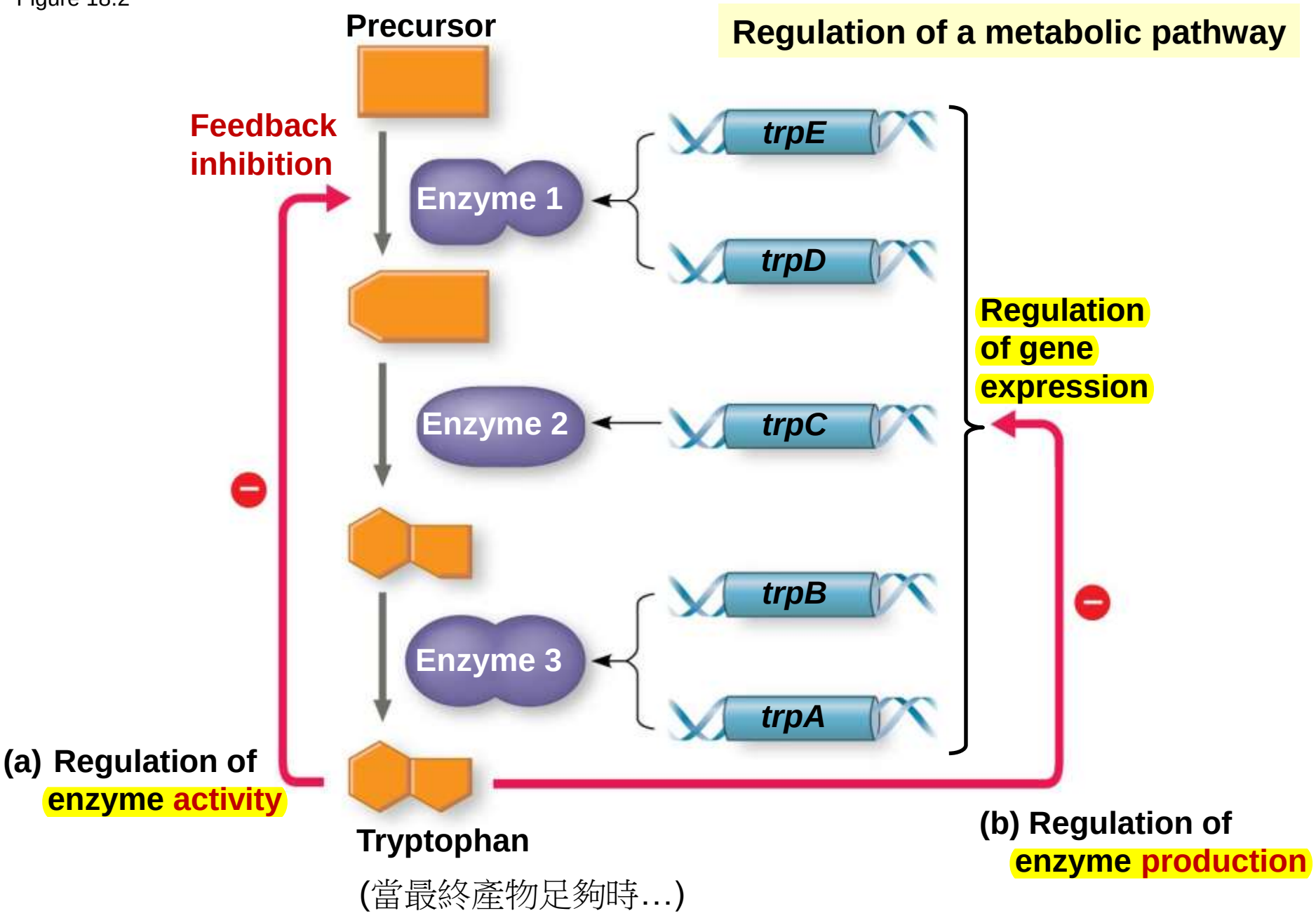
- **Natural selection** has favored bacteria that produce *only the products needed* by that cell
  物競天擇 — 生物個體只製造必須物質;

"許多因素，包跨環境的改變，能開啟基因調控機制"

Pollution drives evolution ?!

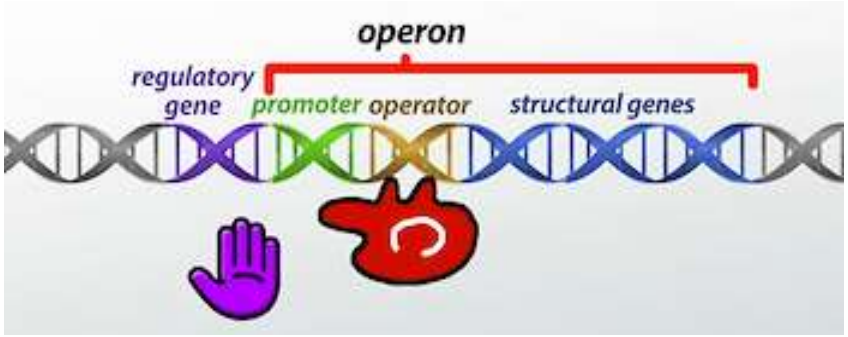
- A cell can regulate the production of enzymes by **feedback inhibition** or by **gene regulation**

Figure 18.2



Operons 操縱組/操縱序列: The Basic Concept

- A cluster of functionally related genes can be under coordinated control by a single on-off "switch" ; The "switch" is a segment of DNA called an **operator** usually positioned within the promoter



- An **operon** is the entire stretch of DNA that includes the operator, the promoter, and the genes that they control

Repressor 抑制子

- The operon can be switched off by a protein **repressor.**
- The repressor prevents gene transcription by binding to the operator and blocking RNA polymerase

(Protein-DNA interaction in gene regulation)

- The repressor is the product of a separate **regulatory gene.**

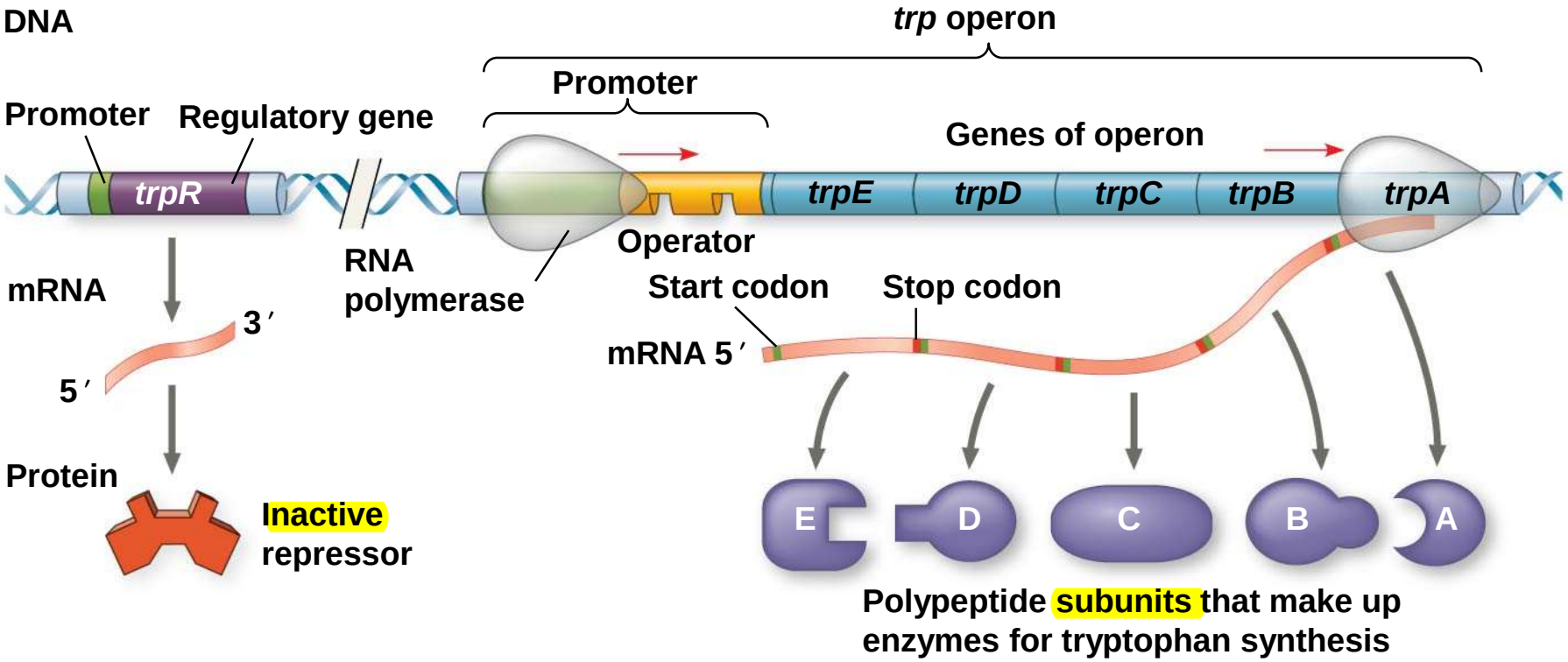
- The repressor can be in an active or inactive form, depending on the presence of other molecules

- A **corepressor** is a molecule that cooperates with a repressor protein to switch an operon off. For example, *E. coli* can synthesize the amino acid tryptophan, which acts as a corepressor.

See Figure Next

Figure 18.3a

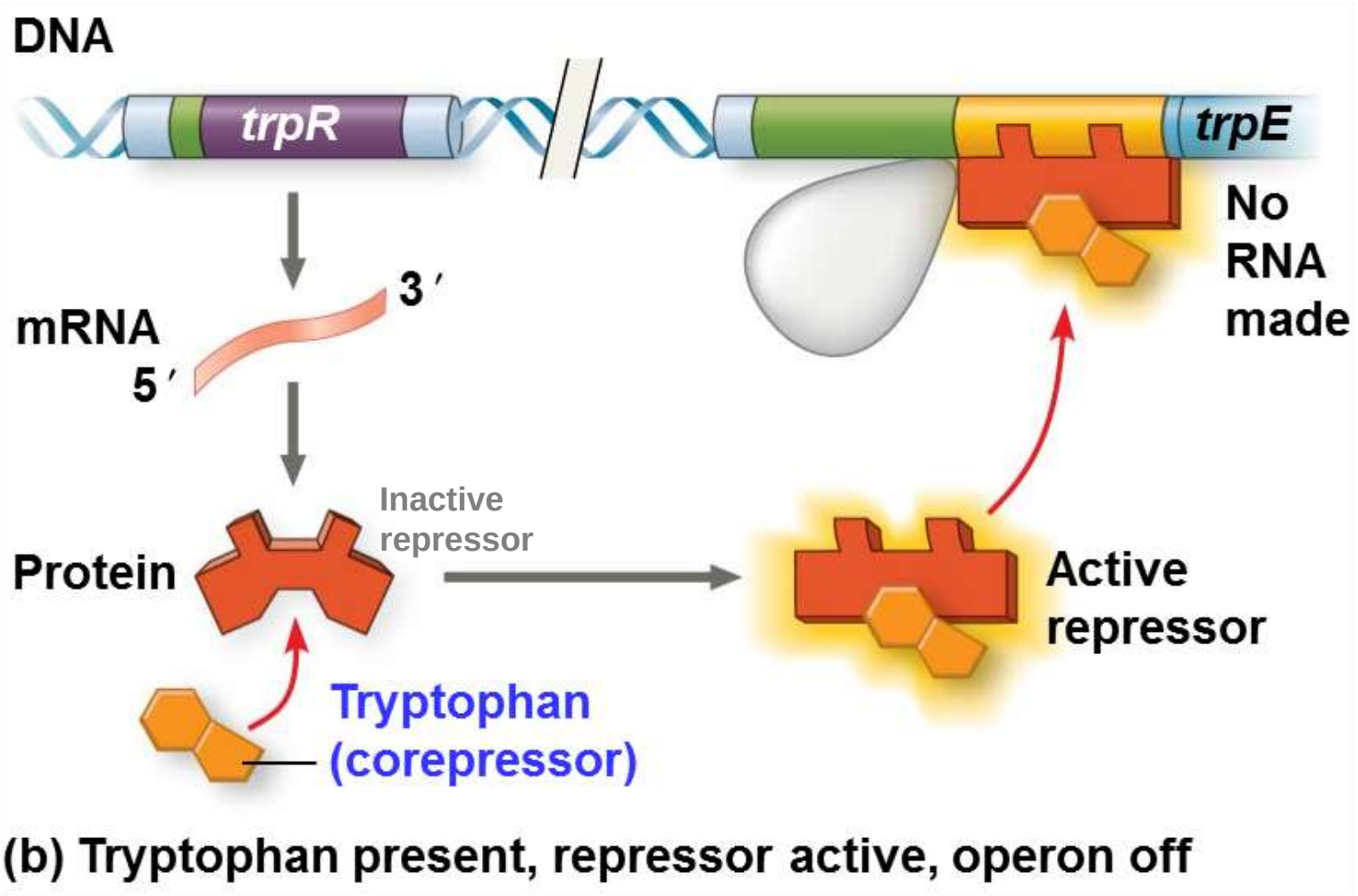
The ***trp* operon** in *E. coli*: regulated synthesis of repressible enzymes



(a) Tryptophan absent, repressor inactive, operon on

Figure 18.3b

The *trp* operon in *E. coli*: regulated synthesis of repressible enzymes



trp operon is a repressible operon

Tryptophan affect transcription via repressor

- By default（系統默認）, the *trp* operon is on and the genes for tryptophan synthesis are transcribed
- When tryptophan is present (最終產物充足), it binds to the *trp* repressor protein, which turns the operon off

Repressible and Inducible Operons: Two Types of Negative Gene Regulation

- A repressible operon is one that is usually on; binding of a repressor to the operator shuts off transcription
  - The *trp* operon is a repressible operon
- An inducible operon is one that is usually off; a molecule called an inducer inactivates the repressor and turns on transcript
  - *lac* operon is an inducible operon

lac operon is an "inducible" operon

- The *lac* operon is an inducible operon (需要時啟動) and contains genes that code for enzymes (i.e. β-Galactosidase, Permease, Transacetylase) used in the hydrolysis and metabolism of lactose 乳糖.
- By itself, the *lac* repressor is active and switches the *lac* operon off.
- A molecule called an **inducer** inactivates the repressor to turn the *lac* operon on.

Figure 18.4a

lac operon is an inducible operon

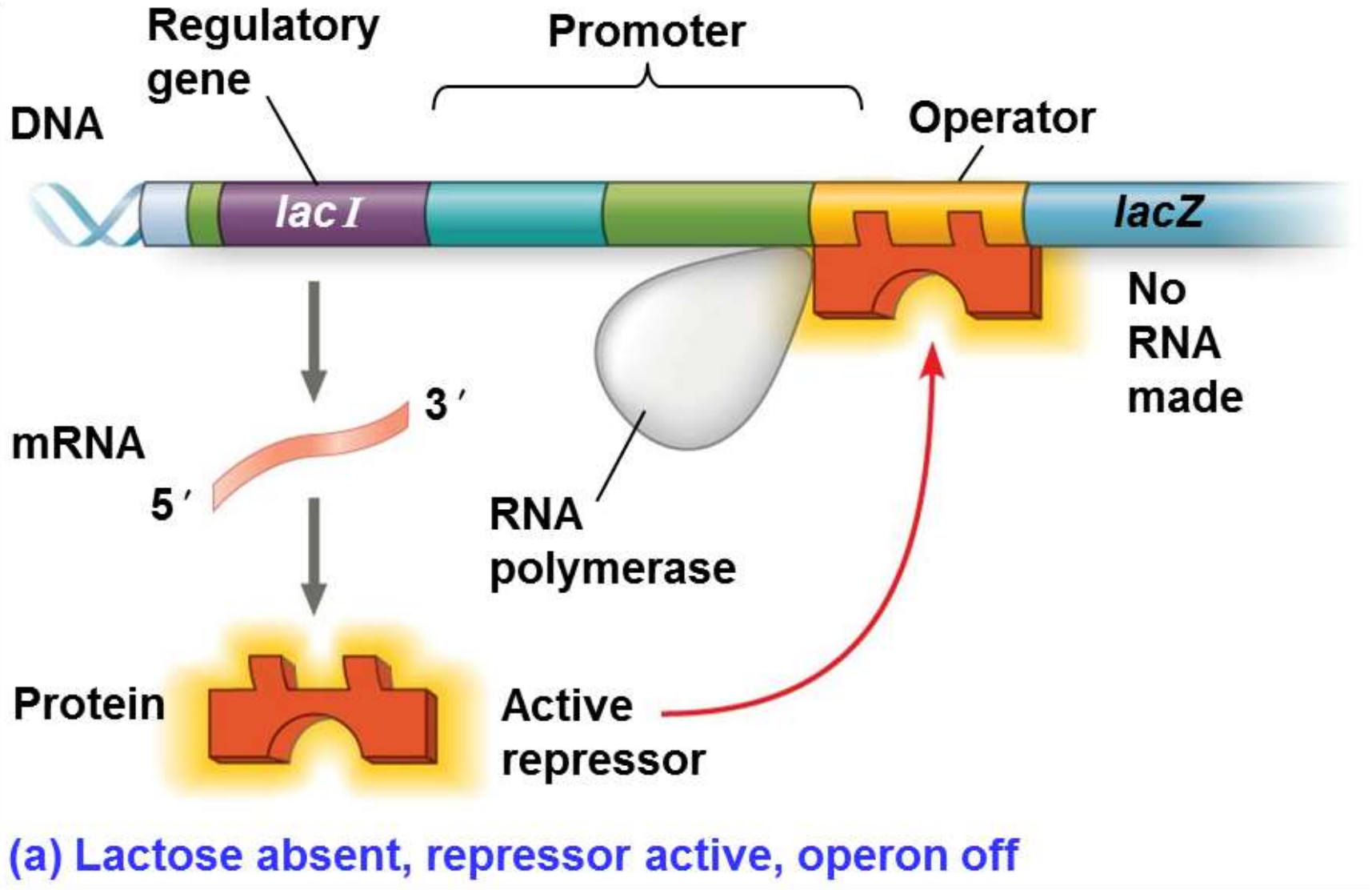
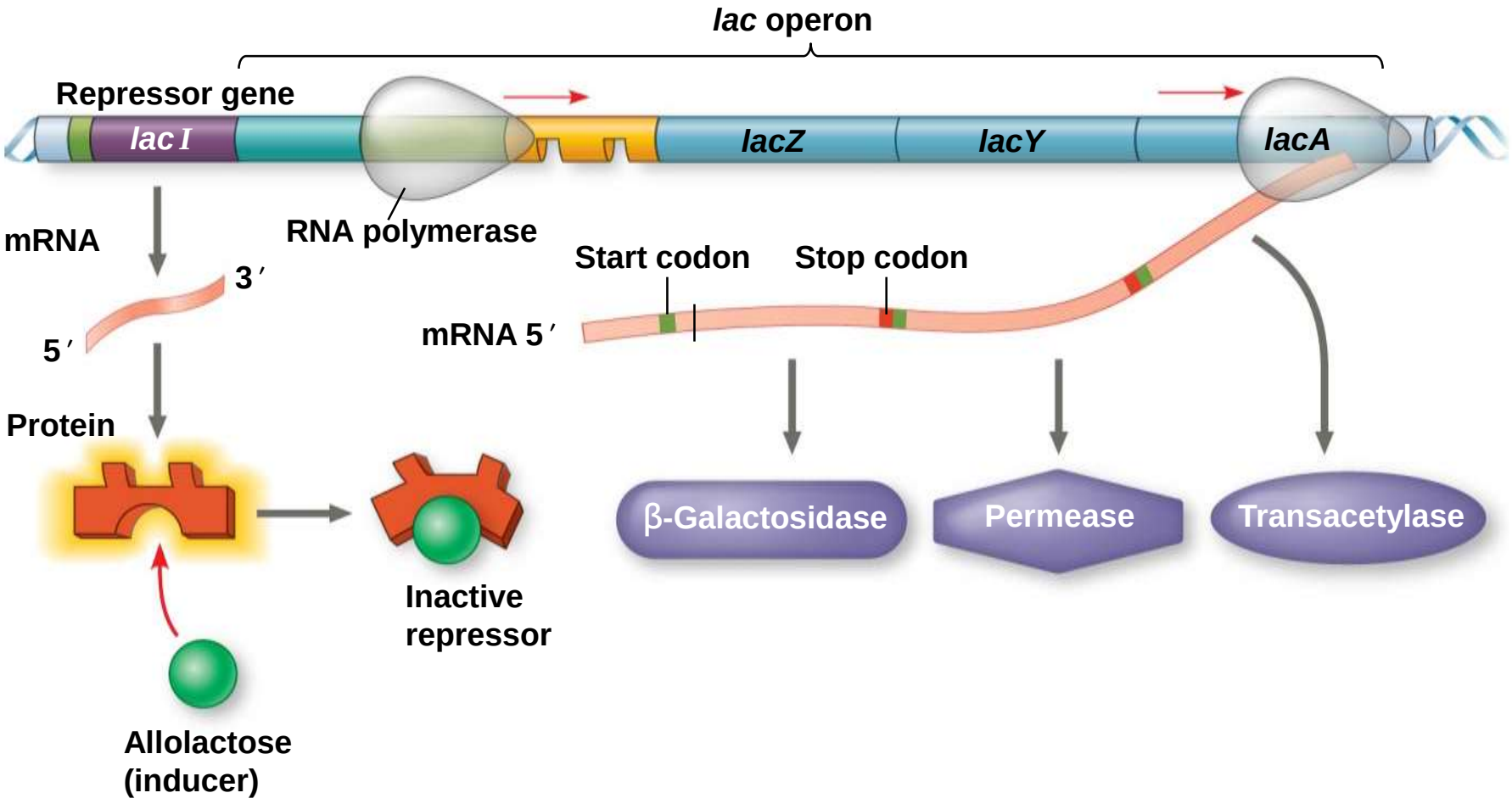


Figure 18.4b

lac operon is an inducible operon



(b) Lactose present, repressor inactive, operon on

Catabolic催化分解 vs. **Anabolic**合成代謝 pathways

- Inducible enzymes usually function in catabolic pathways（催化分解）; their synthesis is induced by a chemical signal
- Repressible enzymes usually function in anabolic pathways（合成代謝）; their synthesis is repressed by high levels of the end product; this involved negative control of genes.

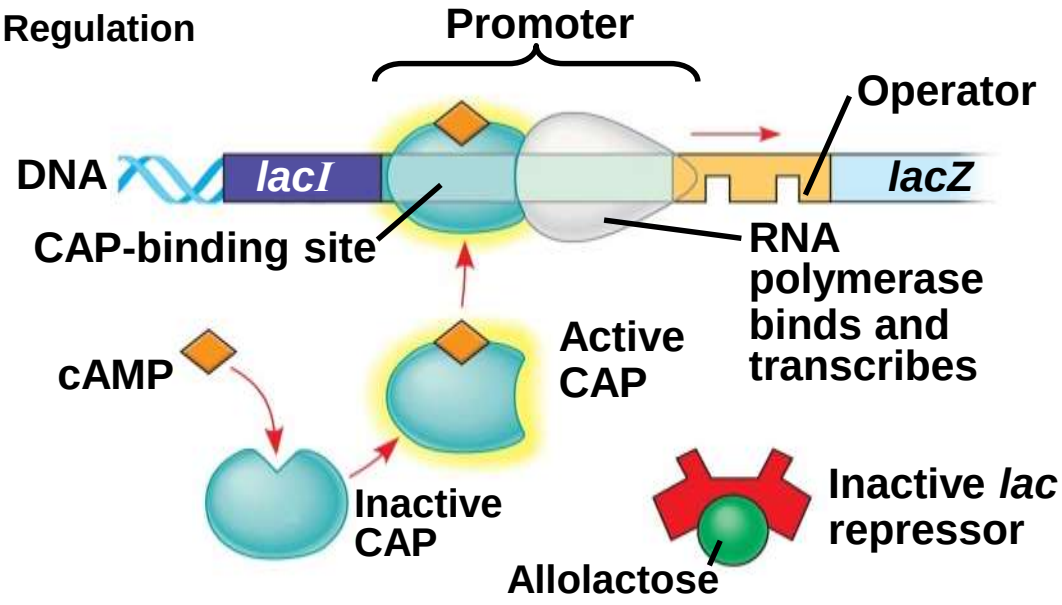
Positive Gene Regulation – 較複雜的調控機制

- Some operons are also subject to positive control through a stimulatory protein, such as catabolite activator protein (CAP), an **activator** of transcription
- When glucose (a preferred food source of *E. coli*) is scarce, CAP is activated by binding with **cyclic AMP**

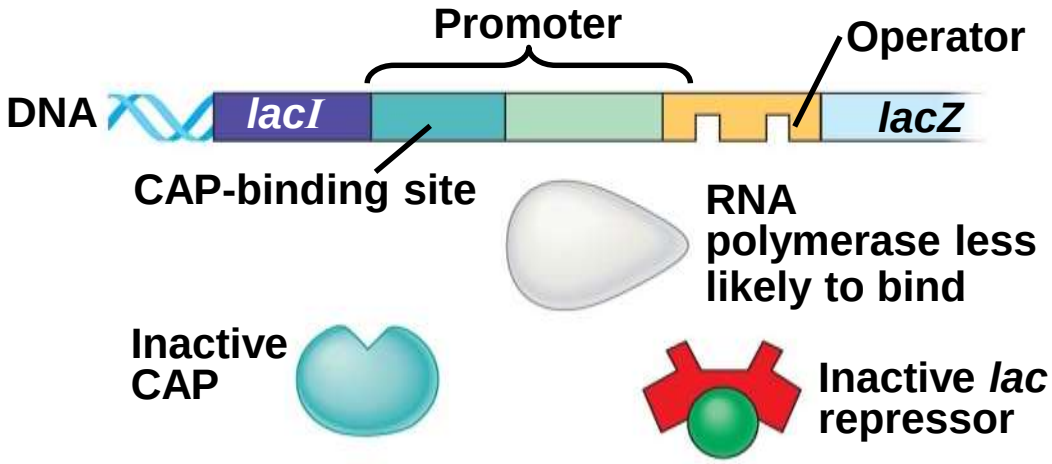
- Activated CAP attaches to the promoter of the *lac* operon and increases the affinity of RNA polymerase, thus *accelerating* transcription
- When glucose levels increase, CAP detaches from the *lac* operon, and transcription returns to a normal rate
- CAP helps regulate other operons that encode enzymes used in catabolic pathways

See figure next page

Fig. 18-5 **Positive Gene Regulation**



(a) Lactose present, glucose scarce (cAMP level high): abundant *lac* mRNA synthesized

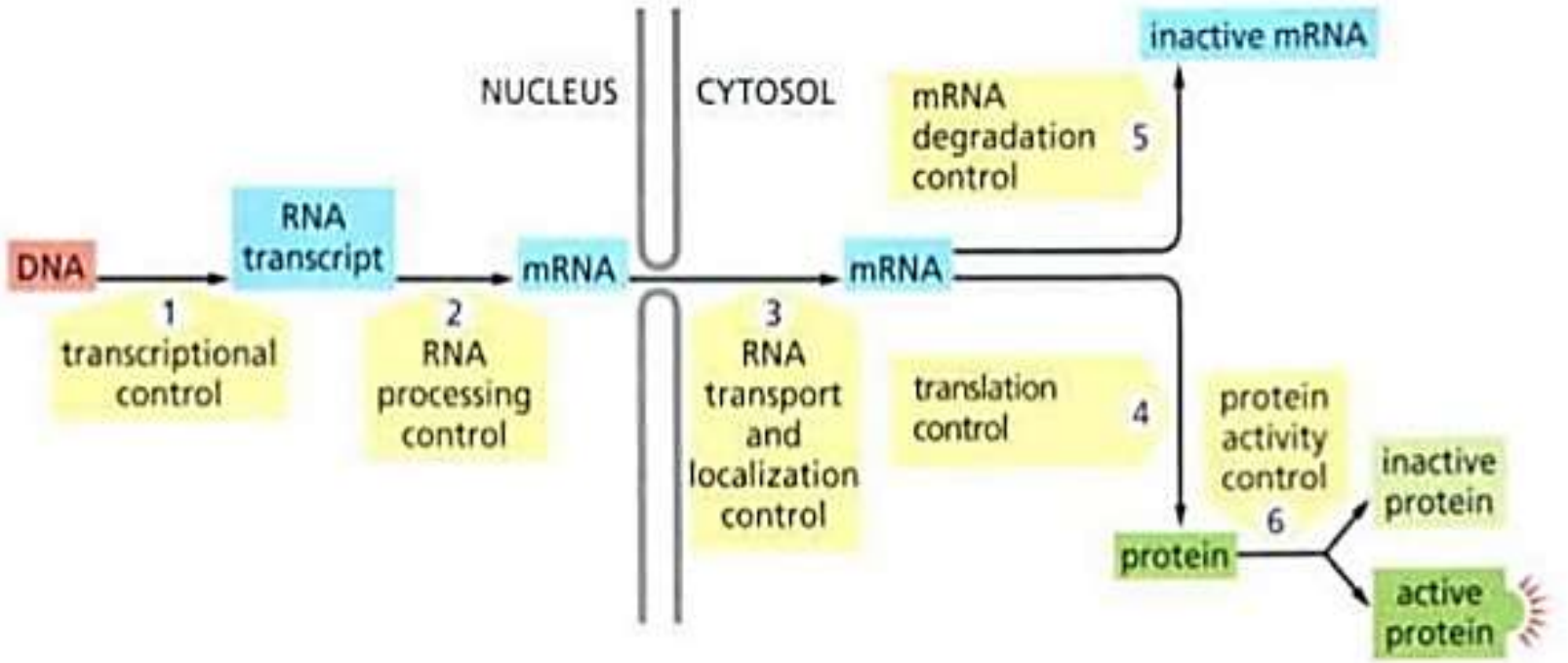


(b) Lactose present, glucose present (cAMP level low): little *lac* mRNA synthesized

Gene regulation differs from Bacteria to Eukaryotes

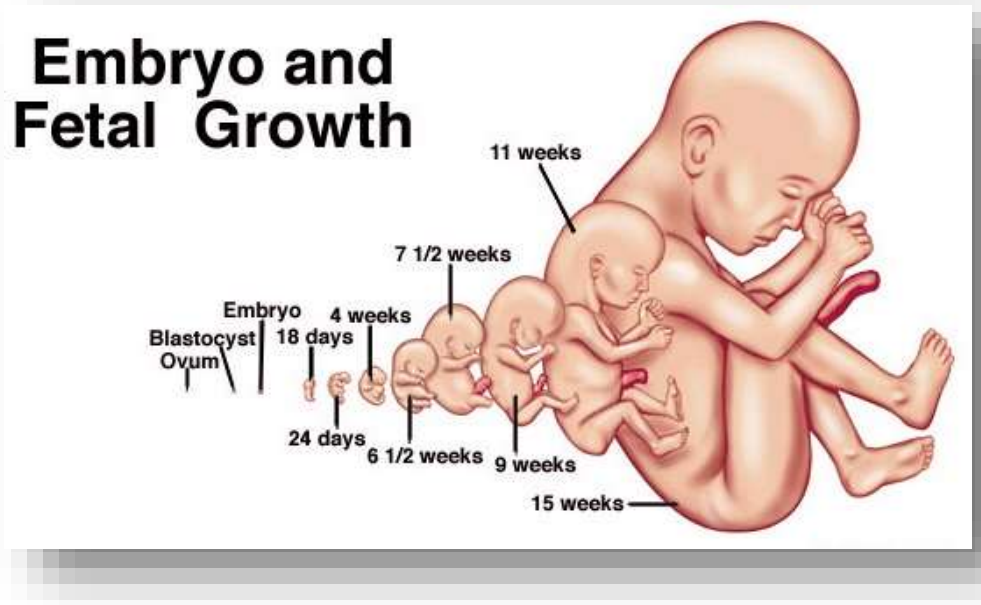
- Absence of operon
- Regulation in each level of expression

Eukaryotes



Concept 18.2: Eukaryotic gene expression is regulated at many stage

- All organisms must regulate which genes are expressed at any given time
- In multicellular organisms gene expression is essential for cell specialization



Differential Gene Expression

- Almost all the cells in an organism are genetically identical
- Differences between cell types result from **differential gene expression**, the expression of different genes by cells with the same genome
- Errors in gene expression can lead to diseases including cancer

Gene expression is regulated at many stages

Figure 18.6a

Stages in gene expression that can be regulated in eukaryotic cells

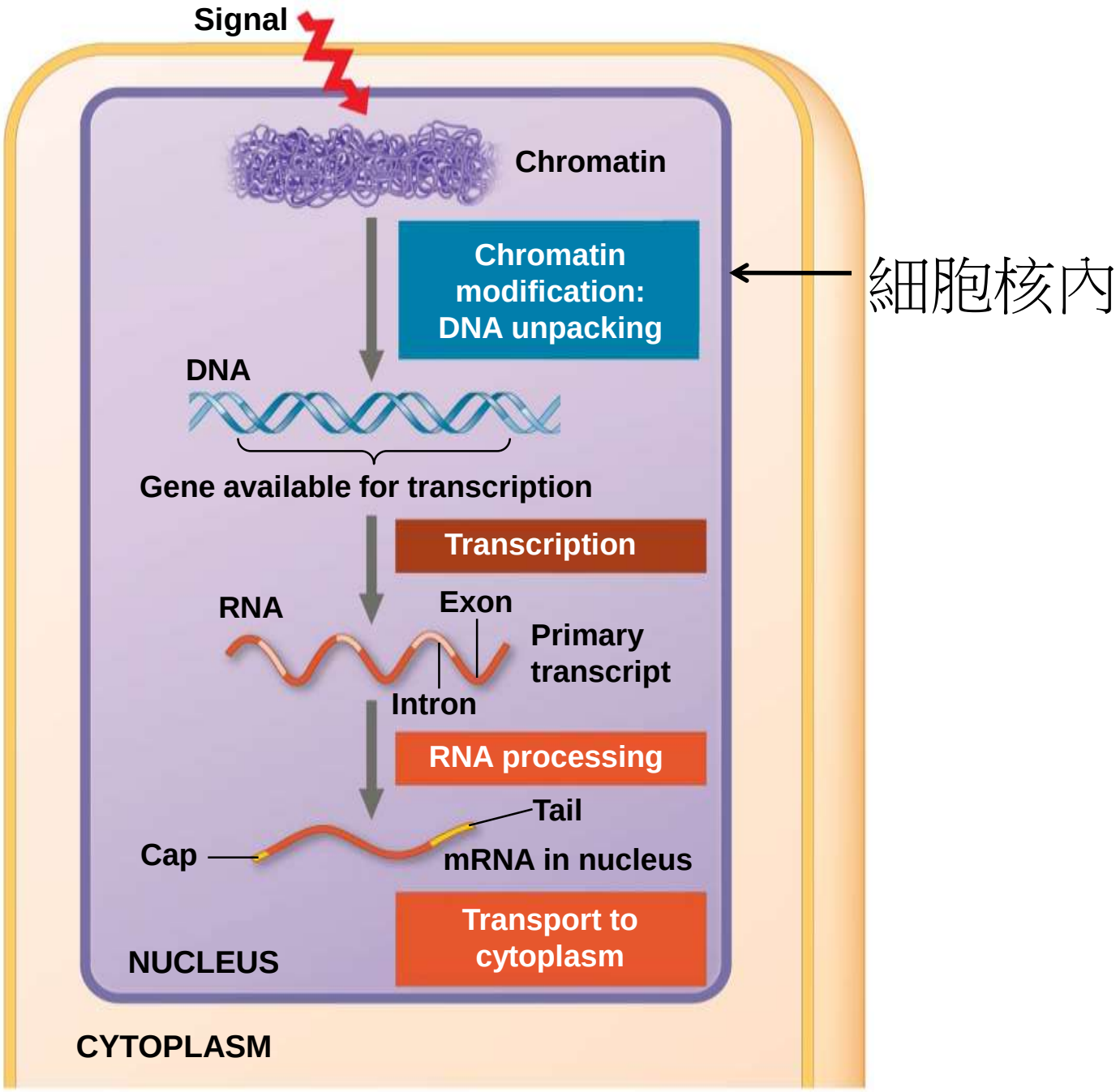
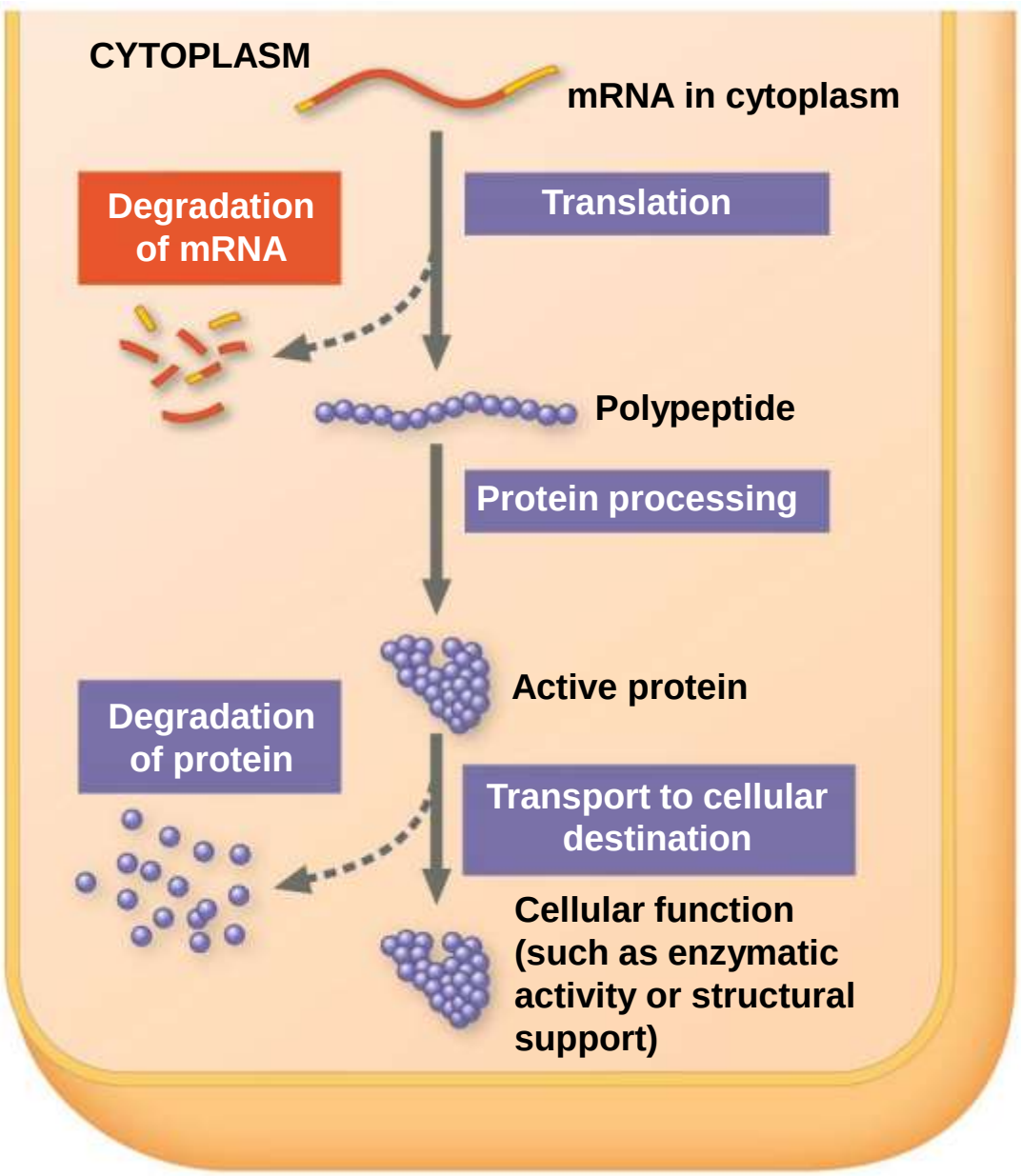


Figure 18.6b

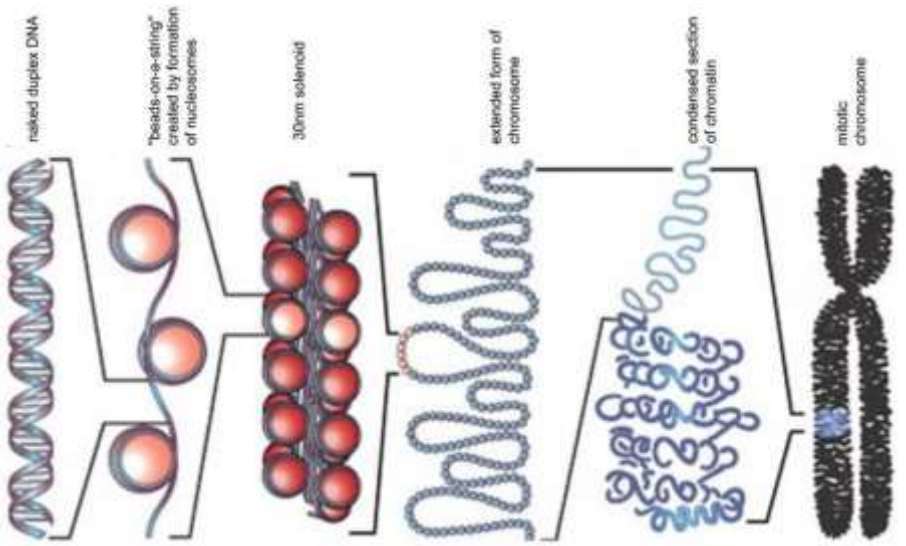
細胞質內



Stages in gene expression that can be regulated in eukaryotic cells

Regulation of Chromatin Structure

- Genes within highly packed heterochromatin are usually not expressed
- Chemical modifications to histones and DNA of chromatin influence both chromatin structure and gene expression

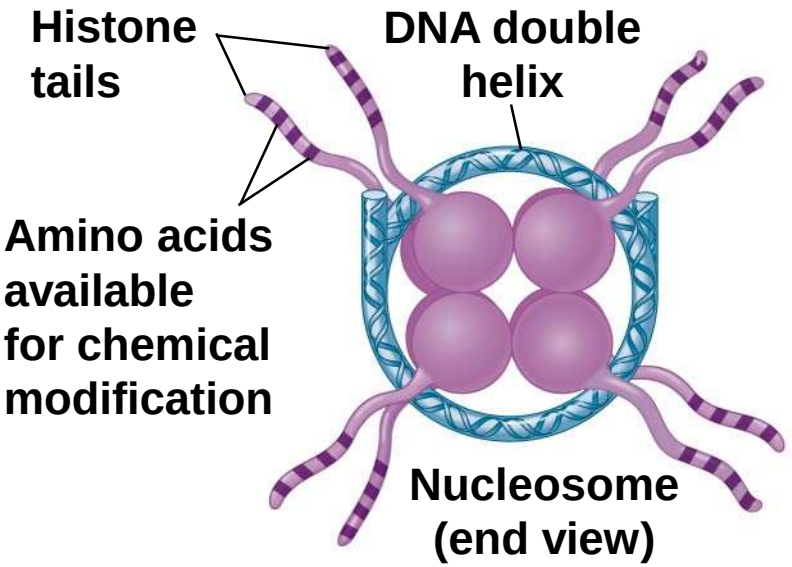


核染色質的堆疊與結構會影響基因表現

Histone Modifications

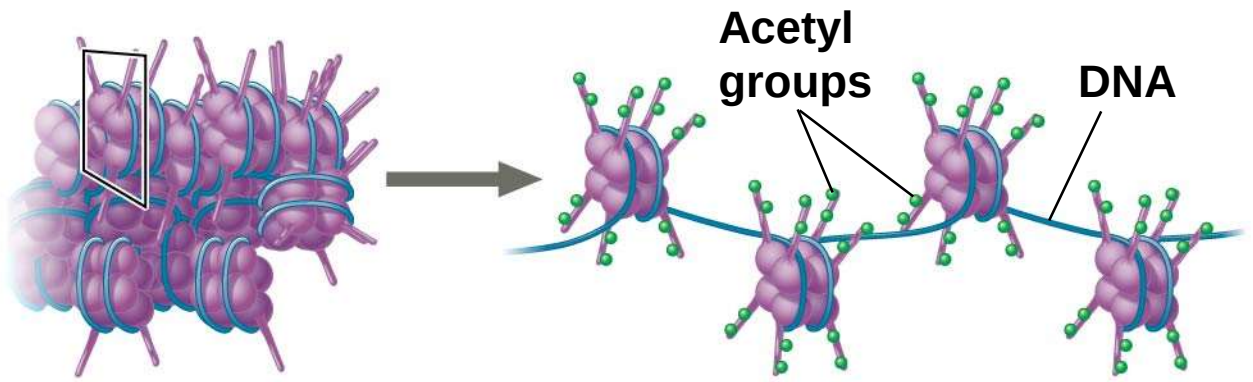
- In **histone acetylation**, acetyl groups are attached to positively charged lysines in histone tails. This process loosens chromatin structure, thereby promoting the initiation of transcription
- The addition of methyl groups (methylation) can condense chromatin; the addition of phosphate groups (phosphorylation) next to a methylated amino acid can loosen chromatin

Figure 18.7



A simple model of histone tails and the effect of histone acetylation

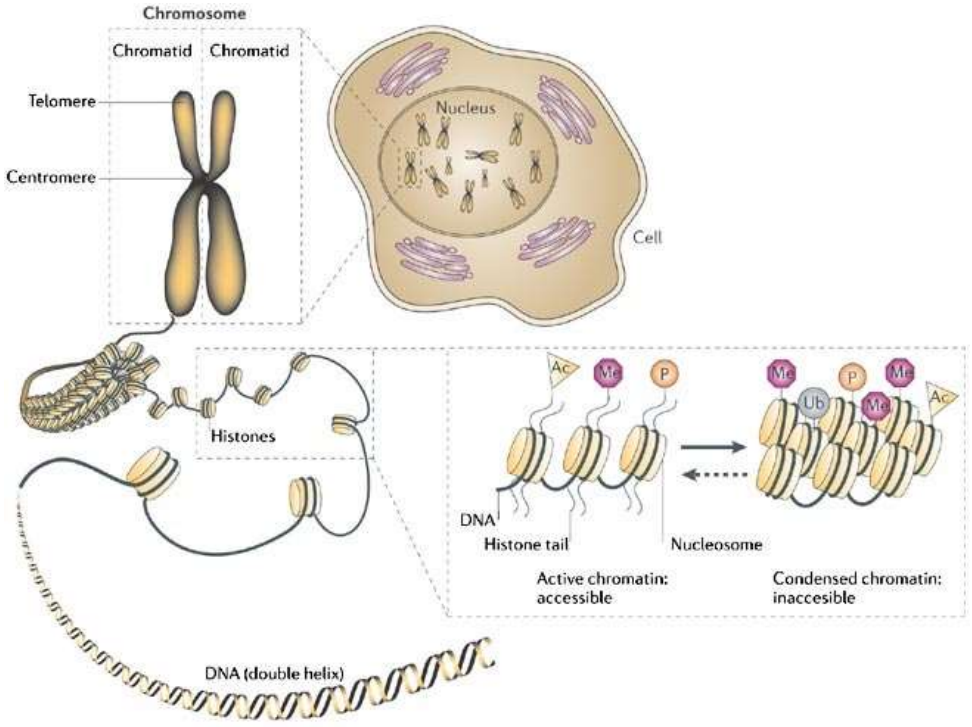
(a) Histone tails protrude outward from a nucleosome



(b) Acetylation of histone tails promotes loose chromatin structure that permits transcription

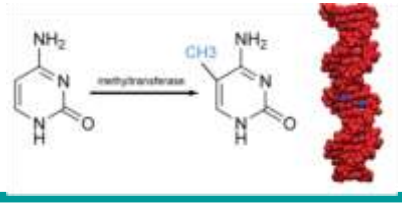
Histone code hypothesis

- The histone code hypothesis proposes that specific combinations of modifications help determine chromatin configuration and influence transcription



Nature Reviews Cancer 6, 846-856 (November 2006)

DNA Methylation



- DNA methylation, the addition of 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

Epigenetic Inheritance

- Although the chromatin modifications just discussed do not alter DNA sequence, they may be passed to future generations of cells
- The inheritance of traits transmitted by mechanisms not directly involving the nucleotide sequence is called **epigenetic inheritance**

遺傳給下一代時，不改變DNA序列，而仍可改變生物體表現型（phenotype）或基因表現的基因調控方式。

Regulation of Transcription Initiation

Chromatin-modifying enzymes provide initial control of gene expression by making a region of DNA either more or less able to bind the transcription machinery

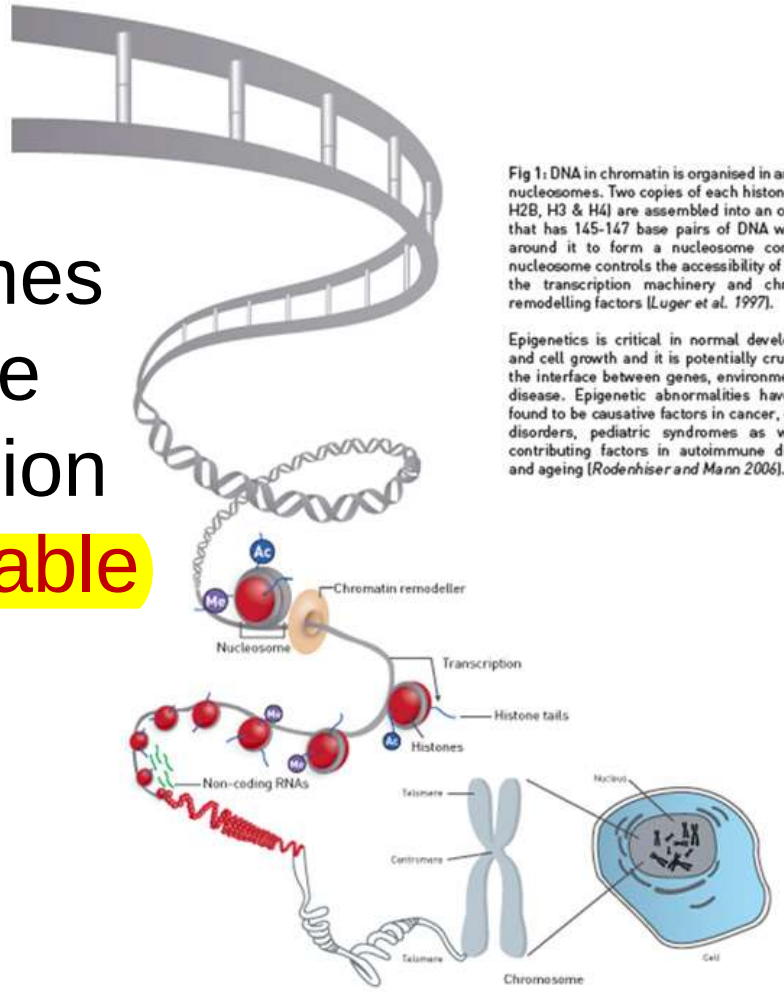


Fig 1: DNA in chromatin is organised in arrays of nucleosomes. Two copies of each histone (H2A, H2B, H3 & H4) are assembled into an octamer that has 145-147 base pairs of DNA wrapped around it to form a nucleosome core. The nucleosome controls the accessibility of DNA to the transcription machinery and chromatin remodelling factors (*Luger et al. 1997*).

Epigenetics is critical in normal development and cell growth and it is potentially crucial for the interface between genes, environment and disease. Epigenetic abnormalities have been found to be causative factors in cancer, genetic disorders, pediatric syndromes as well as contributing factors in autoimmune diseases and ageing (*Rodenhiser and Mann 2006*).

Organization of a Typical Eukaryotic Gene

- Associated with most eukaryotic genes are **control elements**, which are segments of noncoding DNA that help regulate transcription by binding certain proteins.
- Control elements (it is DNA in this case) and the proteins they bind are critical to the precise regulation of gene expression in different cell types.

Figure 18.8a A eukaryotic gene and its transcript

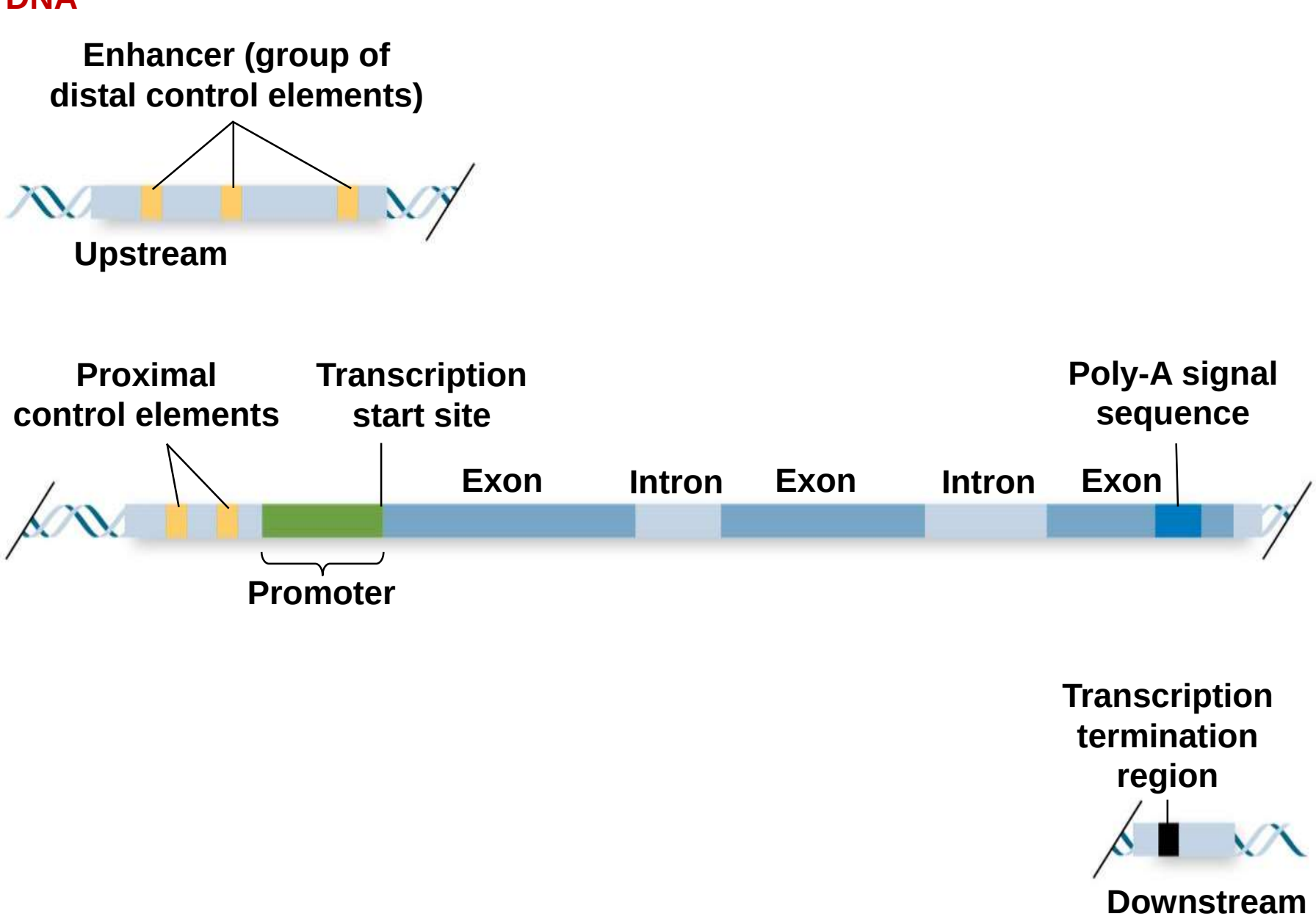


Figure 18.8b-1

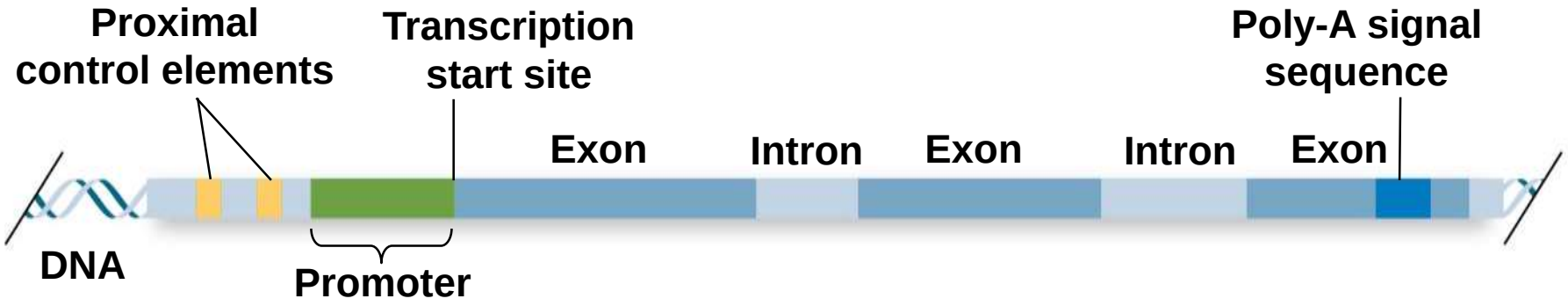


Figure 18.8b-2

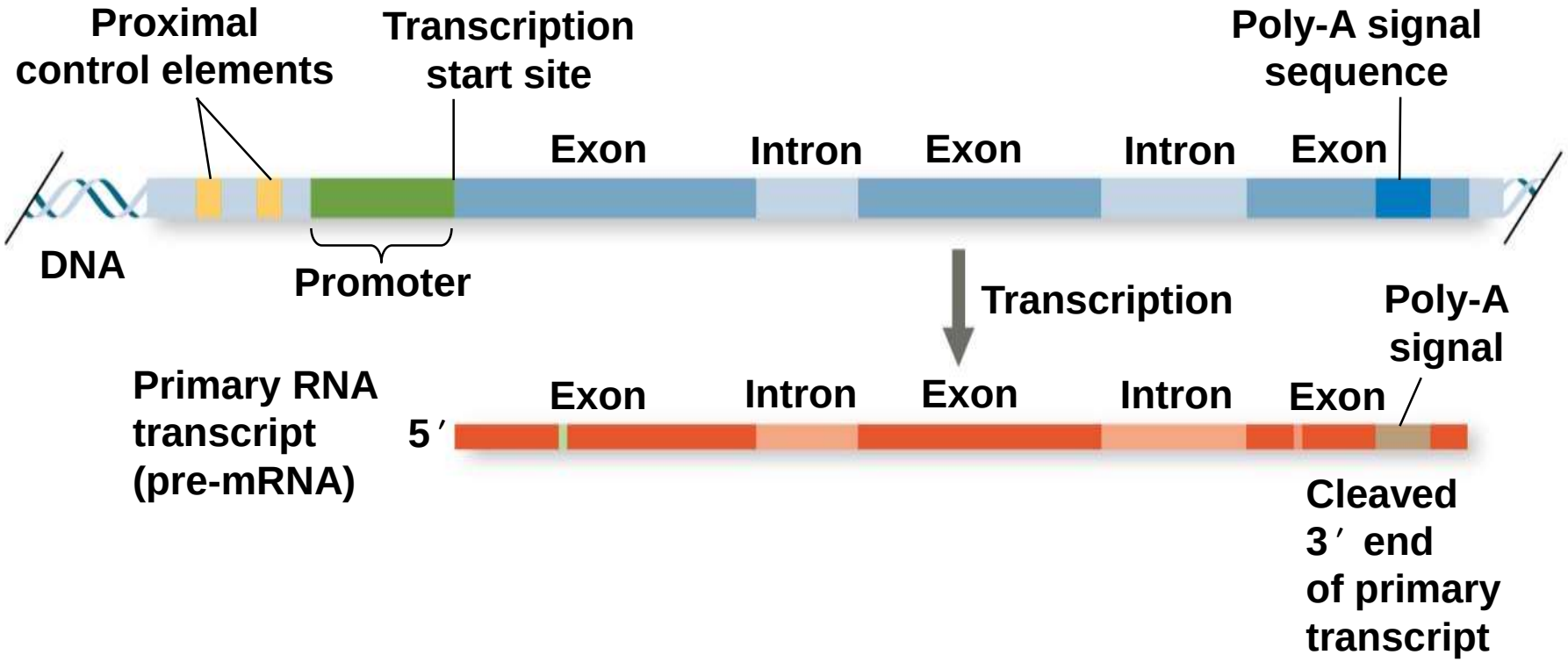
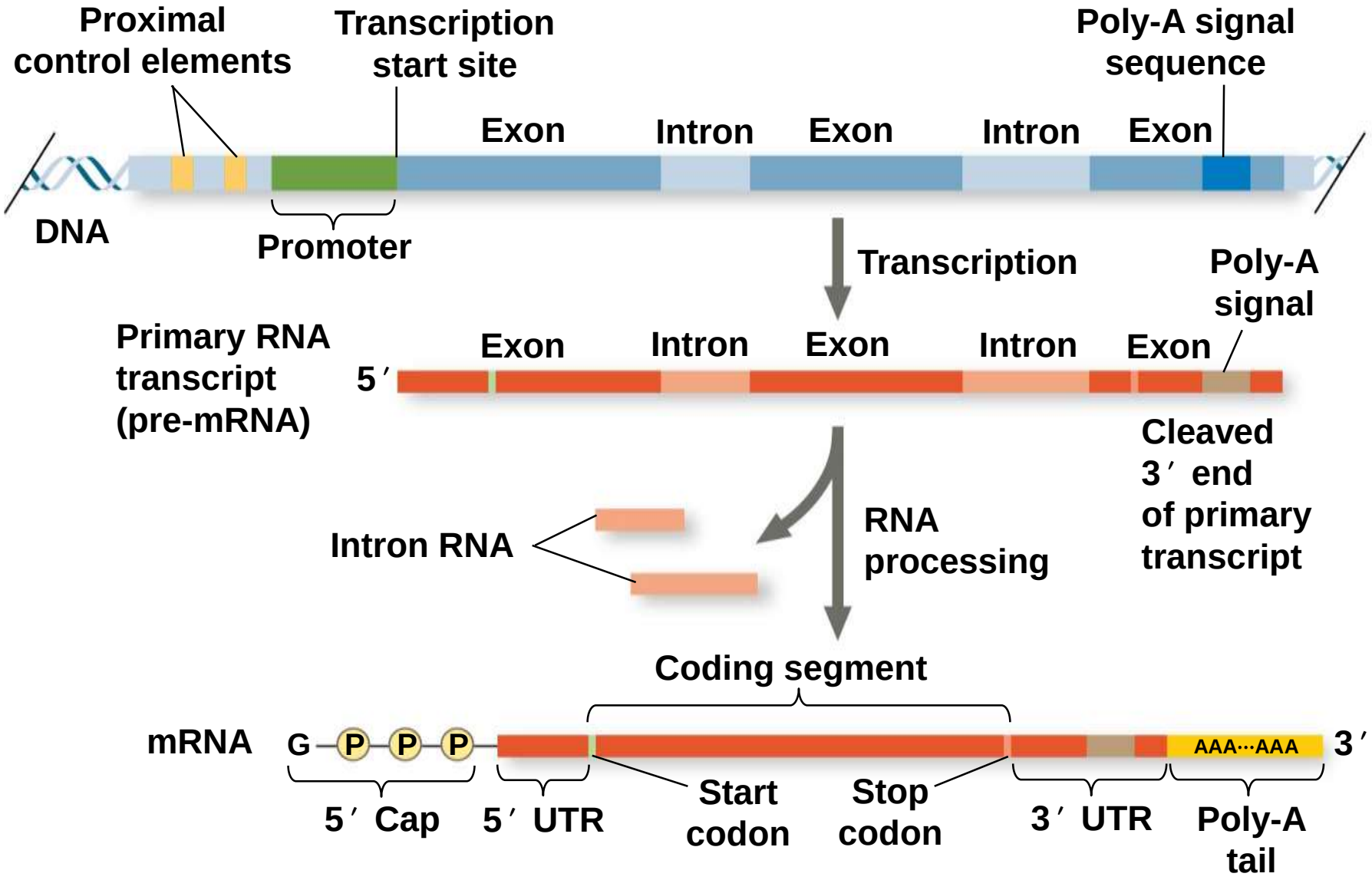


Figure 18.8b-3



The Roles of Transcription Factors

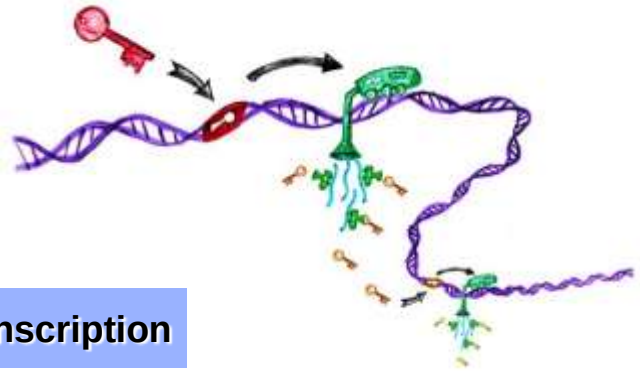
- To initiate transcription, eukaryotic RNA polymerase requires the assistance of proteins called **transcription factors** (轉錄因子)
- General transcription factors are essential for the transcription of all protein-coding genes
- In eukaryotes, high levels of transcription of particular genes depend on control elements interacting with specific transcription factors

Enhancers and Specific Transcription Factors

- **Proximal control elements** are located close to the promoter
- **Distal control elements**, groups of which are called **enhancers**, may be far away from a gene or even located in an intron

Transcription factor as **activator**

- An **activator** is a protein that binds to an enhancer and stimulates transcription of a gene
  - Activators have two domains, one that binds DNA and a second that activates transcription
- Bound activators cause mediator proteins to interact with proteins at the promoter

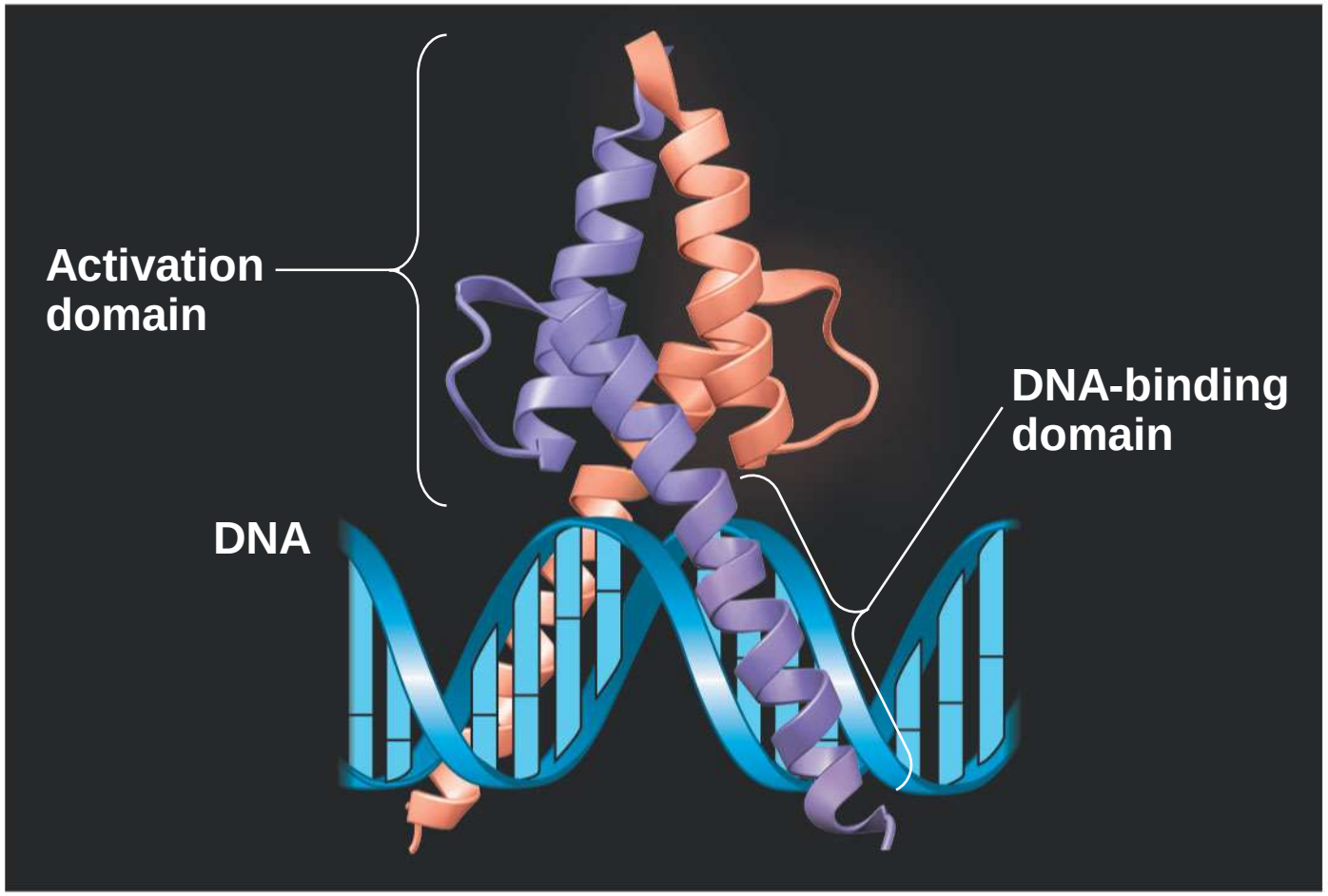


PLAY **Animation: Initiation of Transcription**

http://scienceblogs.com/omnibrain/2006/12/transcription_factors_made_eas.php

Figure 18.9

The structure of MyoD, a specific transcription factor that acts as an activator.

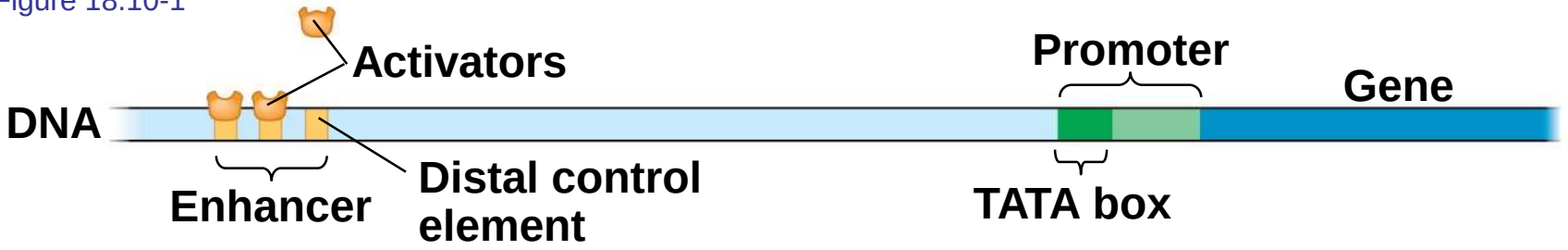


MyoD is involved in muscle development in vertebrate embryos. Its activation domain includes binding sites for other subunit and other proteins.

Transcription factor as **repressor**

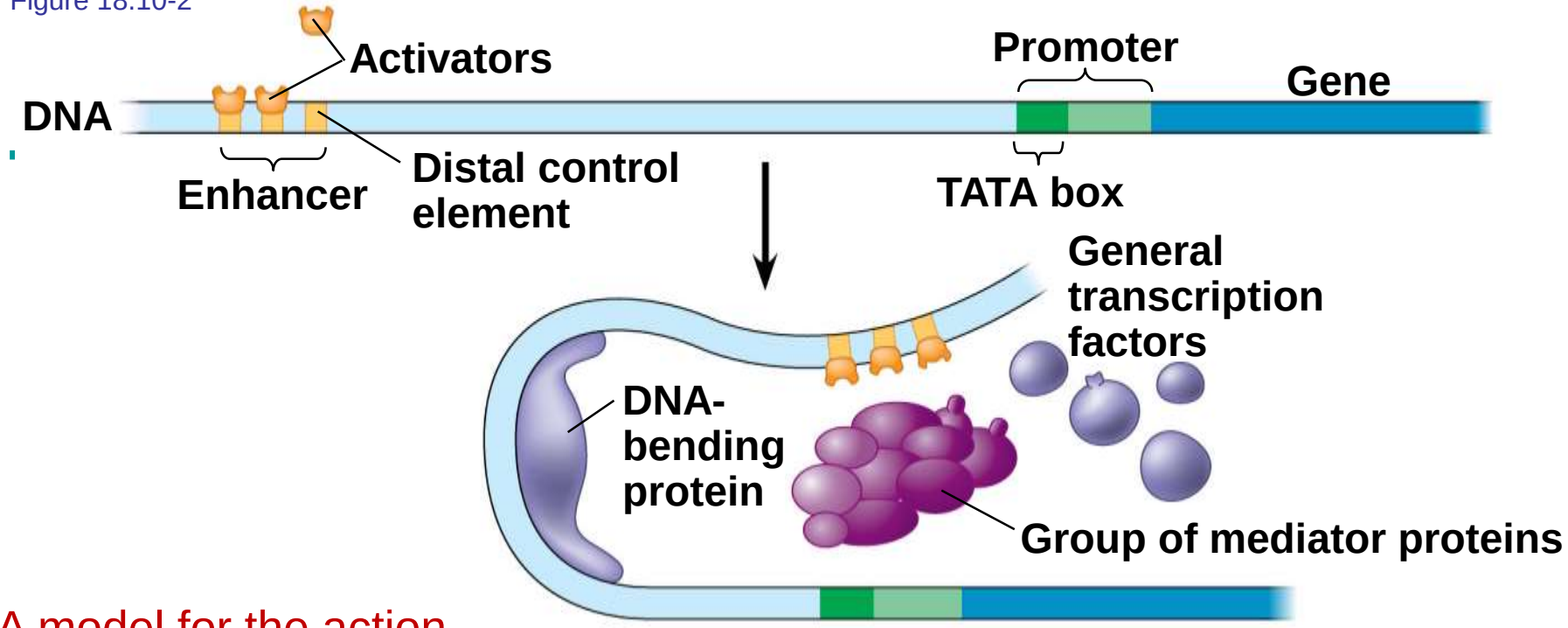
- On the other hand, some transcription factors function as repressors, inhibiting expression of a particular gene by a variety of methods
- Some activators and repressors act indirectly by influencing chromatin structure to promote or silence transcription

Figure 18.10-1



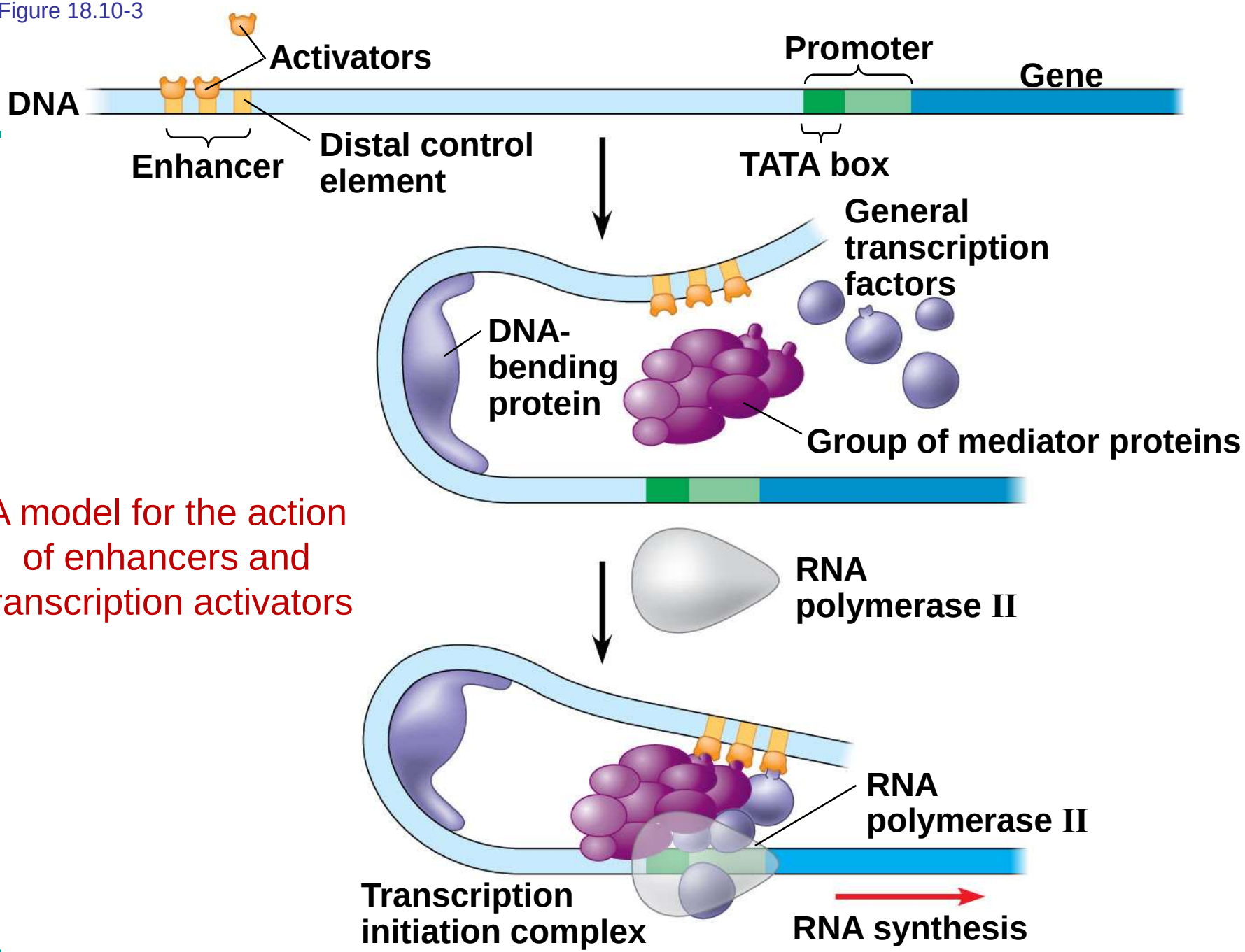
A model for the action of enhancers and transcription activators

Figure 18.10-2



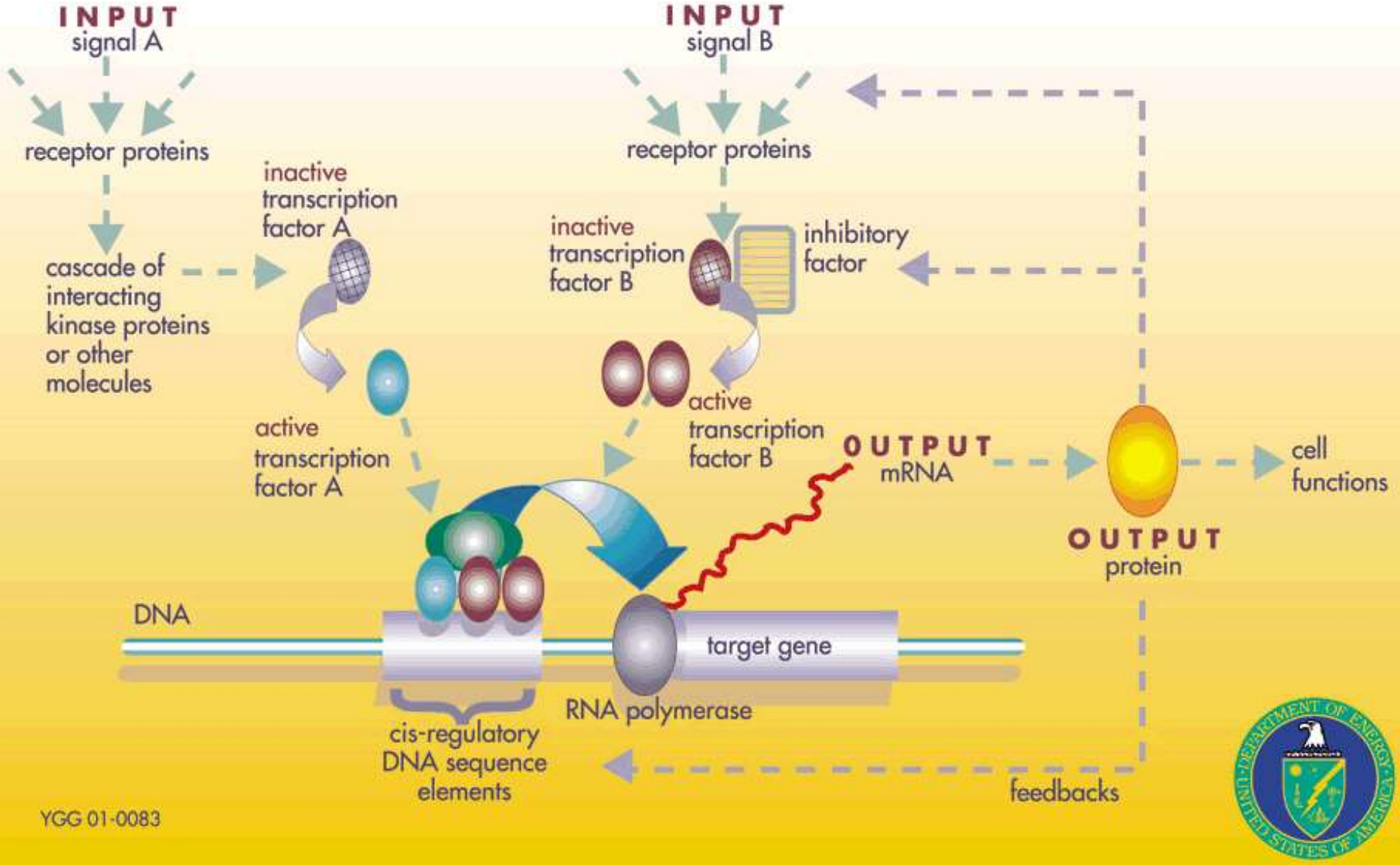
A model for the action of enhancers and transcription activators

Figure 18.10-3



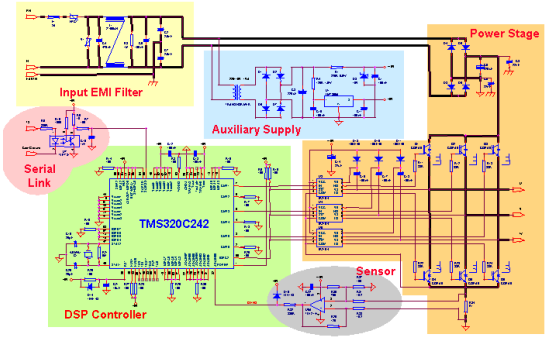
A model for the action of enhancers and transcription activators

A Gene Regulatory Network (GRN)

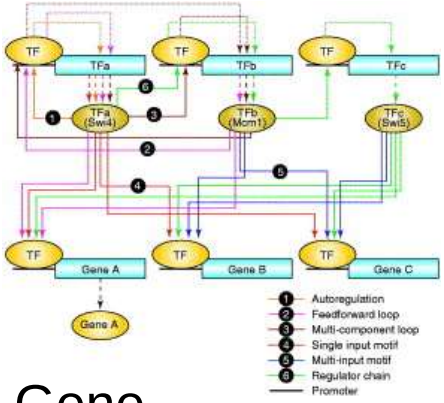


Thinking question

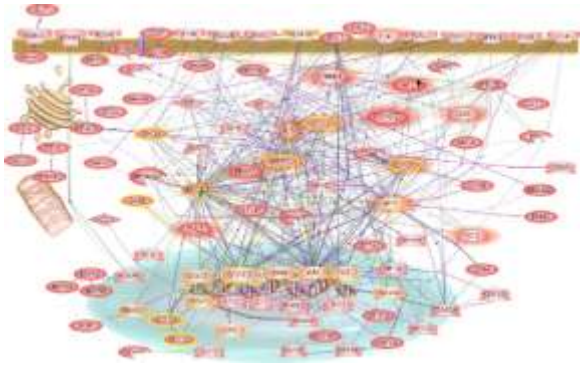
- When activator and repressor become active simultaneously, What will happen?
- What other factors may determine whether the target gene is expressed or silenced?



Circuitry



Gene Regulatory Network

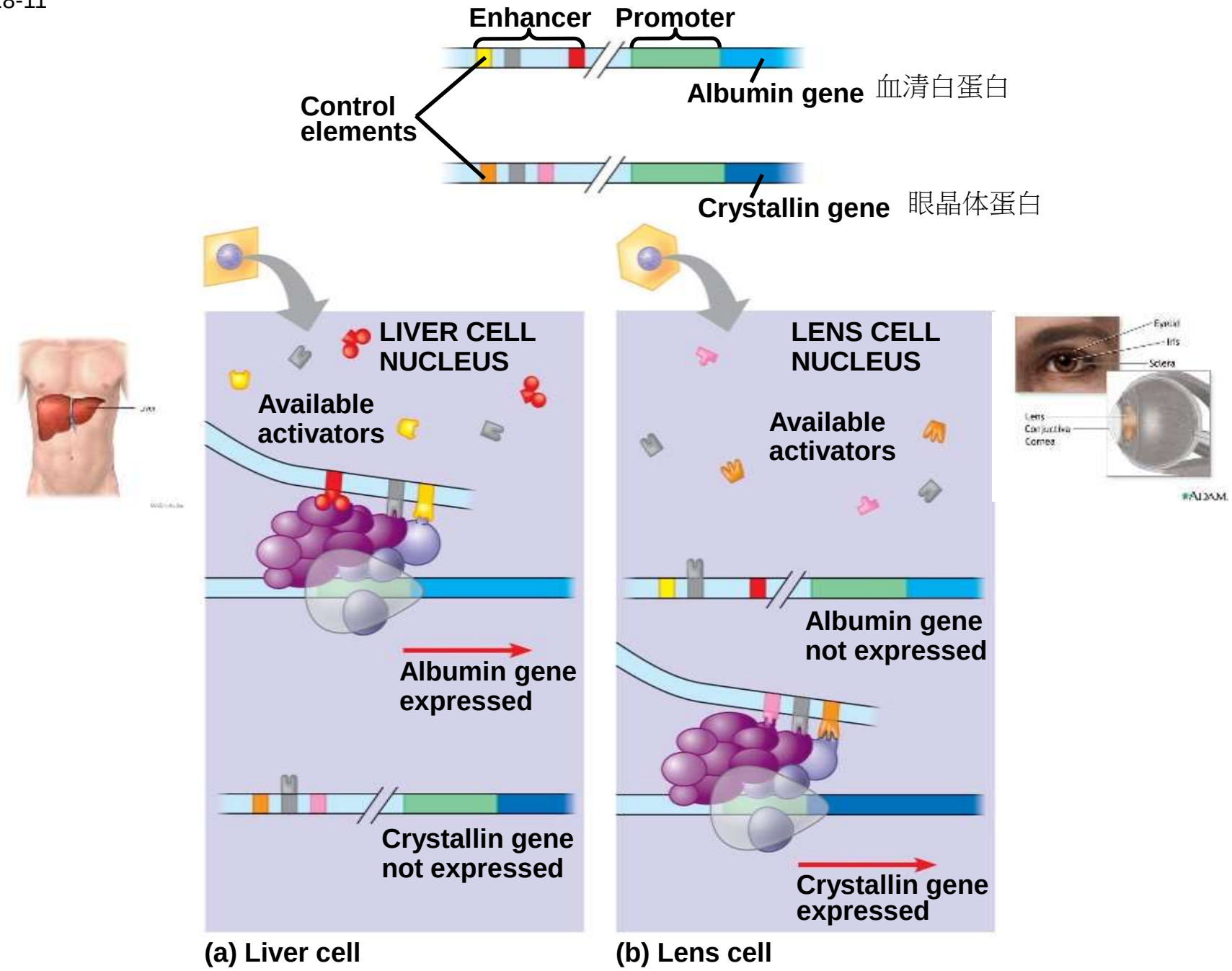


Transcriptional network governing the angiogenic switch in human pancreatic cancer

Abdollahi A et al. PNAS 2007;104:12890-12895

Fig. 18-11

Cell type–specific transcription

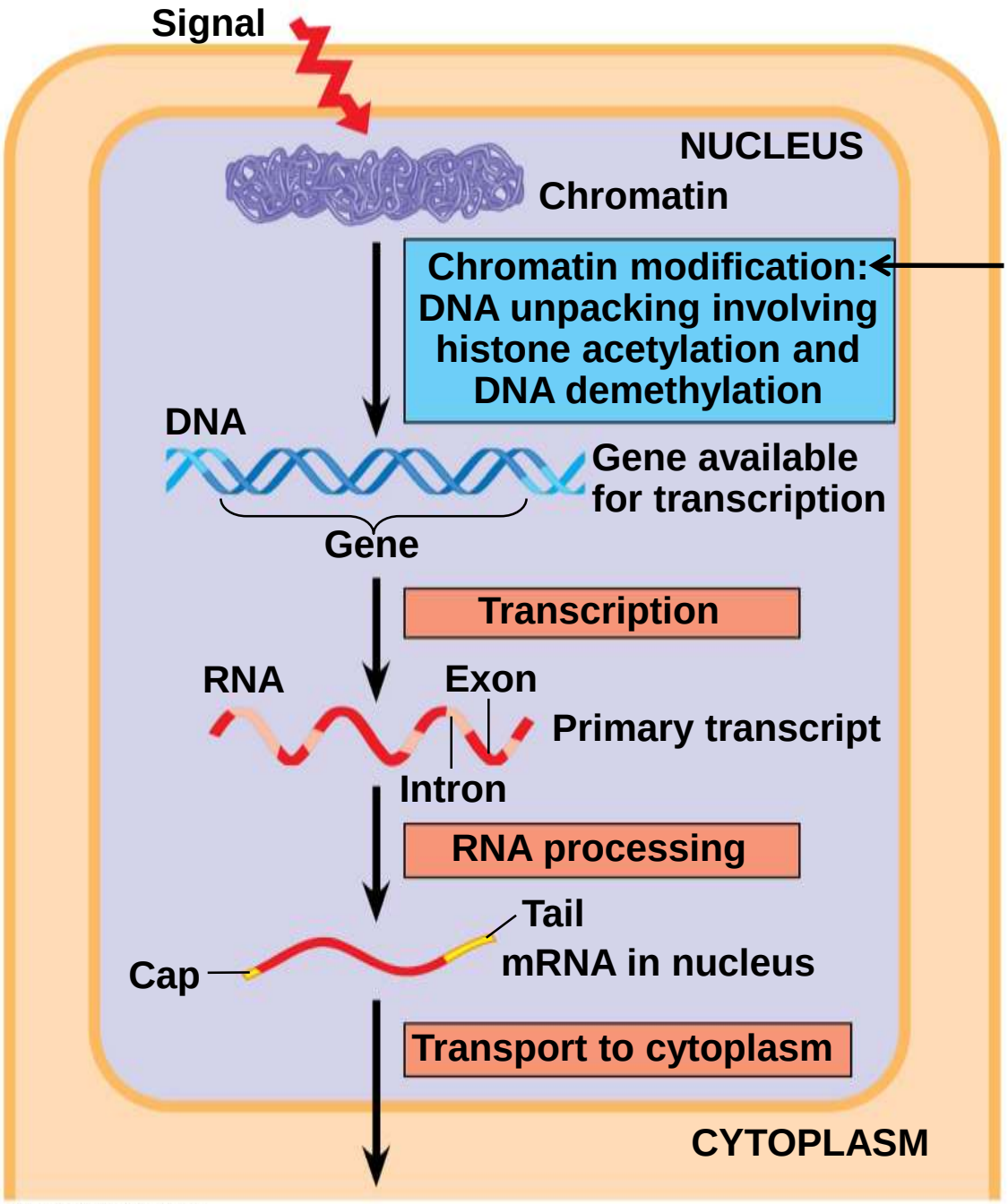


Coordinately Controlled Genes in Eukaryotes

- Unlike the genes of a prokaryotic operon, **each** of the coordinately controlled eukaryotic genes has a promoter and control elements
- These genes can be scattered over different chromosomes, but each has the same combination of control elements
- Copies of the activators recognize specific control elements and promote simultaneous transcription of the genes

Summary

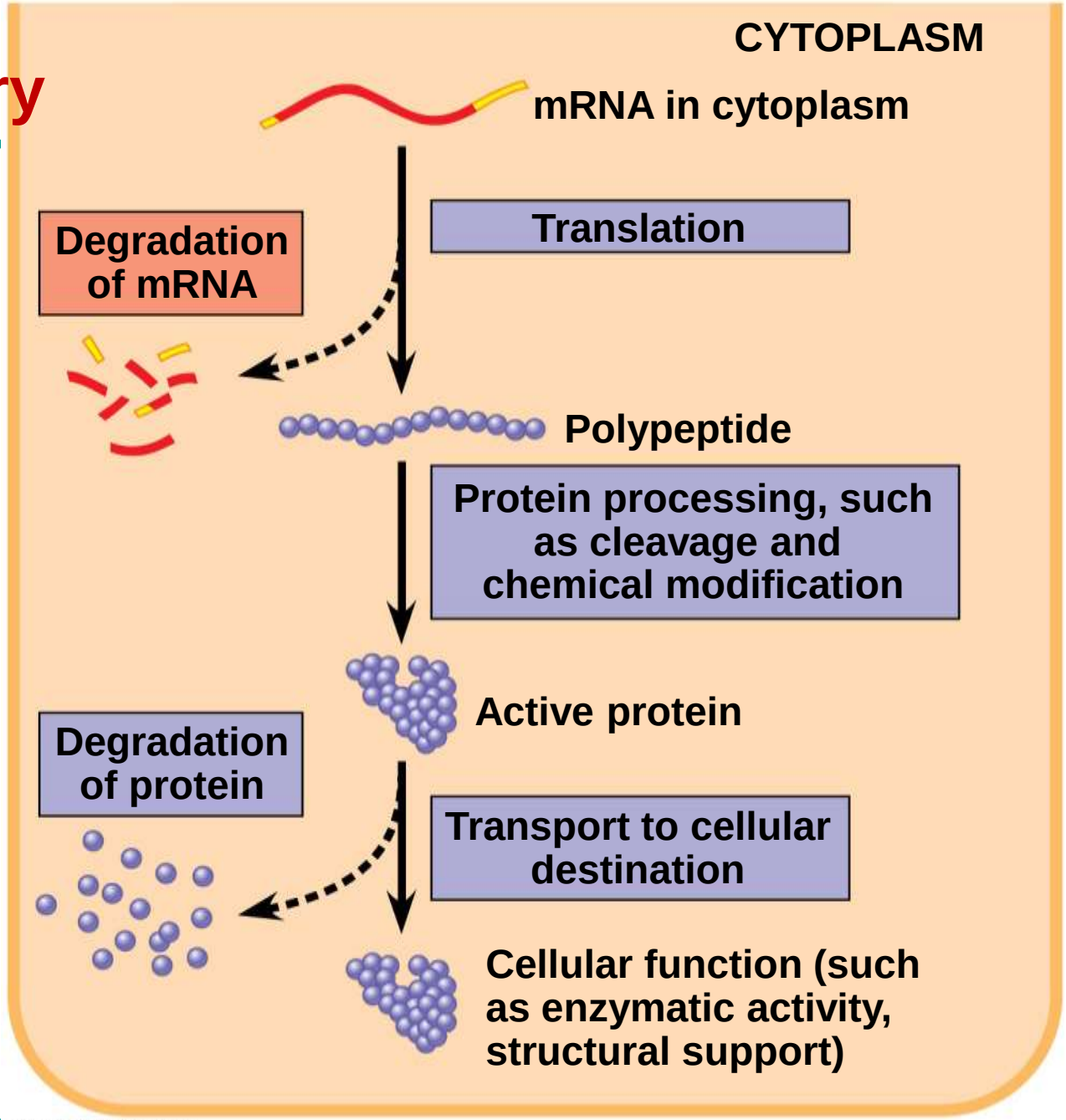
Stages in gene expression that can be regulated in eukaryotic cells.



細胞核內

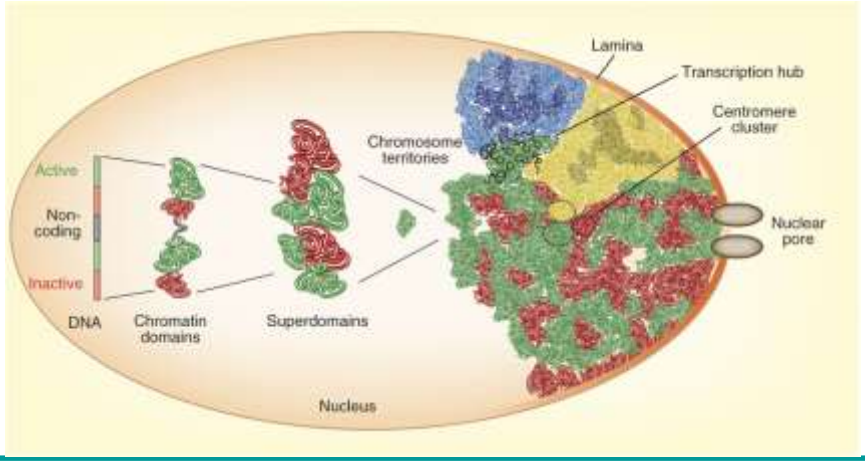
Summary

Stages in gene expression that can be regulated in eukaryotic cells.



Nuclear Architecture and Gene Expression

- Loops of chromatin extend from individual chromosomes into specific sites in the nucleus
- Loops from different chromosomes may congregate at particular sites, some of which are rich in transcription factors and RNA polymerases
- These may be areas specialized for a common function



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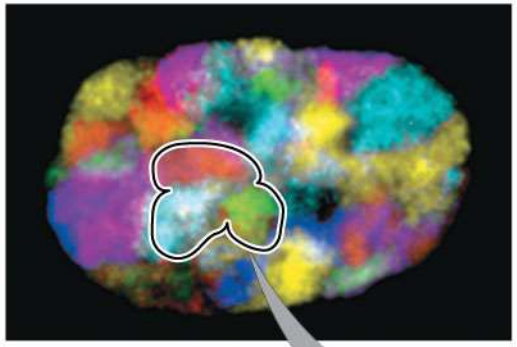
Nature Structural & Molecular Biology **20**, 290–299 (2013)

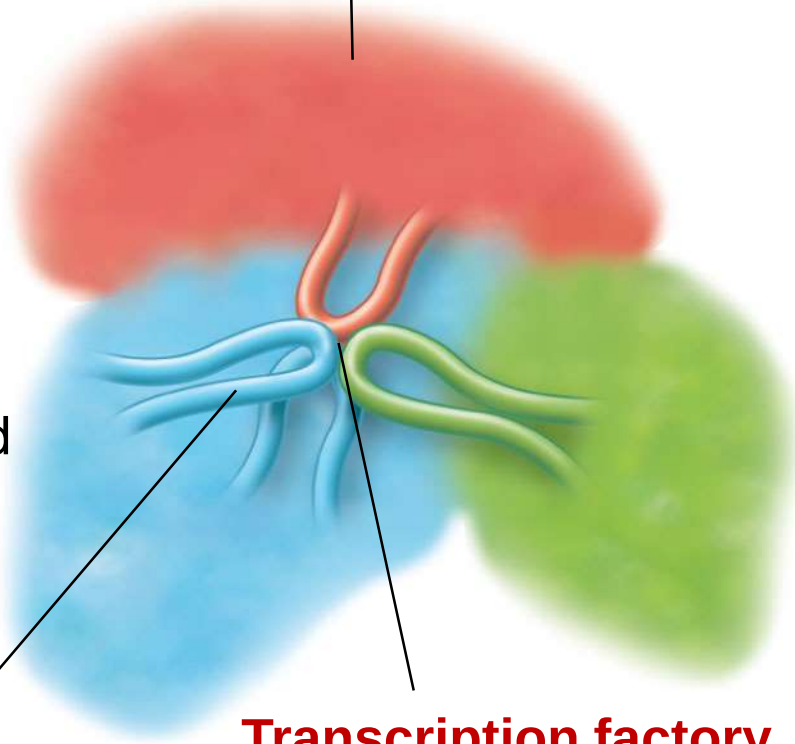
Figure 18.12

Chromosomal interactions in the interphase nucleus

Chromosomes in the interphase nucleus



"Defined architecture and regulated movements"



How does it occurs remains unknown.

Mechanisms of Post-Transcriptional Regulation

- Transcription alone does not account for gene expression
- Regulatory mechanisms can operate at various stages after transcription
- Such mechanisms allow a cell to fine-tune gene expression rapidly in response to environmental changes

Now, let us review a few examples of such regulatory mechanism….

RNA Processing

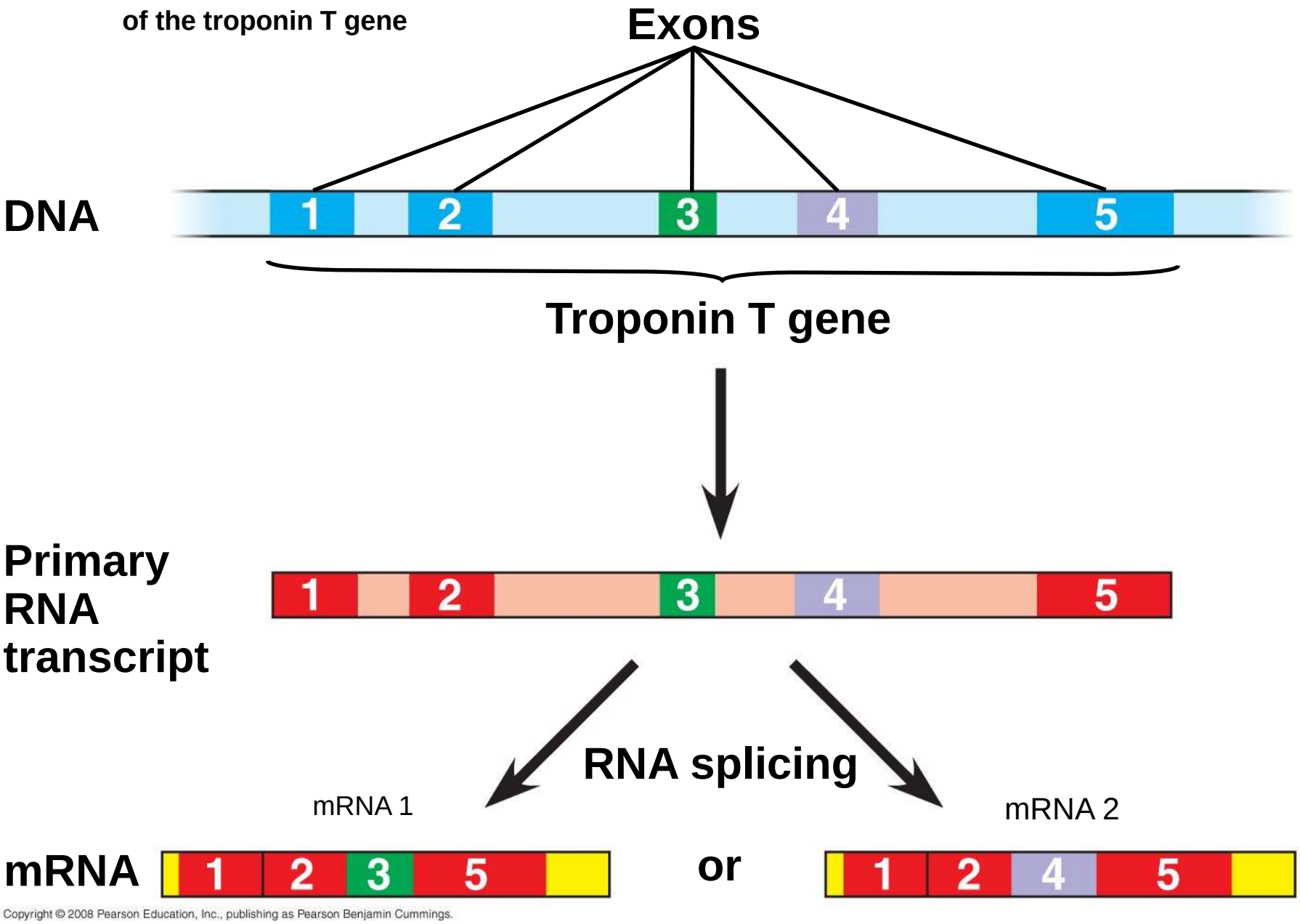
- In **alternative RNA splicing**, different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns

In fruit fly, less than **~13,700 genes** can generate more than **~38,000 proteins** from alternatively spliced exons.

Fig. 18-13

Alternative RNA splicing

of the troponin T gene



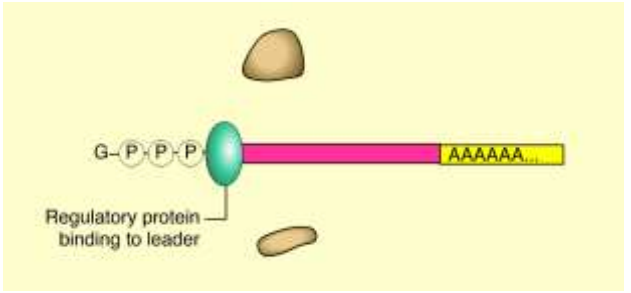
mRNA Degradation

- The **life span** of mRNA molecules in the cytoplasm is a key to determining protein synthesis
  - *Eukaryotic mRNA* is more long lived than *prokaryotic mRNA*
  - The mRNA life span is determined in part by sequences in the leader and trailer regions (i.e. UTRs)

PLAY Animation: mRNA Degradation

Initiation of Translation

- The initiation of translation of selected mRNAs can be blocked by regulatory proteins that bind to sequences or structures of the mRNA



- Alternatively, translation of all mRNAs in a cell may be regulated simultaneously
- For example, translation initiation factors are simultaneously activated in an egg following fertilization.

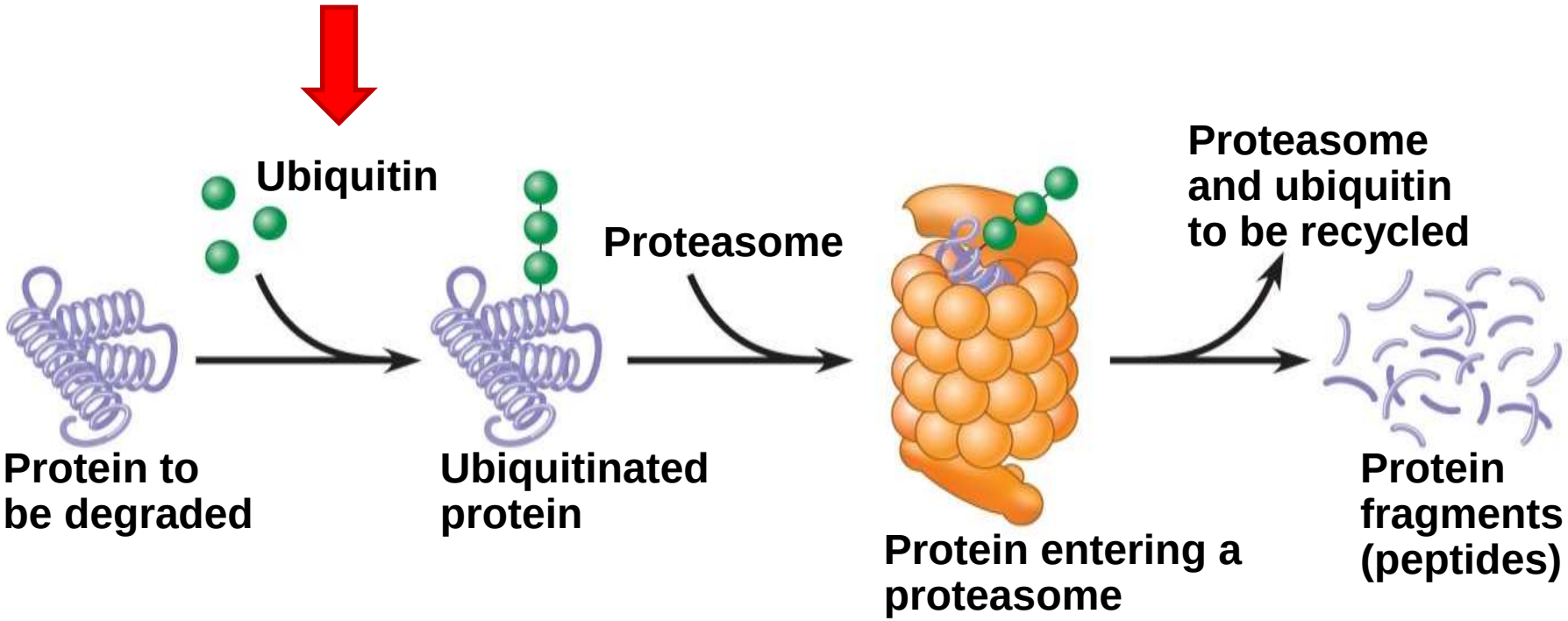
Protein Processing and Degradation

- After translation, various types of protein processing, including: folding, stabilization with disulfide bridges, cleavage and the addition of chemical groups (i.e. carbohydrates), transportation…. are subject to control

What happens to unneeded or damaged proteins?

- **Proteasomes** are giant protein complexes that bind protein molecules and degrade them

Degradation of a protein by a proteasome



PLAY **Animation: Protein Degradation**

2004年化學獎得主Aaron Ciechanover 於2012/06. 2013/12蒞臨清大演講
"for the discovery of ubiquitin-mediated protein degradation".

Concept 18.3: Noncoding RNAs play multiple roles in controlling gene expression

- Only a small fraction of DNA codes for proteins, rRNA, and tRNA
- A significant amount of the genome may be transcribed into noncoding RNAs (ncRNAs)
- Noncoding RNAs regulate gene expression at two points: mRNA translation and chromatin configuration.

Effects on mRNAs by MicroRNAs and Small Interfering RNAs

- **MicroRNAs** (also called **miRNAs**) are small single-stranded RNA molecules that can bind to mRNA
- These can degrade mRNA or block its translation

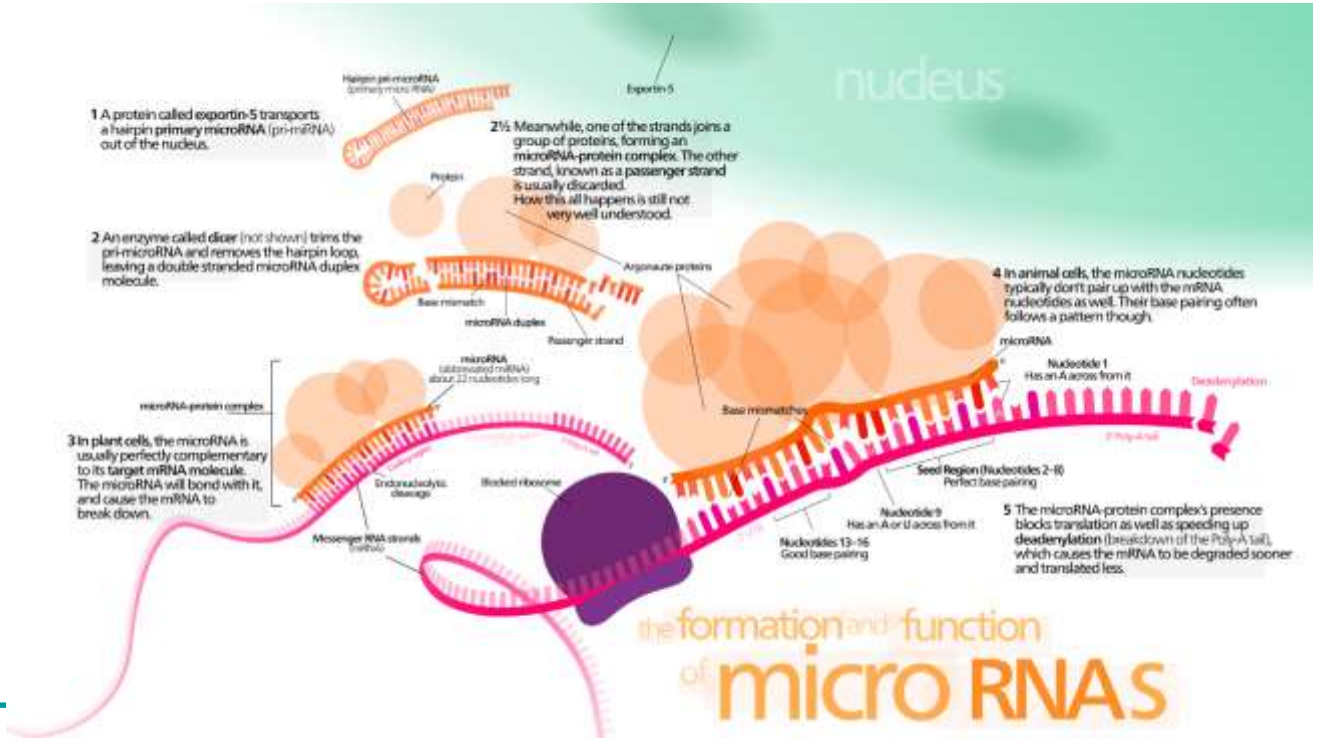
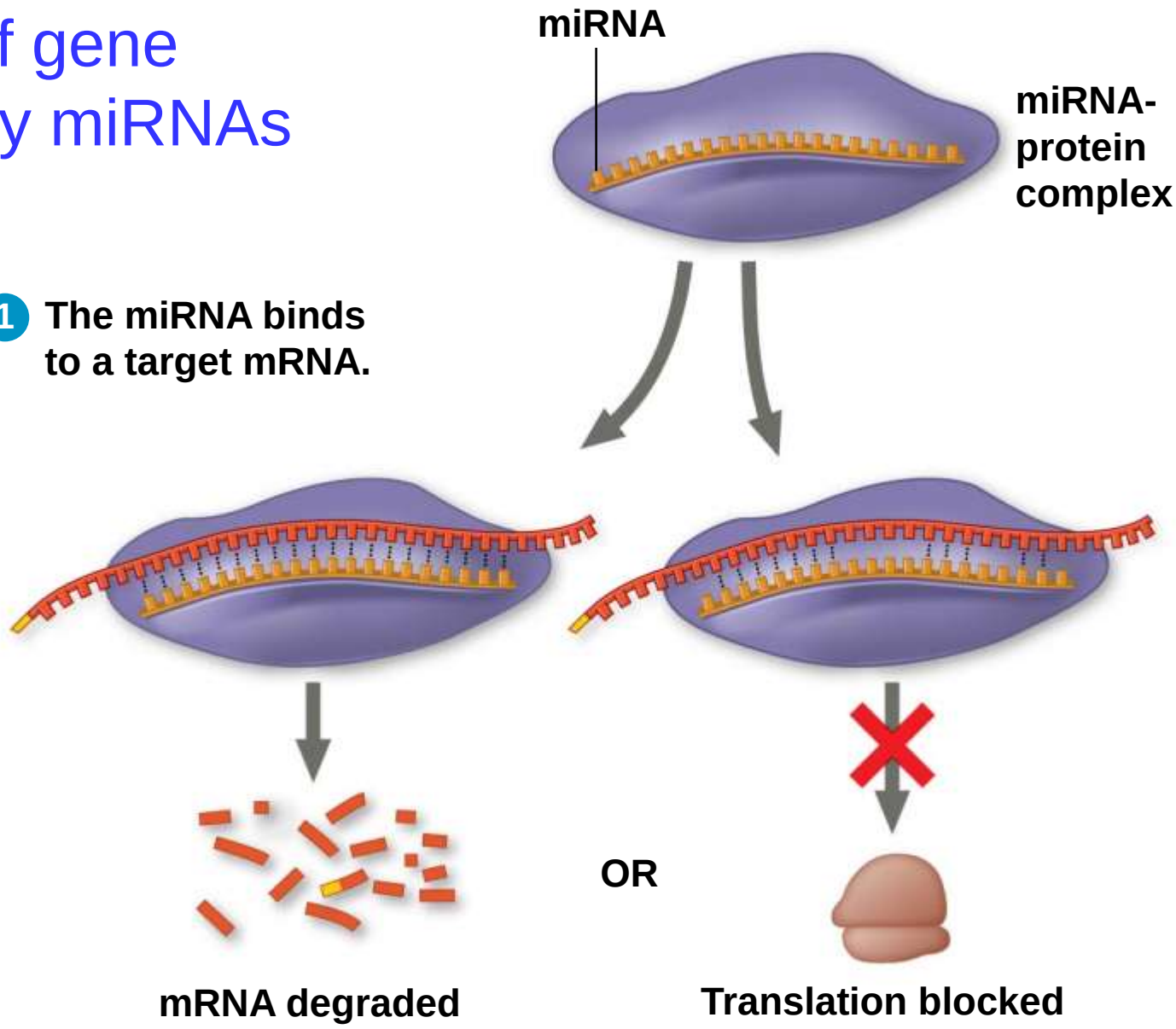


Figure 18.14

Regulation of gene expression by miRNAs



RNA interference

- The phenomenon of inhibition of gene expression by RNA molecules is called **RNA interference (RNAi)**
- RNAi is a blanket term for an important set of pathways that are used to regulate gene expression, which can refer to both small interfering RNAs (siRNAs) and microRNAs (miRNAs).
- siRNAs and miRNAs are similar but form from different RNA precursors

More on this topic in your future molecular biology course.

Chromatin Remodeling and Silencing of Transcription by ncRNAs

- **siRNAs** play a role in heterochromatin formation and can block large regions of the chromosome (see next two slides)
- Furthermore, small RNAs may also block transcription of specific genes
  - *piwi*-interaction RNAs (*piRNAs; 24-31 bp*) – induce formation of heterochromatin, blocking expression of some parasitic DNA elements in transposons. (more in Ch20)
  - Long nonconding RNAs (lncRNAs; 200-10^5 bp) – one type of lncRNA is responsible for X chromosome inactivation

Figure 18.15a

Role of siRNA-protein complex in condensation of chromatin at the centromere

1. **RNA transcripts (red) produced.**
2. **Yeast enzyme synthesizes strands complementary to RNA transcripts.**
3. **Double-stranded RNA processed into siRNAs that associate with proteins.**
4. **The siRNA-protein complexes bind RNA transcripts and become tethered to centromere region.**

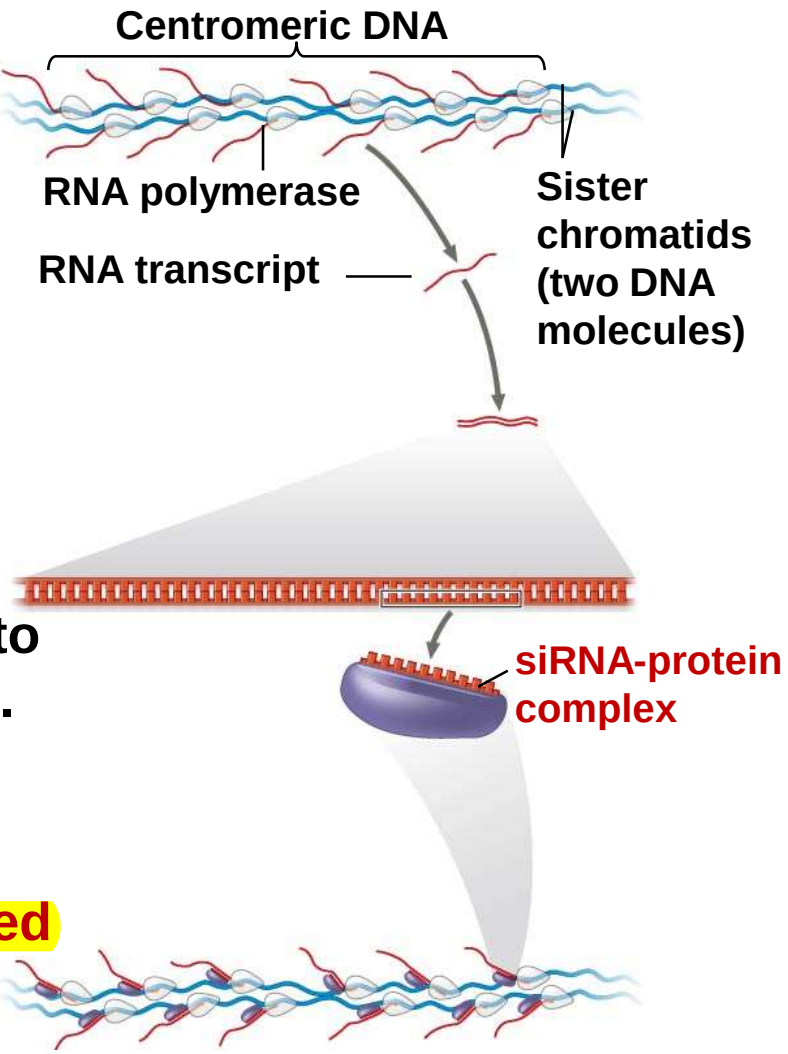
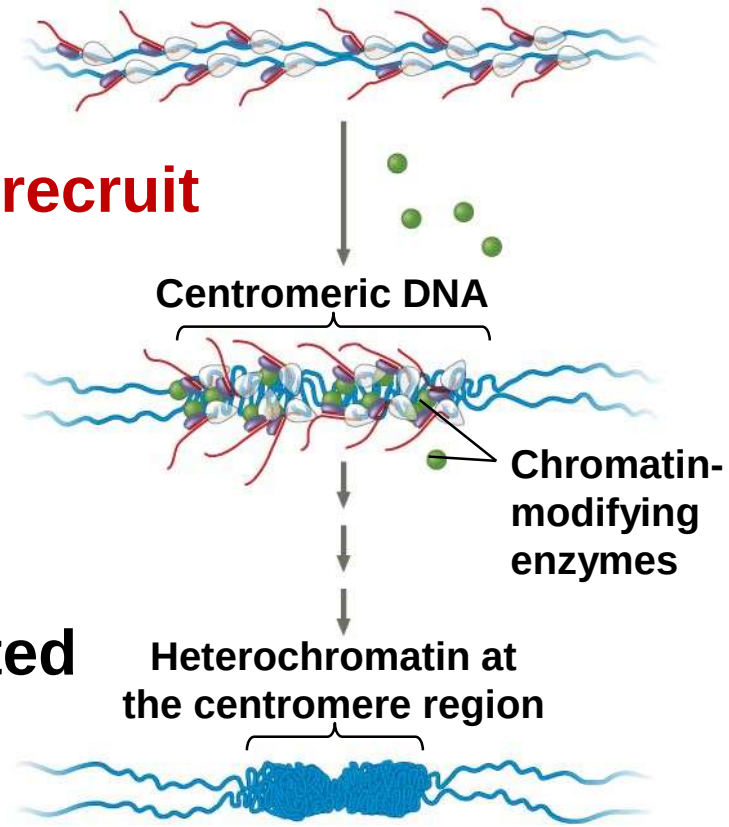


Figure 18.15b

Role of chromatin-modifying enzymes in condensation of chromatin at the centromere

5 The siRNA-protein complexes recruit histone-modifying enzymes.

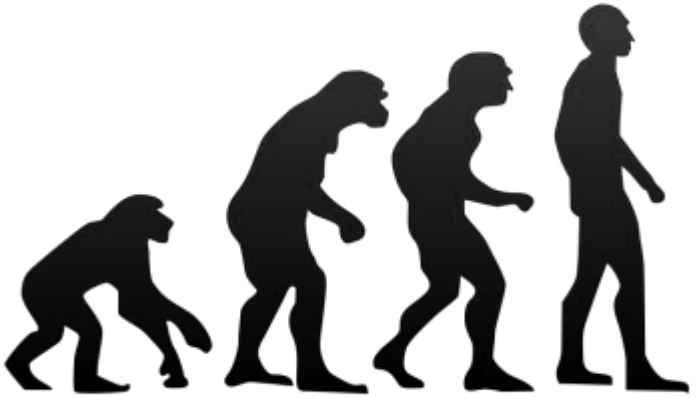


6 Chromatin condensation is initiated and heterochromatin is formed.

RNA-based regulation of chromatin structure plays an important role in gene regulation

The Evolutionary Significance of Small ncRNAs

- Small ncRNAs can regulate gene expression at multiple steps and in many ways
- An increase in the number of miRNAs in a species may have allowed morphological complexity to increase over evolutionary time
- siRNAs may have evolved first, followed by miRNAs and later piRNAs

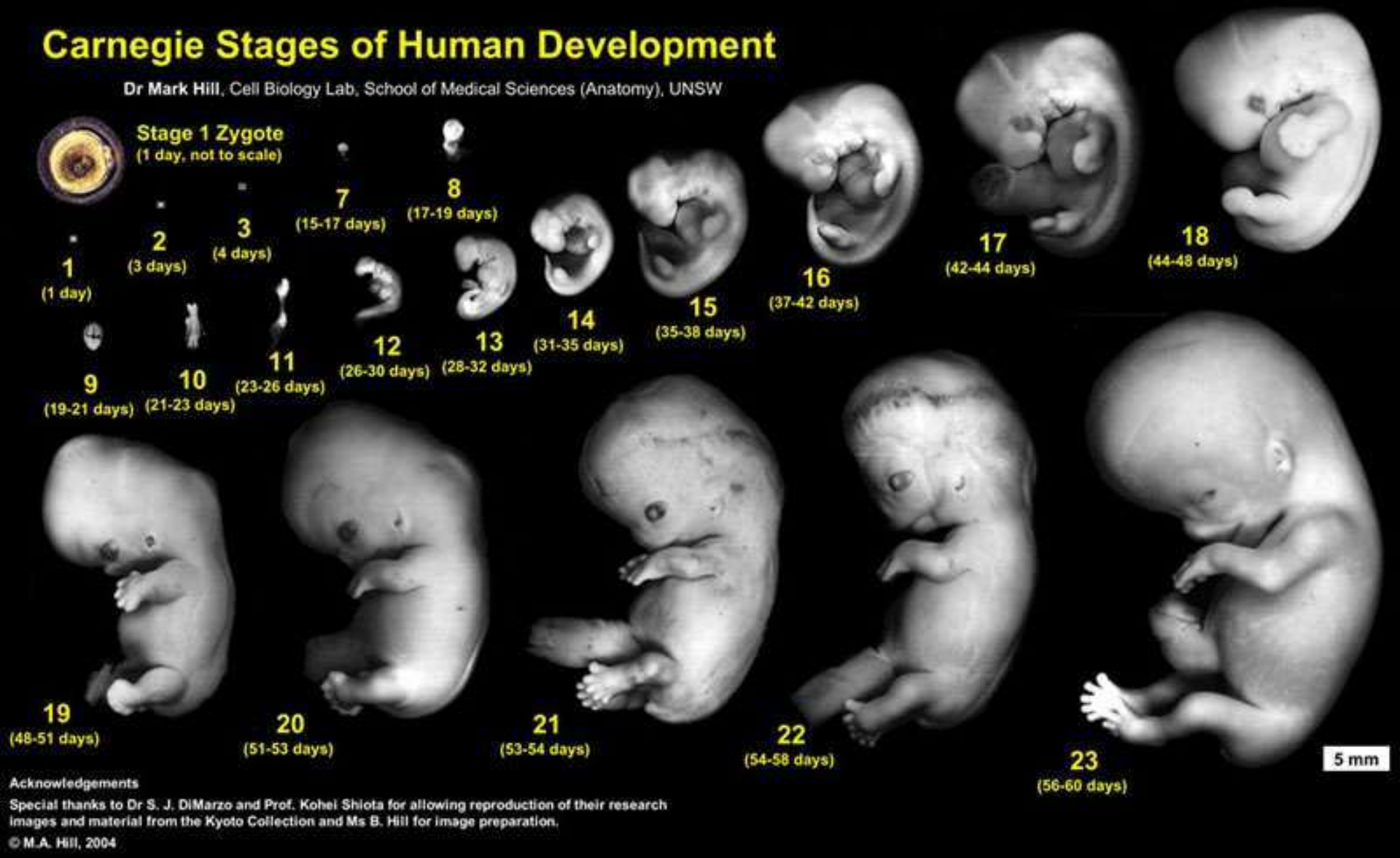


Concept 18.4: A program of differential gene expression leads to the different cell types in a multicellular organism

- During embryonic development, a fertilized egg gives rise to many different cell types

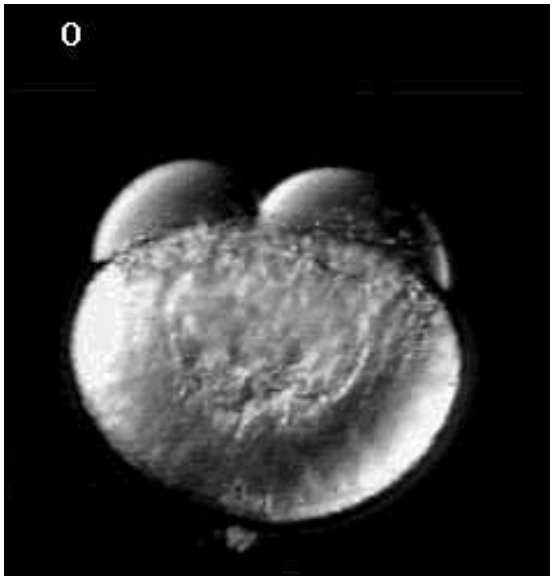
- Cell types are organized successively into tissues, organs, organ systems, and the whole organism
- **Gene expression** orchestrates the developmental programs of animals

As for human, What a difference 60 days can makes



A Genetic Program for Embryonic Development

- The transformation from zygote 受精卵 to adult results from



重要名詞

  - Cell division (分裂)
  - Cell differentiation (分化)
  - Morphogenesis (形態發生；形態演化)

Cells undergo Division; Expansion, Movement, Apoptosis

Cell differentiation & Morphogenesis

重要名詞

- **Cell differentiation** is the process by which cells become specialized in structure and function
- The physical processes that give an organism its shape constitute **morphogenesis**
- **Differential gene expression** results from genes being regulated differently in each cell type
- Materials in the egg can set up gene regulation that is carried out as cells divide (**Maternal effects**)

Cytoplasmic Determinants & Inductive Signals

- An egg's cytoplasm contains RNA, proteins, and other substances that are distributed unevenly in the unfertilized egg
- **Cytoplasmic determinants** are maternal substances in the egg that influence early development
- As the zygote divides by mitosis, cells contain different cytoplasmic determinants, which lead to different gene expression

Figure 18.17a

Sources of developmental information for the early embryo

(a) Cytoplasmic determinants in the egg

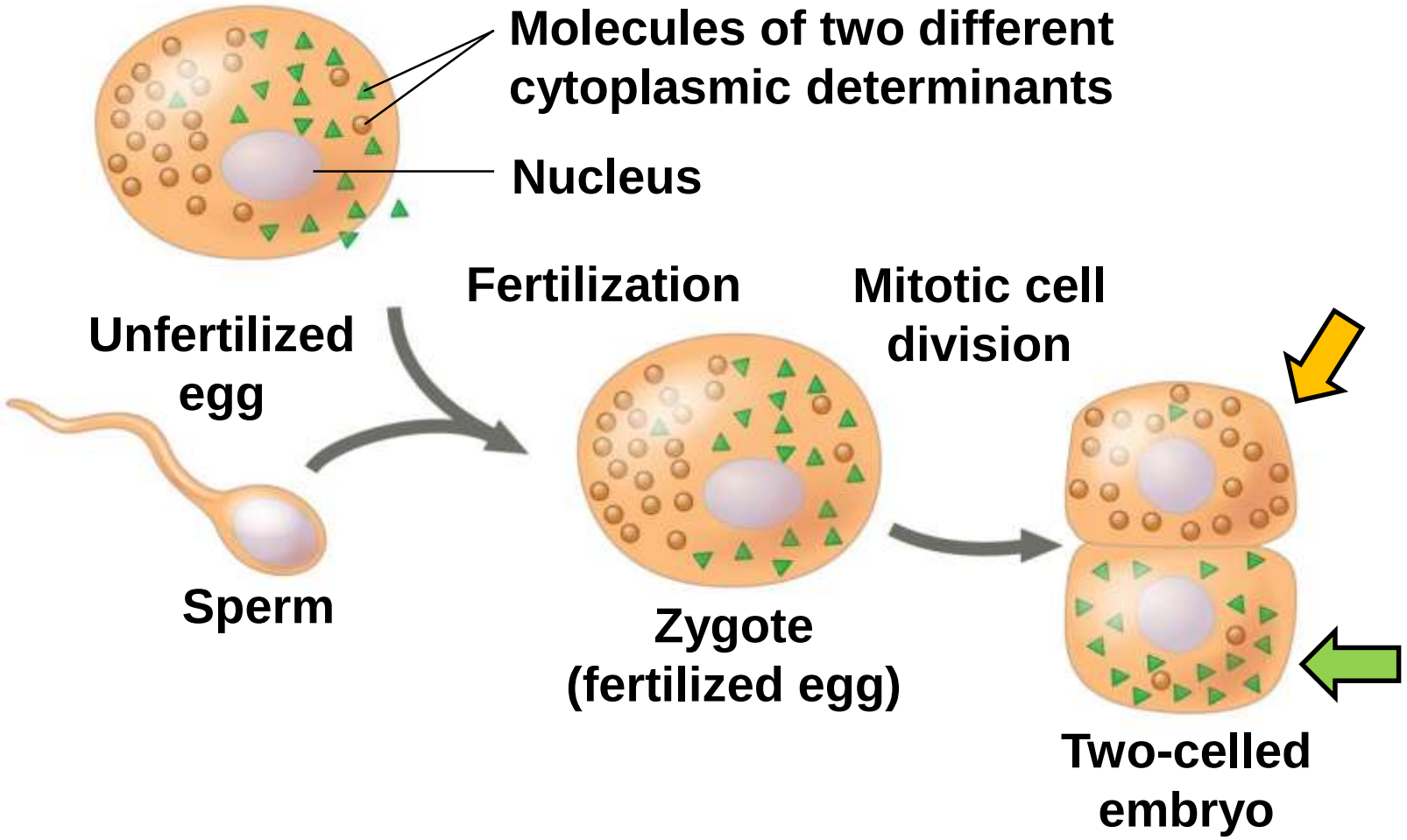
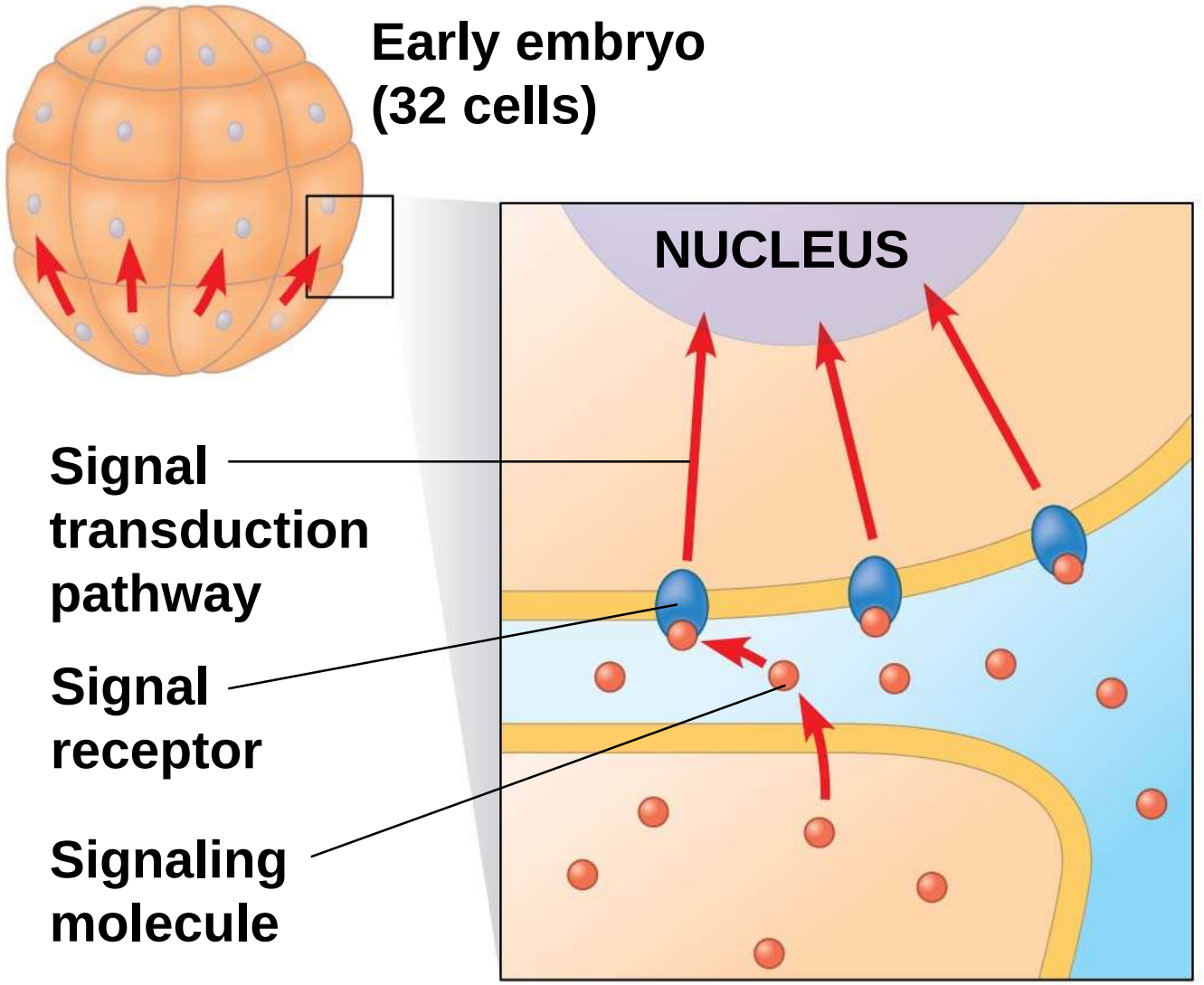


Figure 18.17b

Sources of developmental information for the early embryo

(b) Induction by nearby cells



Paracrine signaling
細胞分泌的激素通過細胞外液擴散而作用於臨近靶細胞的作用方式

Induction

- The other important source of developmental information is the **environment** around the cell, especially signals from nearby embryonic cells
- In the process called **induction**, signal molecules from embryonic cells cause transcriptional changes in nearby target cells
- Thus, interactions between cells induce differentiation of specialized cell types

PLAY Animation: Cell Signaling

Sequential Regulation of Gene Expression During Cellular Differentiation

- **Determination** (cell fate determination) commits a cell to its final fate
- Determination precedes differentiation
- Cell differentiation is marked by the production of **tissue-specific proteins**

Master regulatory gene

- **Myoblasts** produce muscle-specific proteins and form skeletal muscle cells
- ***MyoD*** is one of several "master regulatory genes" that produce proteins that commit the cell to becoming *skeletal muscle*
- The MyoD protein is a transcription factor that binds to enhancers of various target genes

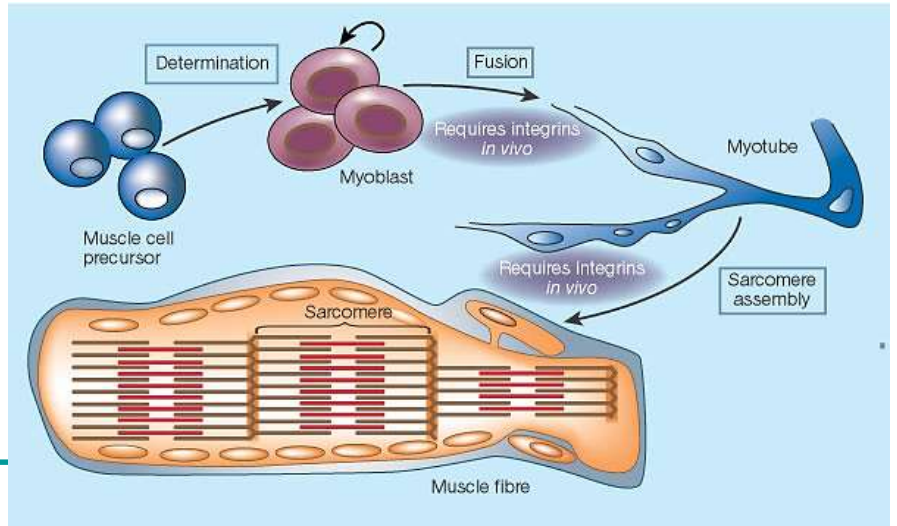


Figure 18.18-1

Determination and differentiation of muscle cells

Figure 18.18-2

Determination and differentiation of muscle cells

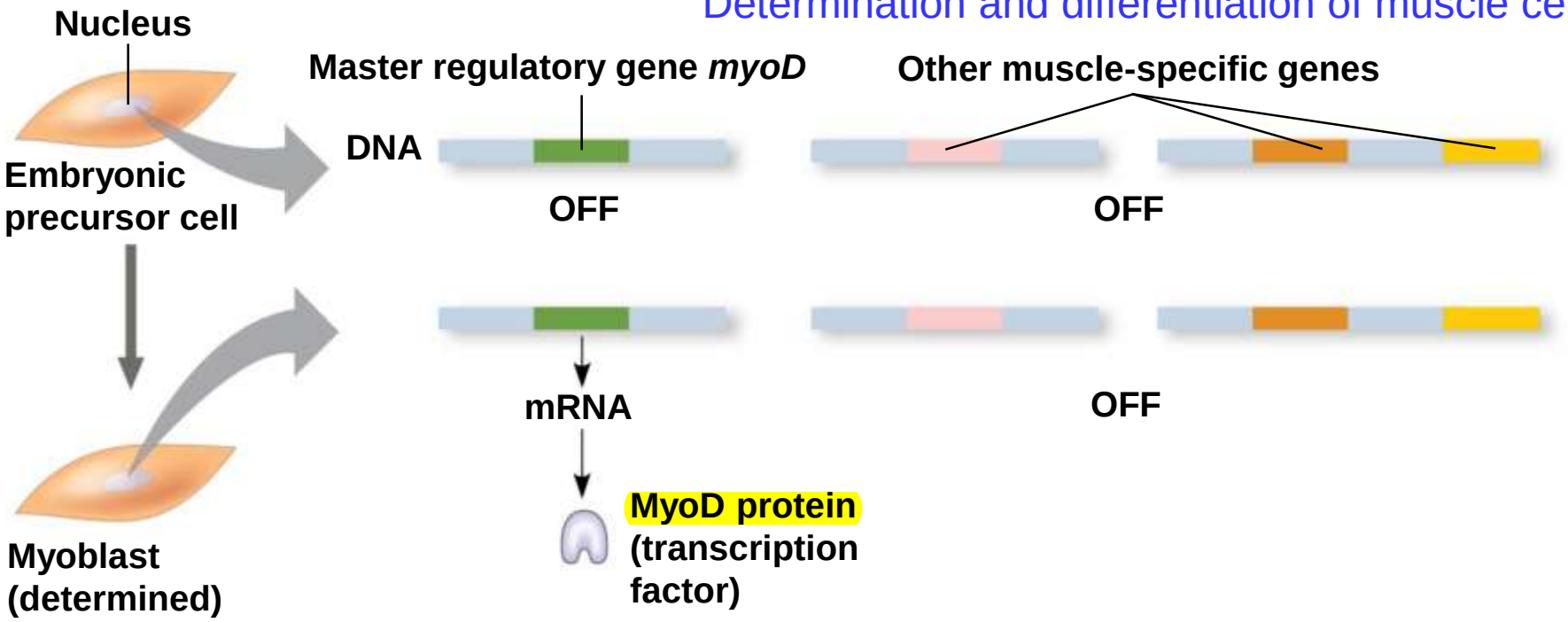
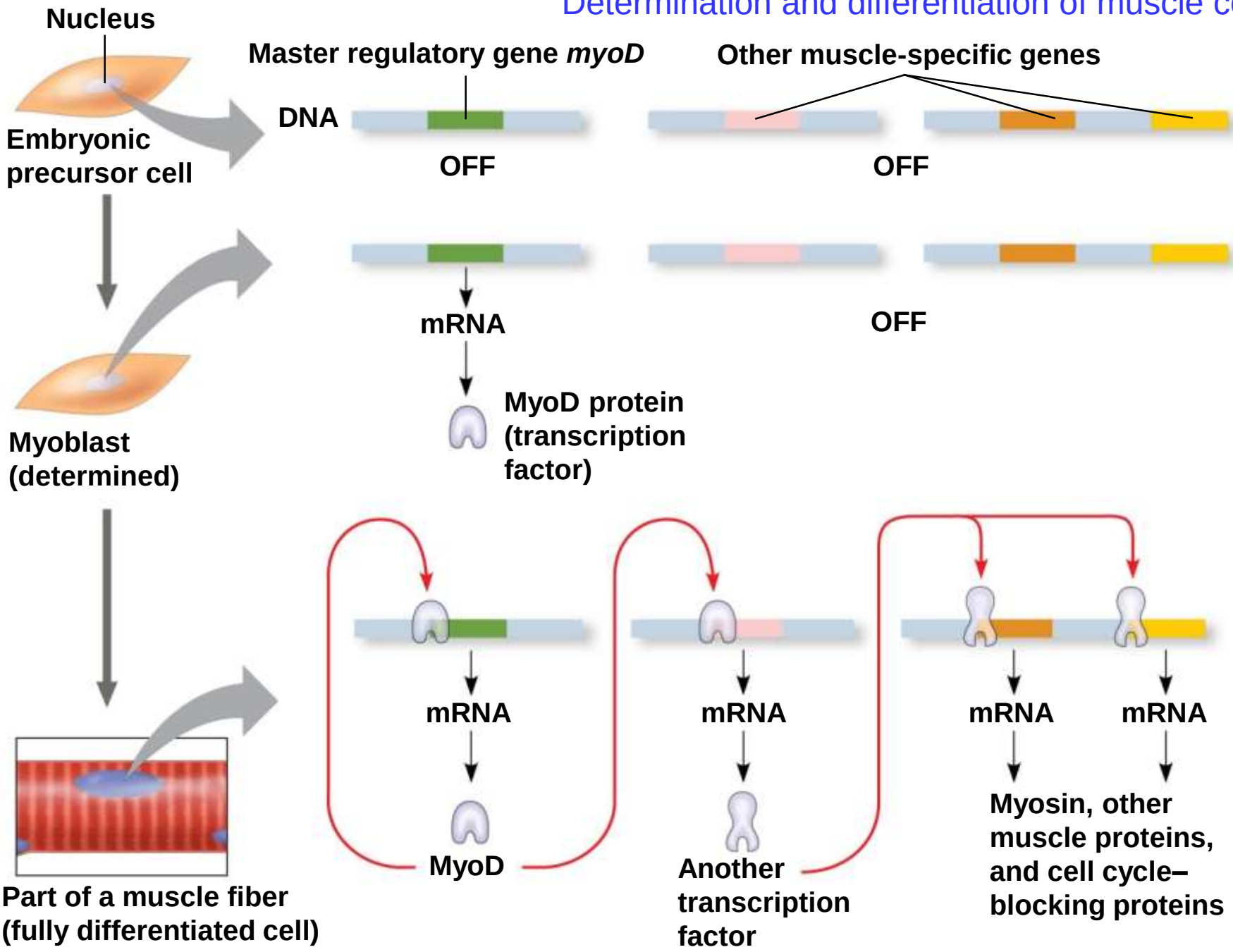
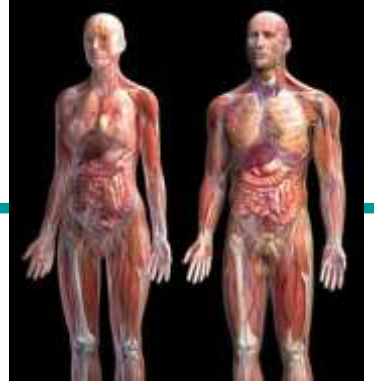


Figure 18.18-3

Determination and differentiation of muscle cells



Pattern Formation: Setting Up the Body Plan

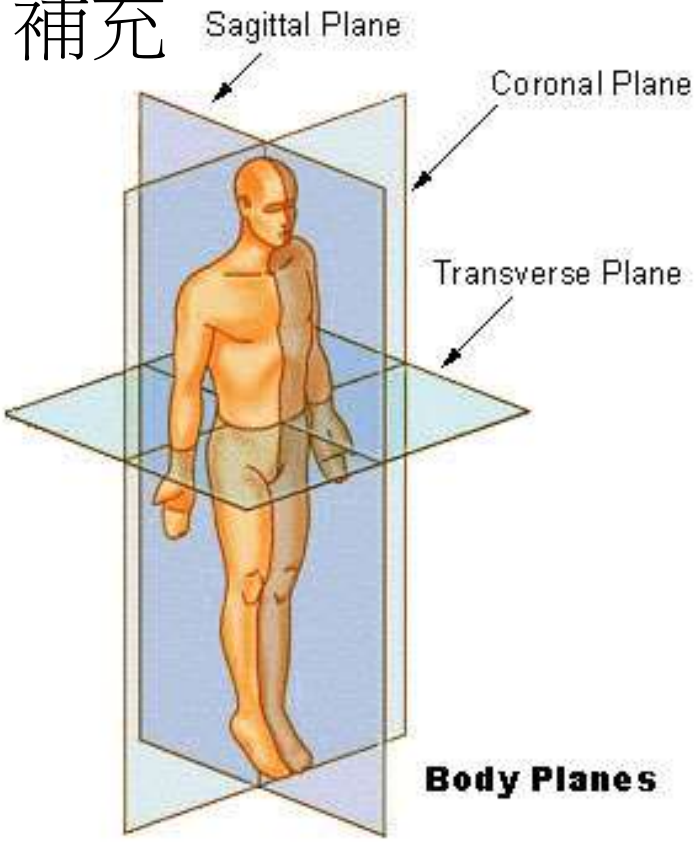


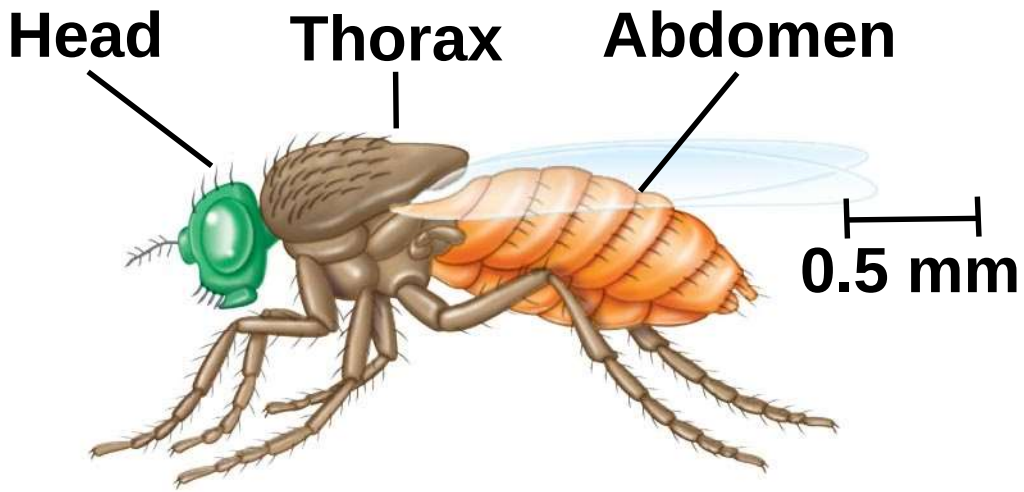
- **Pattern formation** is the development of a spatial organization of tissues and organs
- In animals, pattern formation begins with the establishment of the major axes
- **Positional information**, the molecular cues that control pattern formation, tells a cell its location relative to the body axes and to neighboring cells

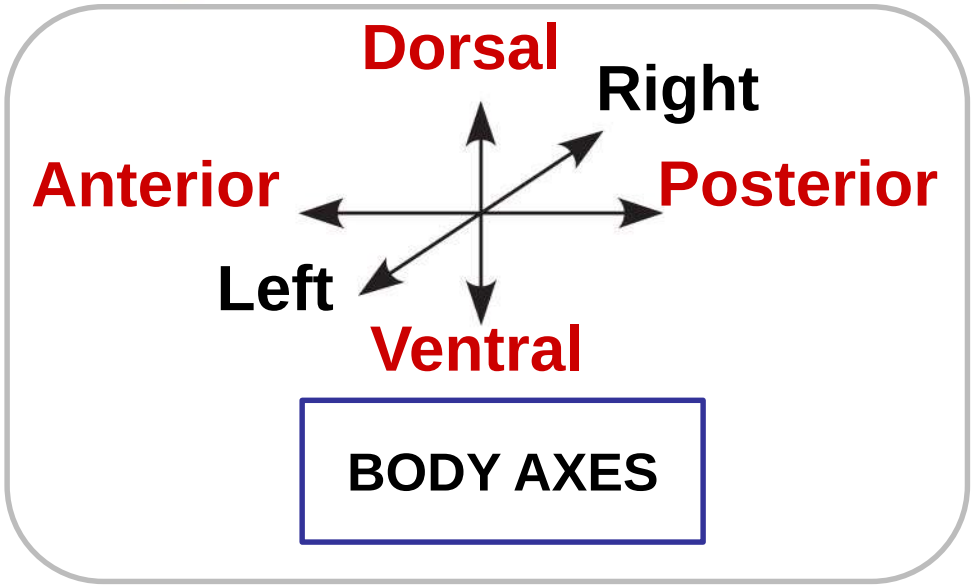
Fig. 18-19a

Pattern formation and body axes

補充







Pattern formation during development

- Pattern formation has been extensively studied in the fruit fly (*Drosophila melanogaster) (~13700 genes)*
- Combining anatomical, genetic, and biochemical approaches, researchers have discovered developmental principles common to many other species, including humans

The Development of Drosophila

- In *Drosophila*, **cytoplasmic determinants** in the unfertilized egg determine the axes before fertilization
- After fertilization, the embryo develops into a segmented larva, which goes through three stages, forms a cocoon, and metahorphoses into the adult.

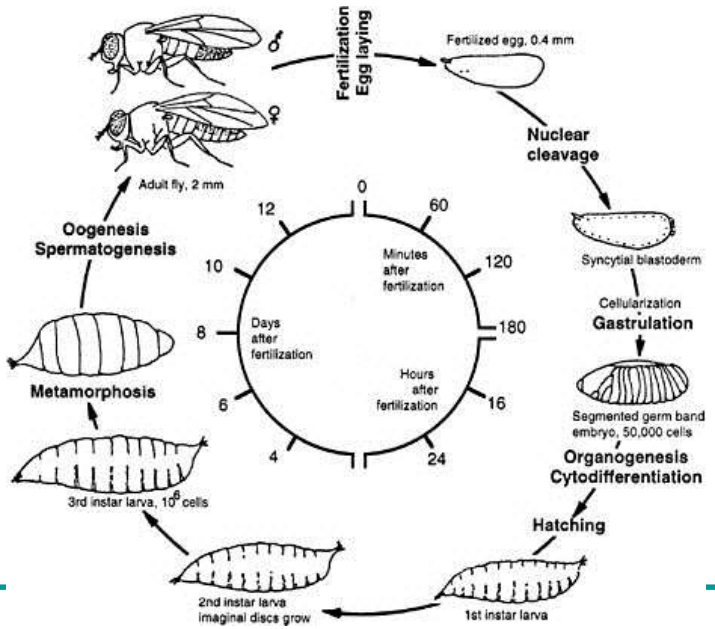
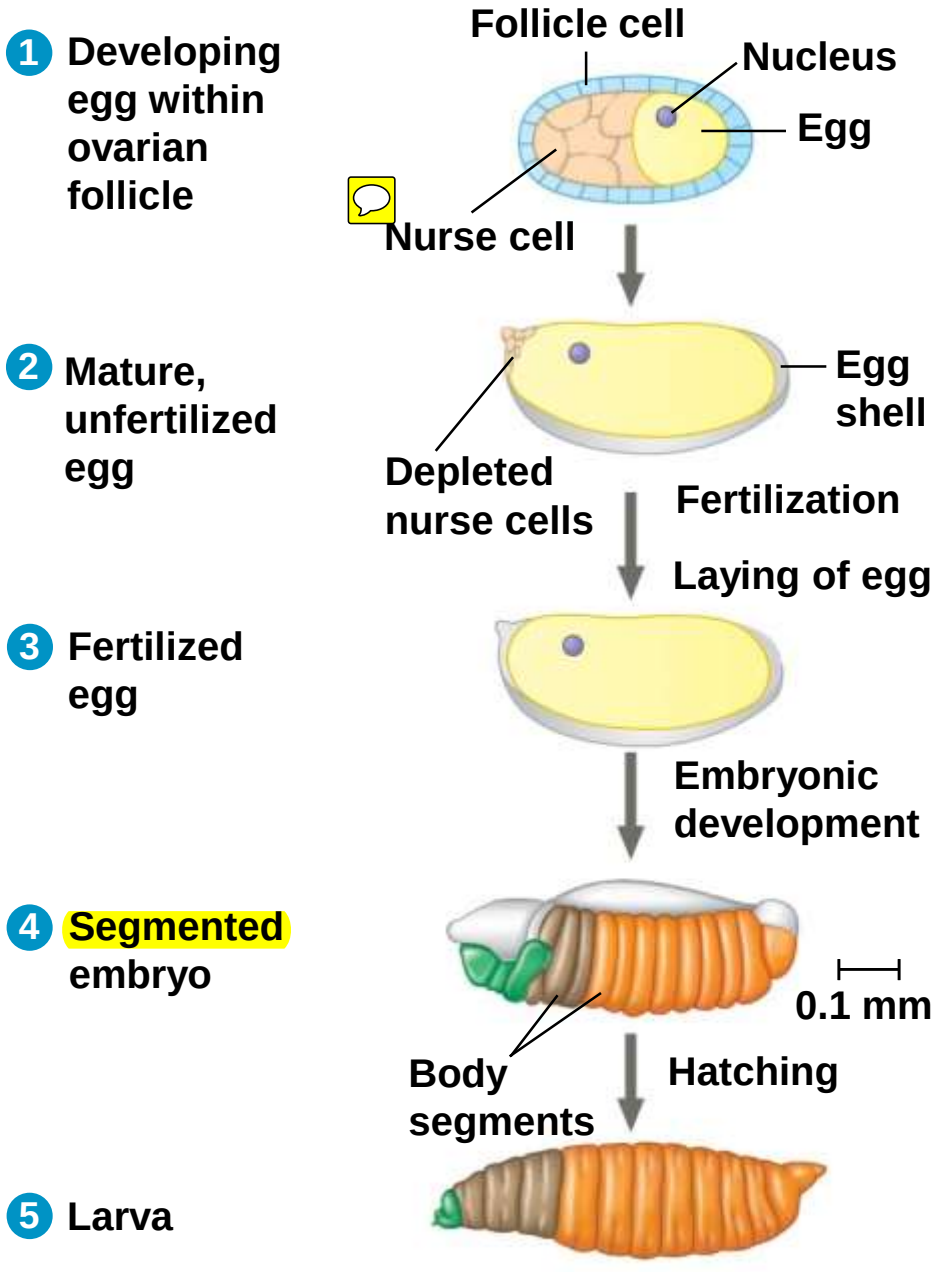


Figure 18.19b-5

Key developmental events in the life cycle of *Drosophila*

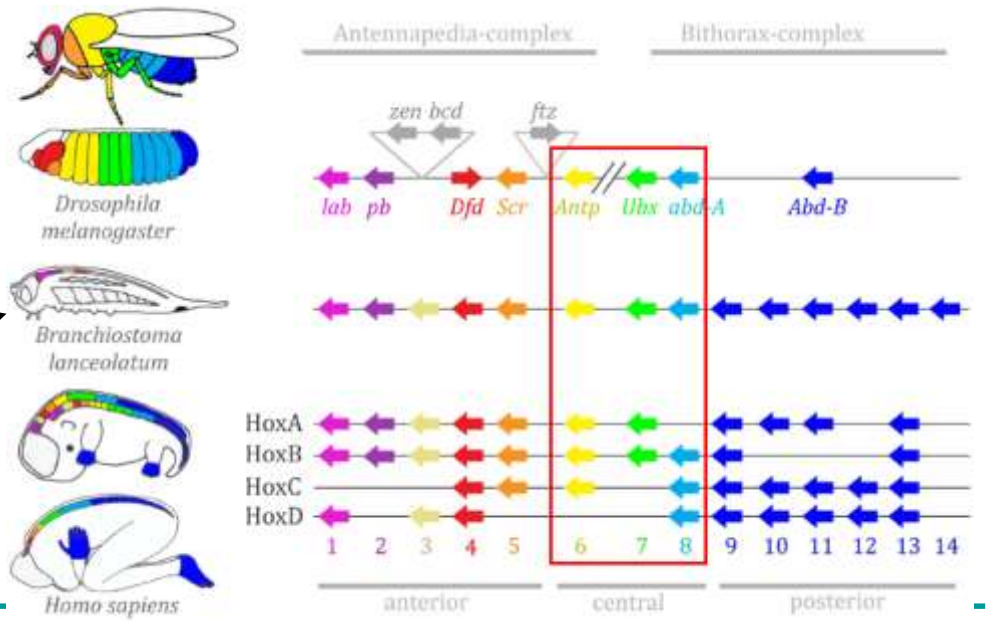


(b) Development from egg to larva

Genetic Analysis of Early Development: Scientific Inquiry

- Edward B. Lewis, Christiane Nüsslein-Volhard, and Eric Wieschaus won a Nobel 1995 Prize for decoding **pattern formation** in *Drosophila*
- Lewis demonstrated that genes direct the developmental process – **homeotic genes (Hox genes 同源基因)**

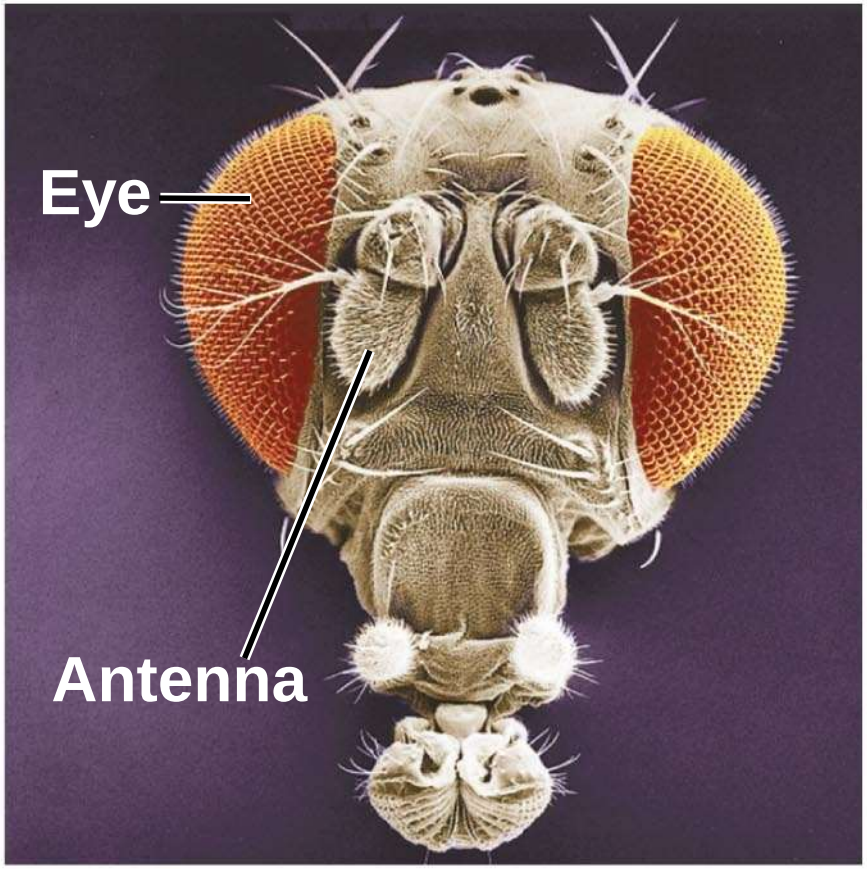
文昌魚:生物演化研究中的模式生物，它揭示了現存脊椎動物的起源



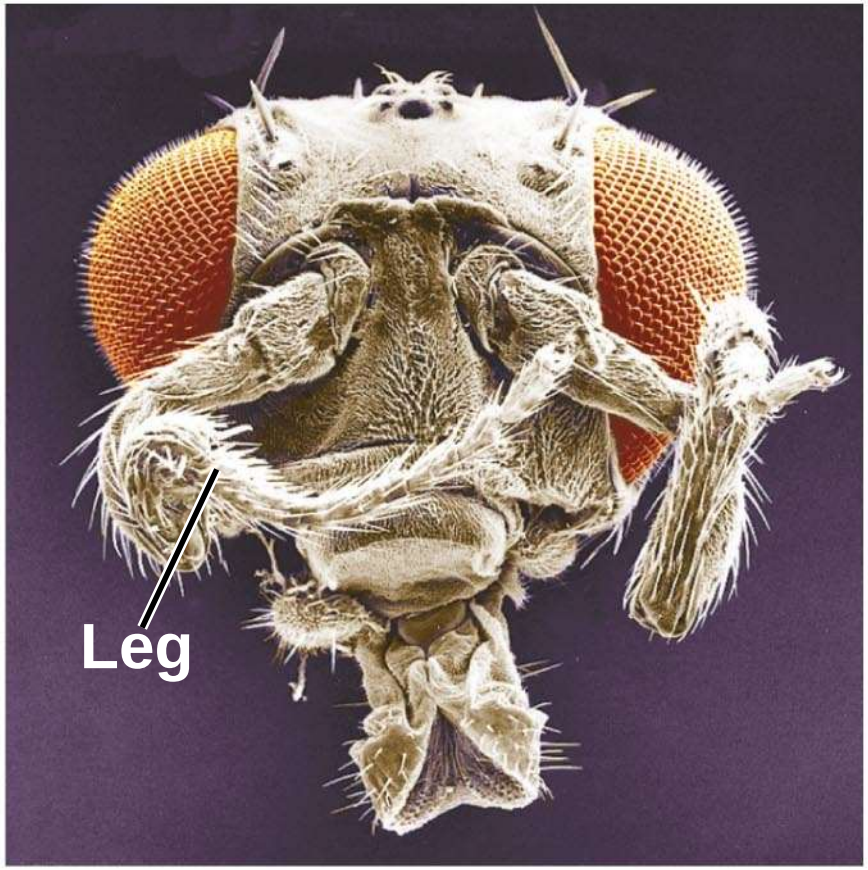
http://bioinformatics.uni-konstanz.de/HueberHox/Research/Classification.php

Fig. 18-20

Abnormal pattern formation in *Drosophila*



Wild type



Mutant

Homeotic gene mutation caused a misplacement of structures. In this case, a pair of legs in place of antennae

Segment formation by **mutational approach**

- Nüsslein-Volhard and Wieschaus studied segment formation
  - They created mutants, conducted breeding experiments, and looked for corresponding genes
  - Breeding experiments were complicated by **embryonic lethality** (embryos with lethal致死的mutations)
  - They found 120 genes essential for normal segmentation

Axis Establishment

- **Maternal effect genes** encode for cytoplasmic determinants that initially establish the axes of the body of *Drosophila*

- These maternal effect genes are also called **egg-polarity genes** because they control **orientation (polarity)** of the egg and consequently the fly development and pattern formation

PLAY **Animation: Development of Head-Tail Axis in Fruit Flies**

Case study: Bicoid

Question: Is Bicoid a morphogen that determines the anterior end of a fruit fly?

Bicoid: A Morphogen Determining Head Structures

- One maternal effect gene, the ***bicoid*** gene, affects the front half of the body

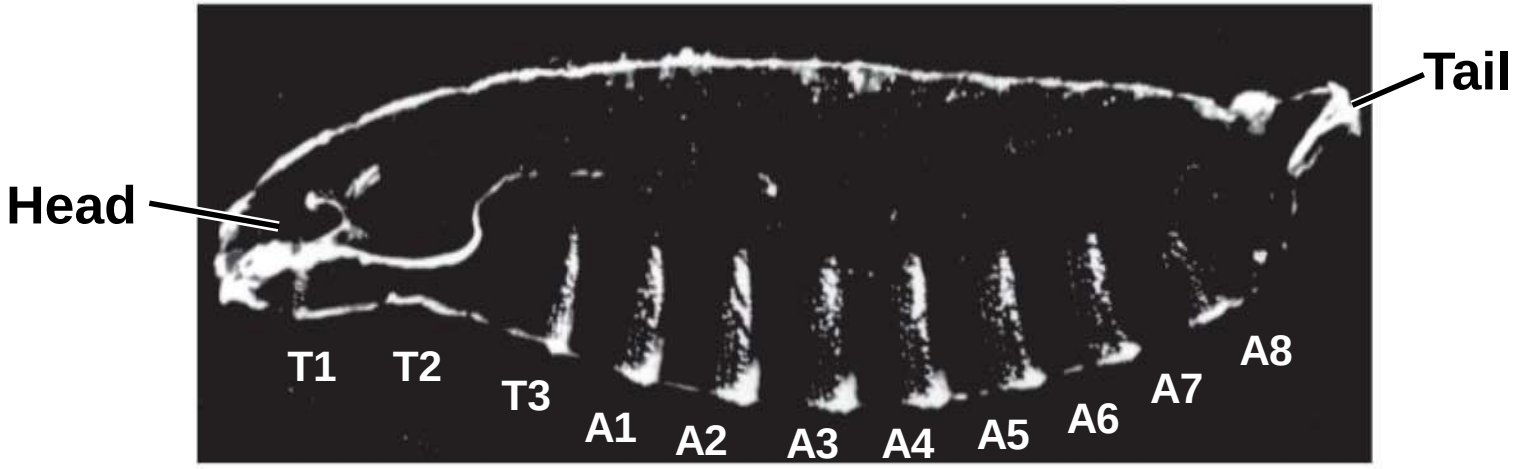
- An embryo whose mother has a **mutant *bicoid*** gene lacks the front half of its body and has duplicate posterior structures at both ends

See next figure

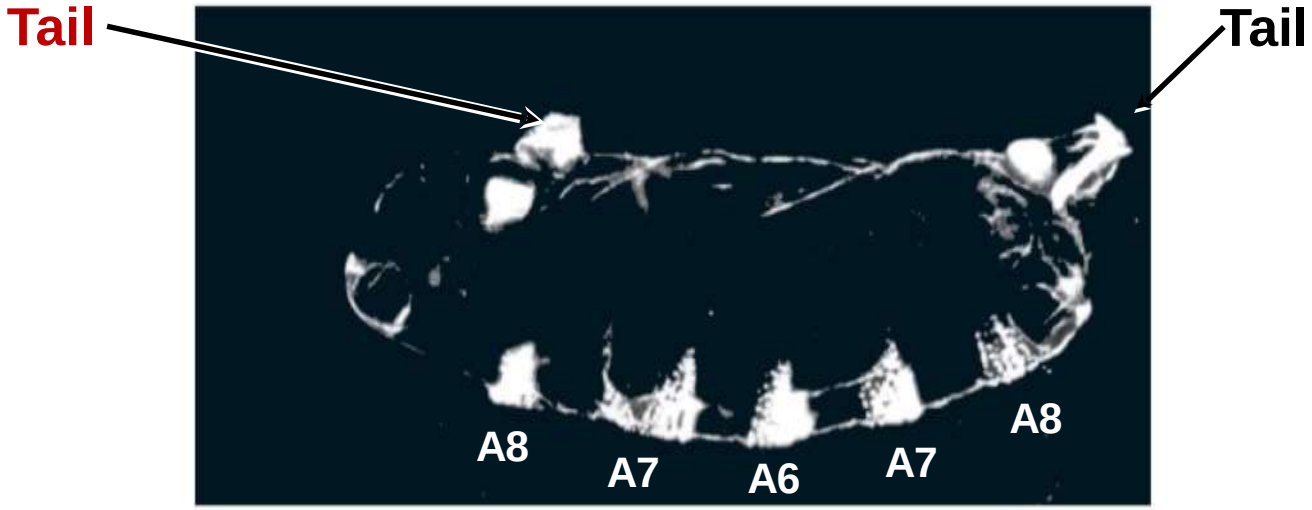
Fig. 18-21

Effect of the bicoid gene on Drosophila development:

is it a morphogen that determines the anterior end of a fruit fly?



Wild-type larva

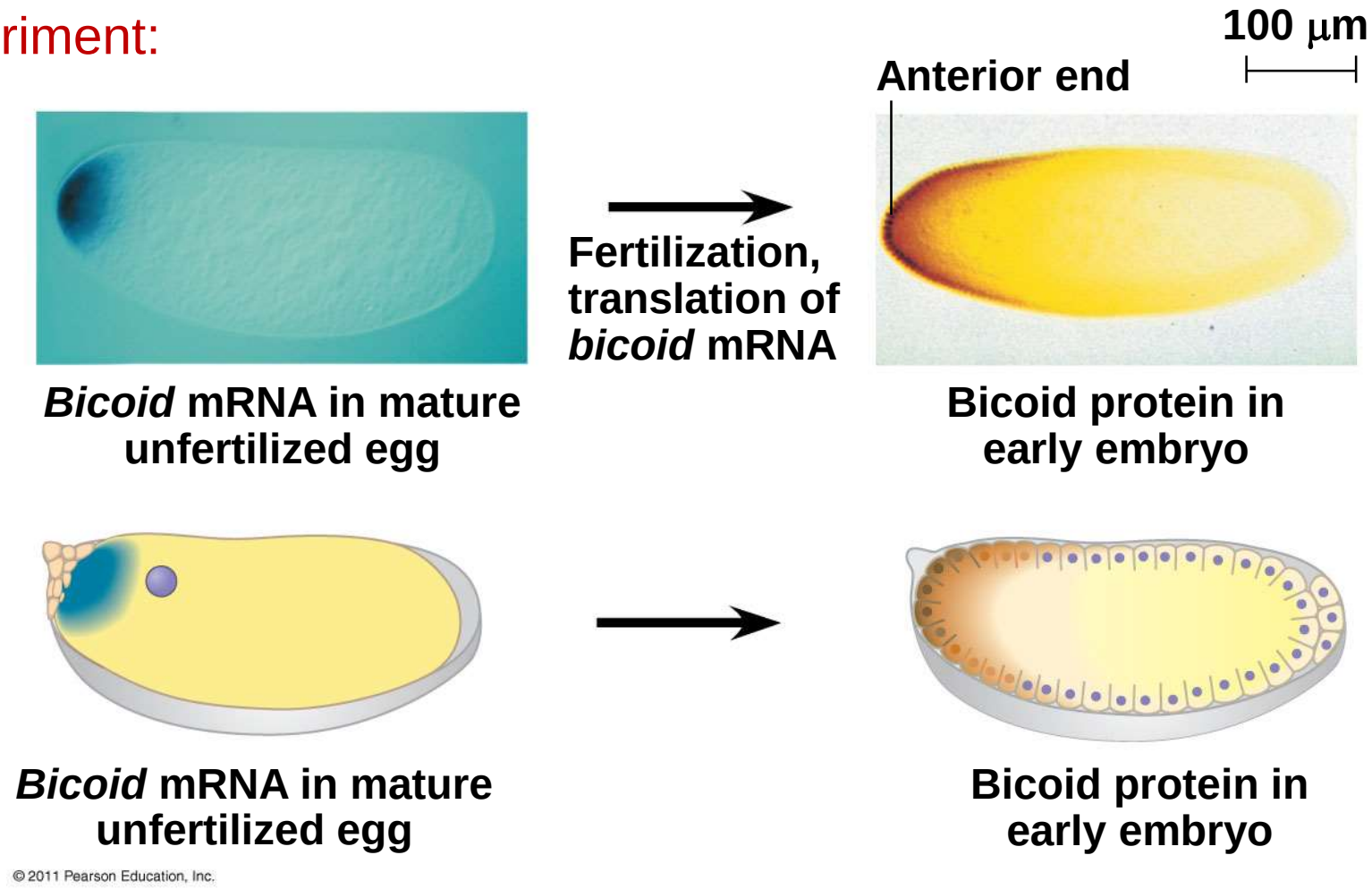


Mutant larva (*bicoid*)

Figure 18.22

Question: Is Bicoid a morphogen that determines the anterior end of a fruit fly?

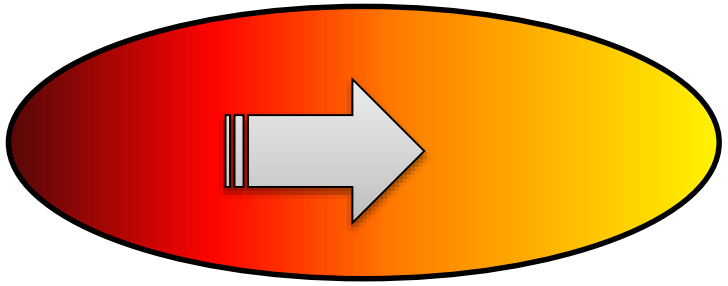
Experiment:



Discussion: The expression pattern and diffusion gradient of Bicoid support it to be a morphogen specifying formation of the head-specific structures.

Morphogen　　Morpho- 表示"形,形體,形態"之義

- This phenotype suggests that the product of the mother's *bicoid* gene is concentrated at the future anterior end
- This hypothesis is an example of the gradient hypothesis, in which gradients of substances called **morphogens** establish an embryo's axes and other features



Significance of the *bicoid* research

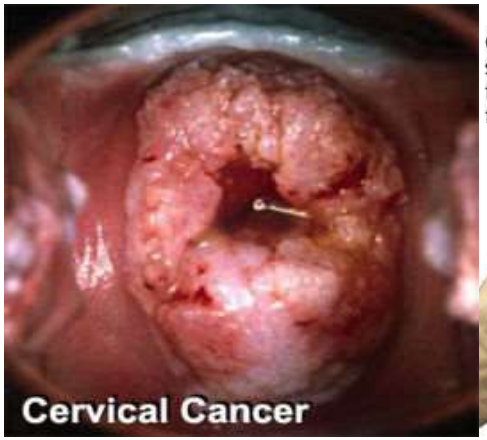
- The *bicoid* research is important for three reasons:

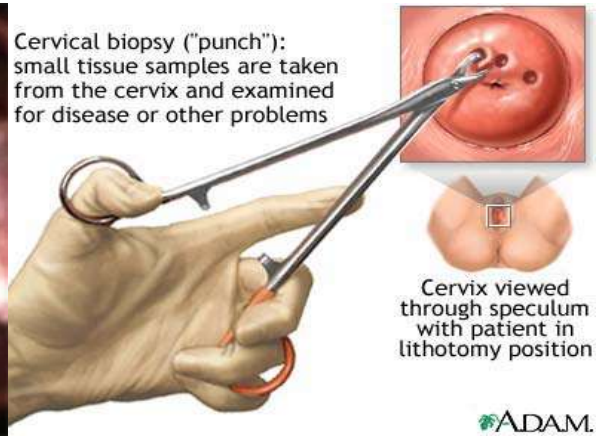
  1. It identified a specific protein required for some early steps in pattern formation
  2. It increased understanding of the mother's role in embryo development
  3. It demonstrated a key developmental principle that a gradient of molecules can determine polarity and position in the embryo

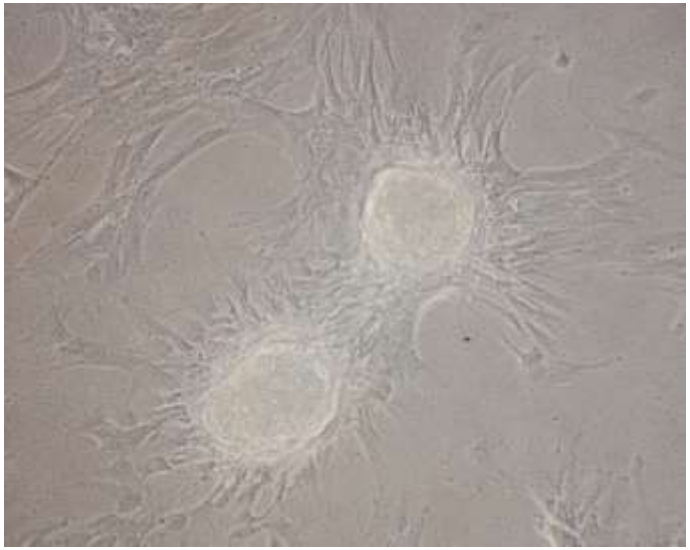
Thinking question: How about left-right patterning?

Concept 18.5: Cancer results from genetic changes that affect cell cycle control

- The gene regulation systems that go wrong during cancer are the very same systems involved in embryonic development







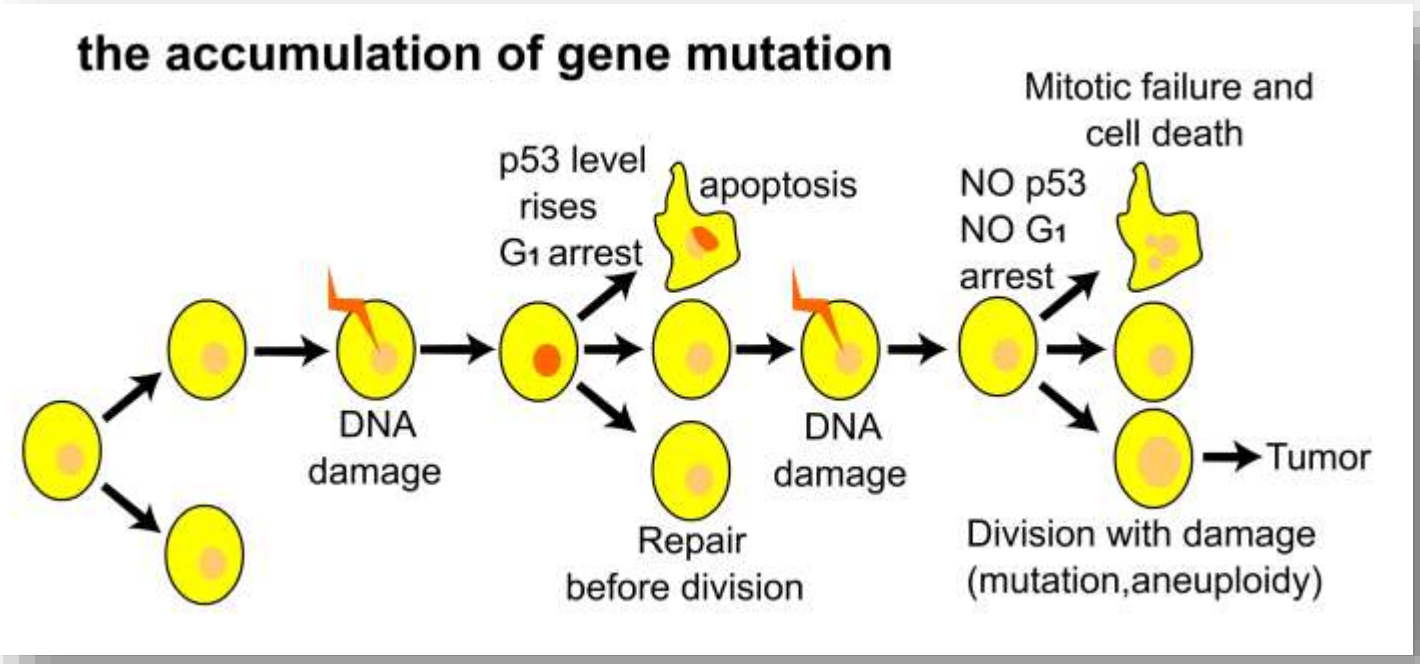
Cancer research in my lab:
Combinational Therapy & BNCT

Primary culture of
neuroendocrine cancer of the cervix

清大醫科系 莊永仁實驗室

Types of Genes Associated with Cancer

- Cancer can be caused by mutations to genes that regulate cell growth and division
- **Tumor viruses** (for example, HPV) can cause cancer in animals including humans

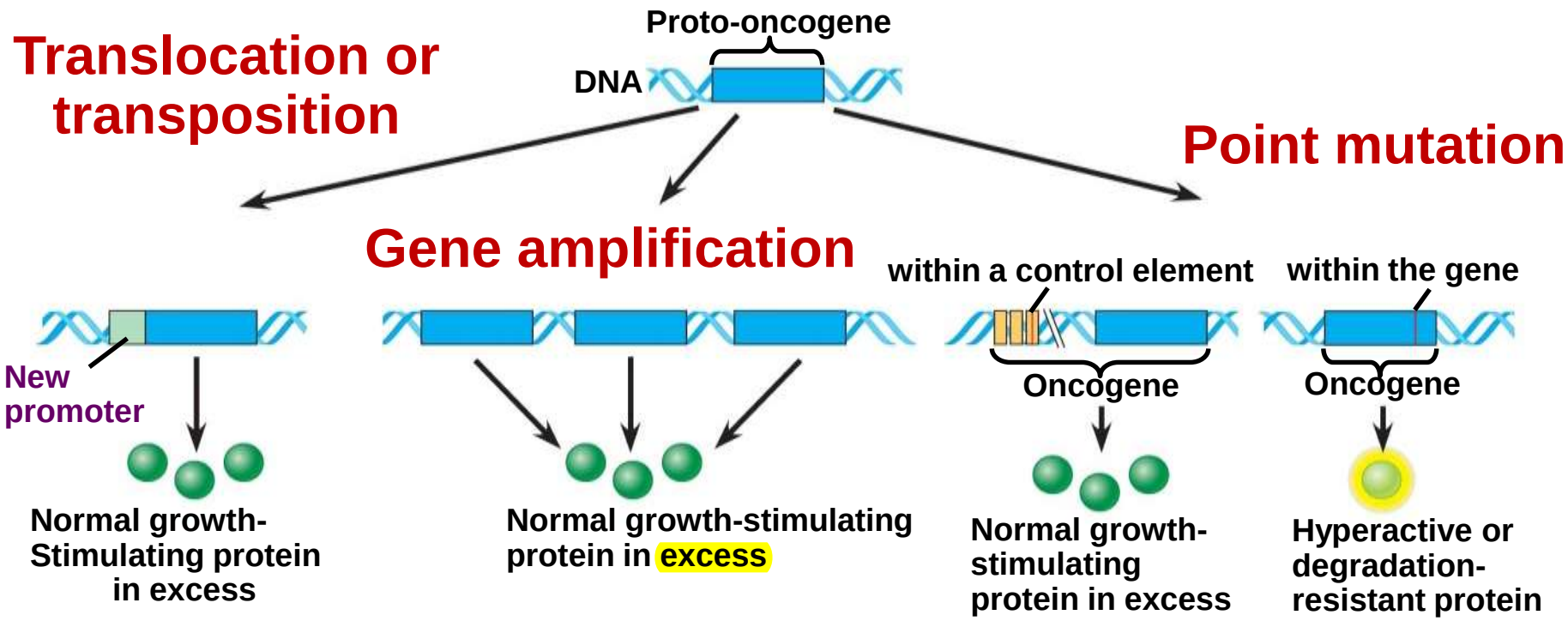


Oncogenes and Proto-Oncogenes

- **Oncogenes** are cancer-causing genes
- **Proto-oncogenes** are the corresponding normal versions of the cellular genes that are responsible for normal cell growth and division
- Conversion of a proto-oncogene to an oncogene can lead to abnormal stimulation of the cell cycle

Fig. 18-23

Genetic changes that can turn proto-oncogenes into oncogenes



More description on next slide

Genetic Changes that can create oncogenes

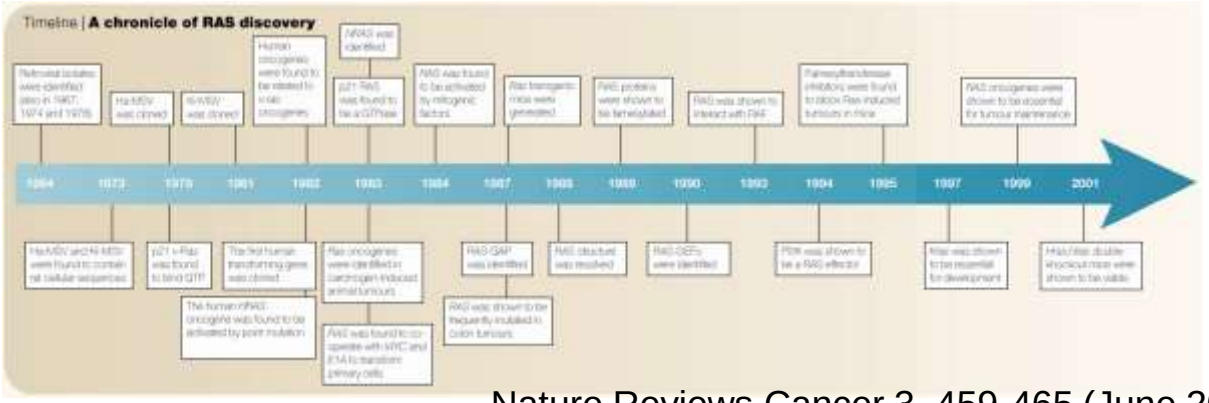
- Proto-oncogenes can be converted to oncogenes by
  - **Movement (translocation or transportation) of DNA** within the genome: if it ends up near an active promoter, transcription may increase
  - **Amplification** of a proto-oncogene: increases the number of copies of the gene
  - **Point mutations** in the proto-oncogene or its control elements: causes an increase in gene expression

Tumor-Suppressor Genes

- **Tumor-suppressor genes** help prevent uncontrolled cell growth
- Mutations that decrease protein products of tumor-suppressor genes may contribute to cancer onset
- Tumor-suppressor proteins
  - Repair damaged DNA
  - Control cell adhesion
  - Inhibit the cell cycle in the cell-signaling pathway

Interference with Normal Cell-Signaling Pathways

- Mutations in the ***ras* proto-oncogene** and ***p53* tumor-suppressor gene** are common in human cancers
- Mutations in the ***ras* gene** can lead to production of a hyperactive Ras protein and increased cell division



Nature Reviews Cancer 3, 459-465 (June 2003)

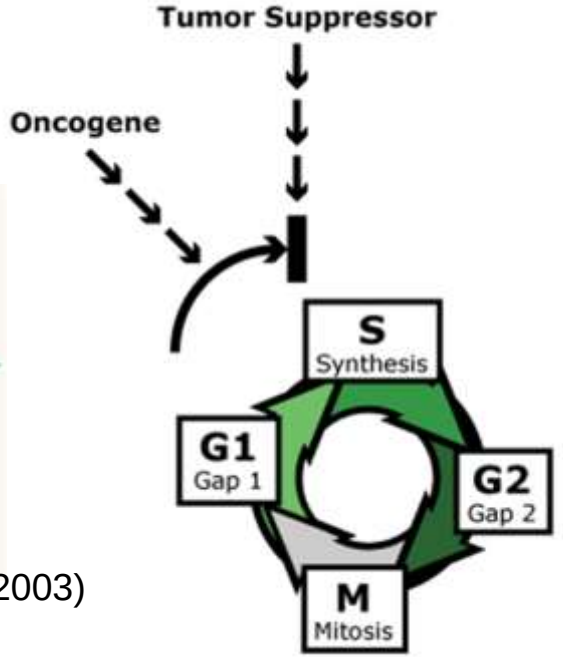


Figure 18.24

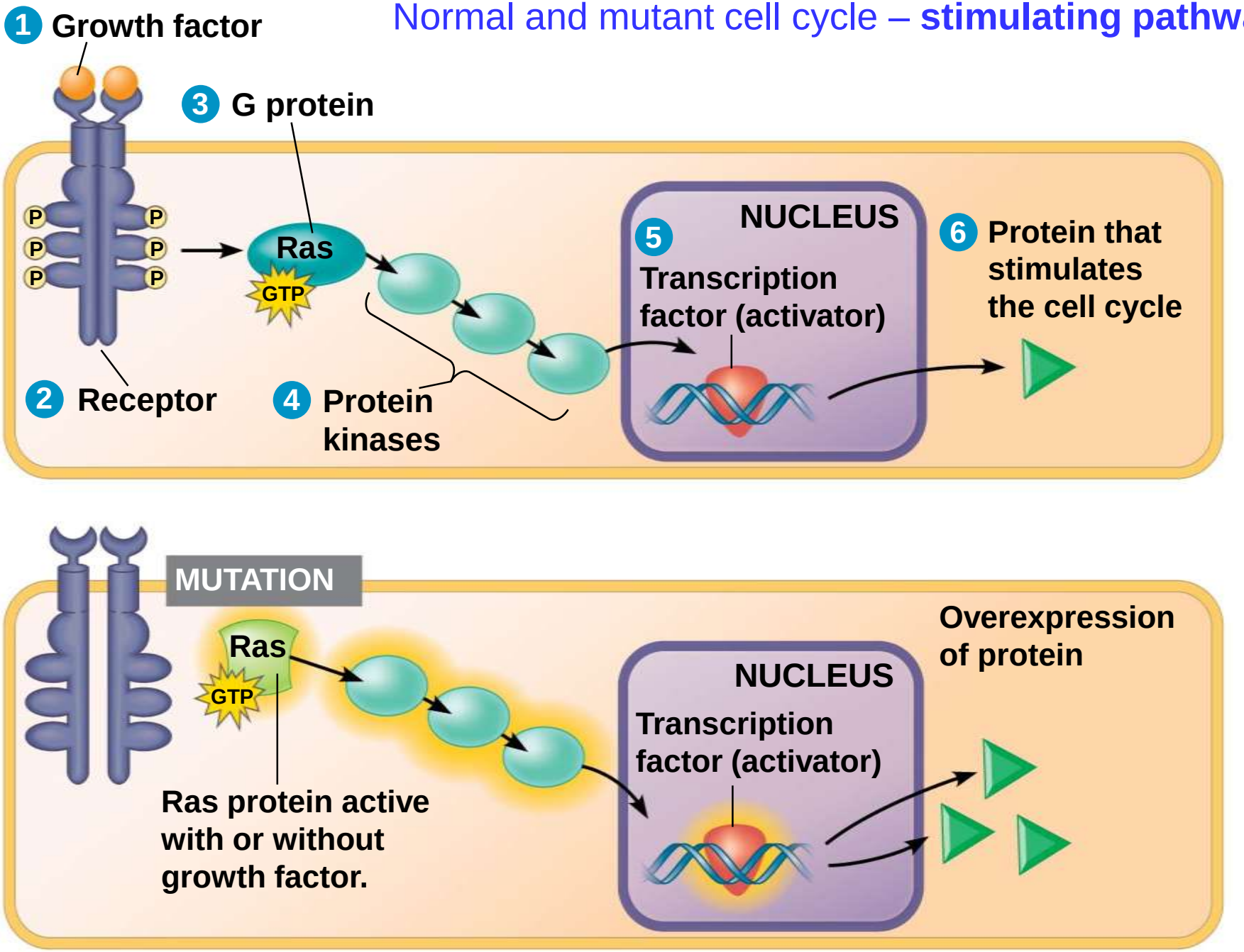
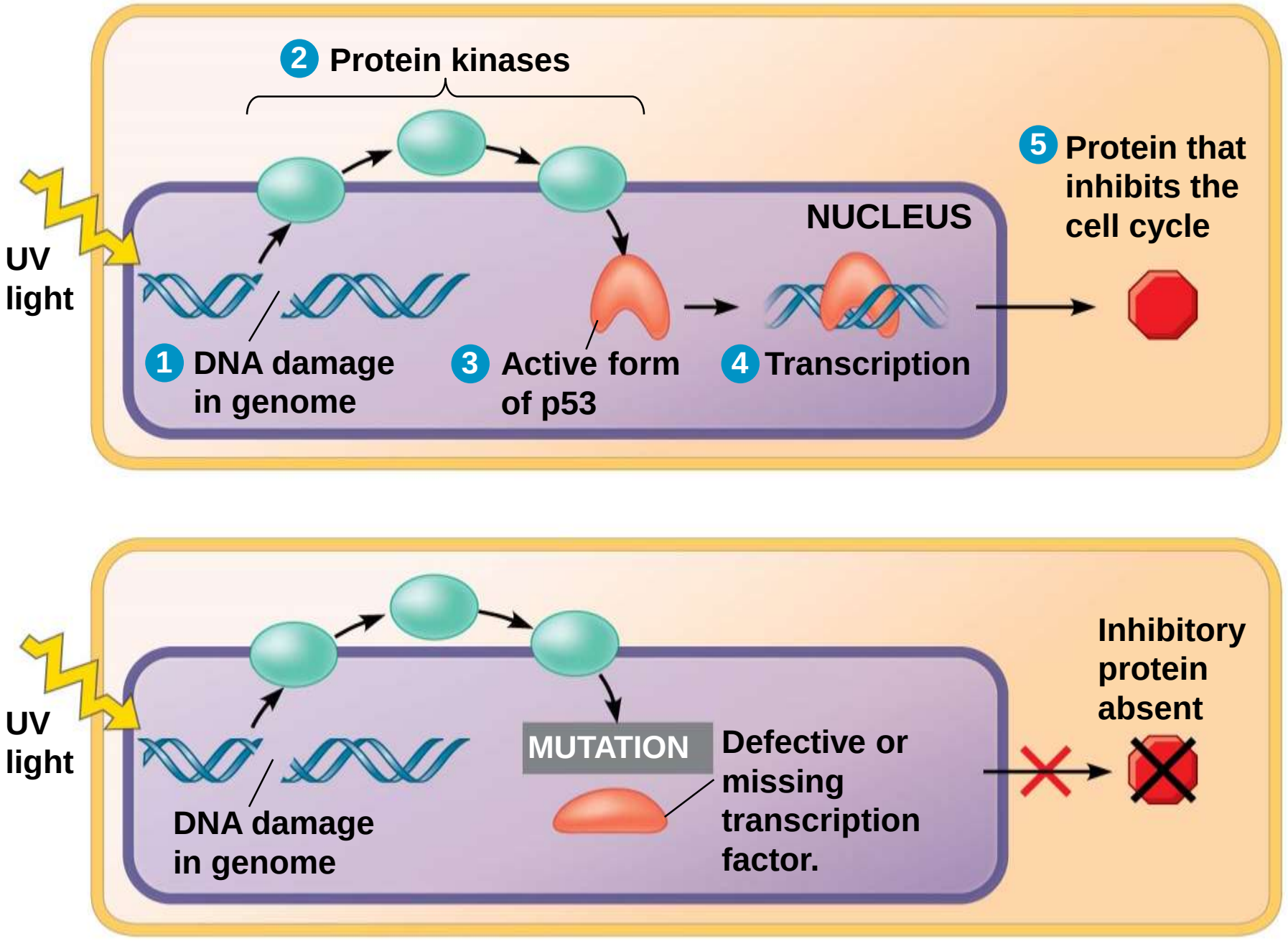


Figure 18.25

Normal and mutant cell cycle – **inhibiting pathway**



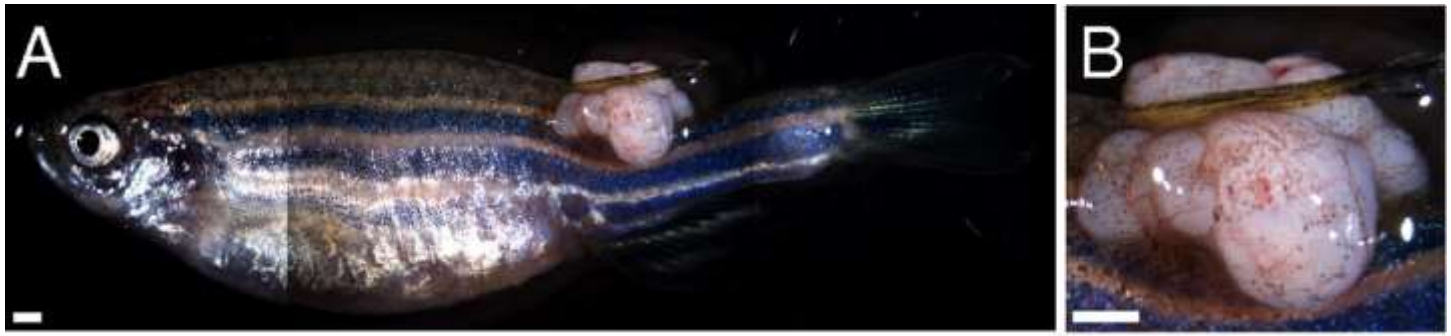
油門大開 + 煞車又壞了… Caner!

oncogene　　Tumor-suppressor gene　　Out of control cell proliferation

- Suppression of the cell cycle can be important in the case of damage to a cell's DNA; *p53* prevents a cell from passing on mutations due to DNA damage. Elephants have 20 copies of p53 → lower change of cancer!

- Mutations in the ***p53* gene** prevent suppression of the cell cycle

Zebrafish cancer model: Oncogene (AKT) activation with P53 $^{-/-}$



Proc Natl Acad Sci U S A. 2011 Sep 27;108(39):16386-91. Epub 2011 Sep 19.

The Multi-step Model of Cancer Development

- Multiple mutations are generally needed for full-fledged cancer; thus the incidence increases with age

- At the DNA level, a cancerous cell is usually characterized by at least one active oncogene and the mutation of several tumor-suppressor genes

A **multistep model** for the development of colorectal cancer

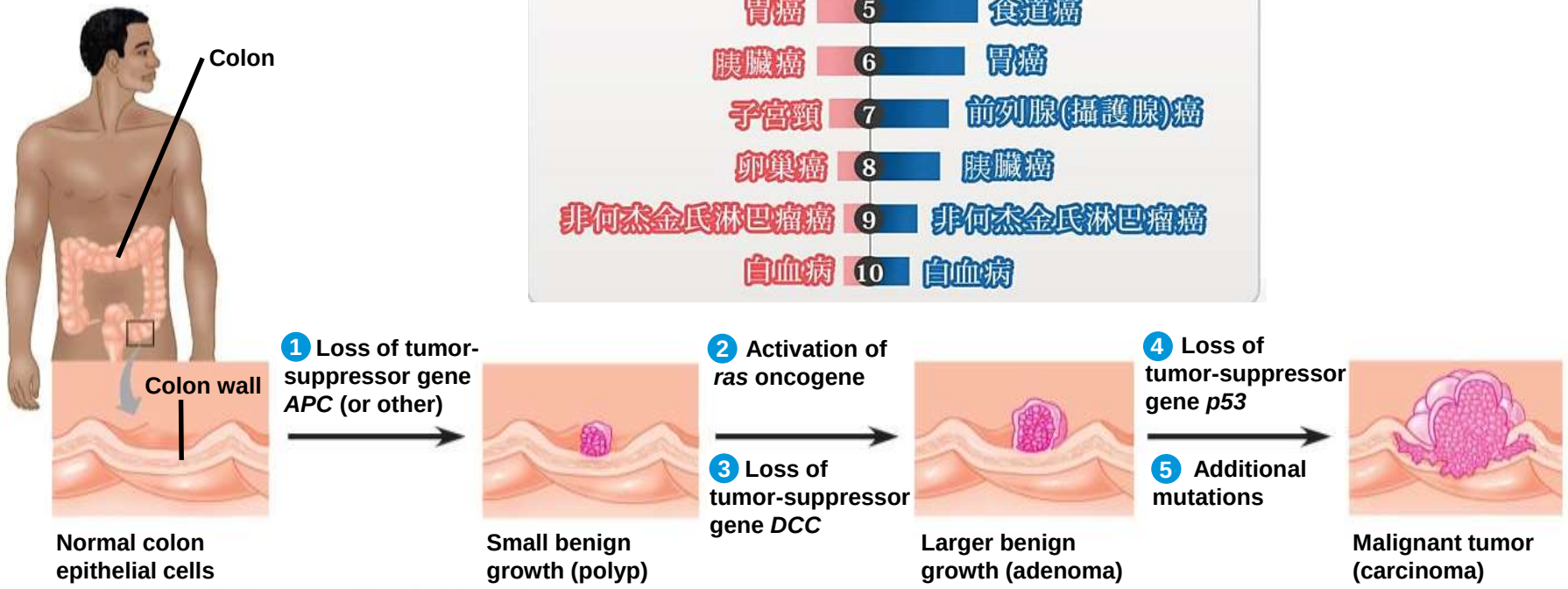
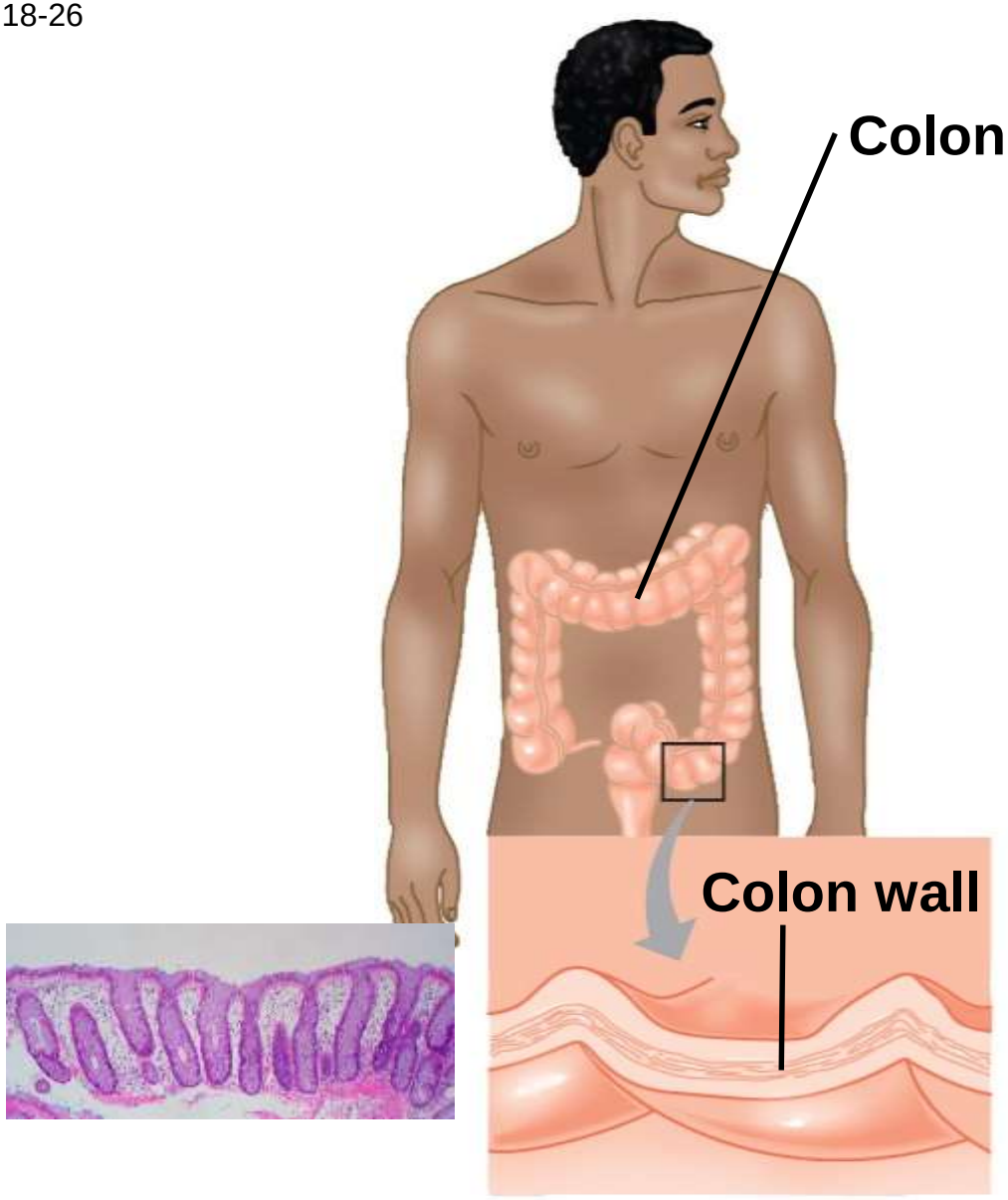
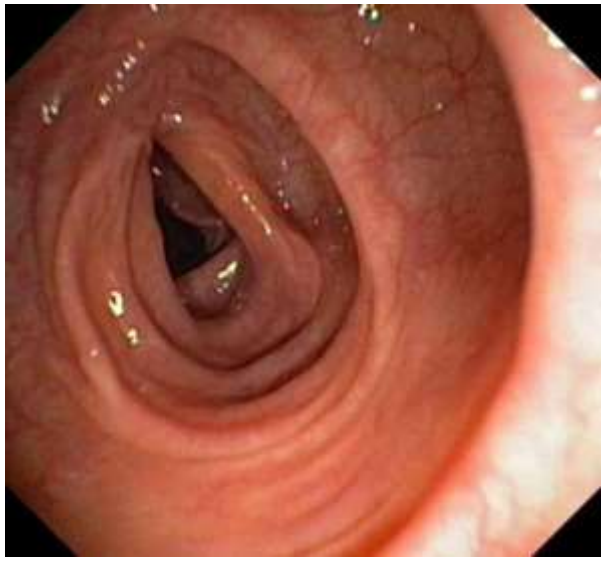


Fig. 18-26



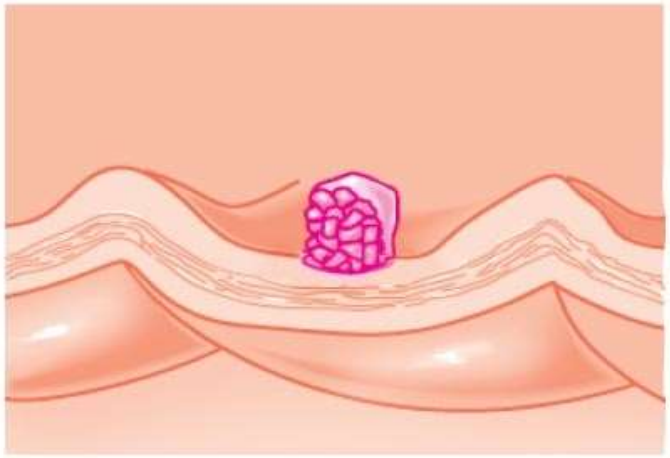
Normal colon epithelial cells

A multistep model for the development of colorectal cancer



A multistep model for the development of colorectal cancer

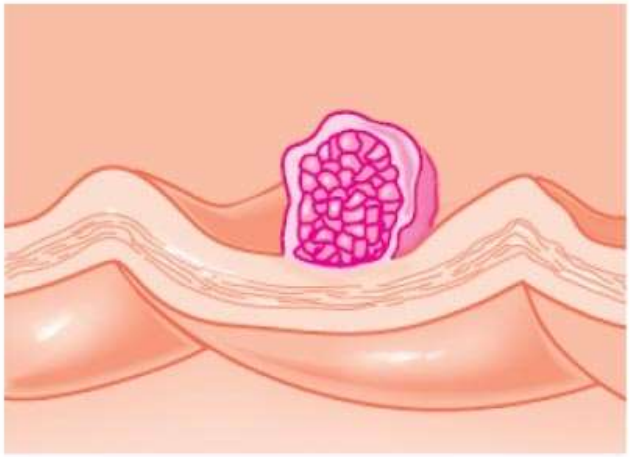
1 **Loss of tumor-suppressor gene *APC* (or other)**



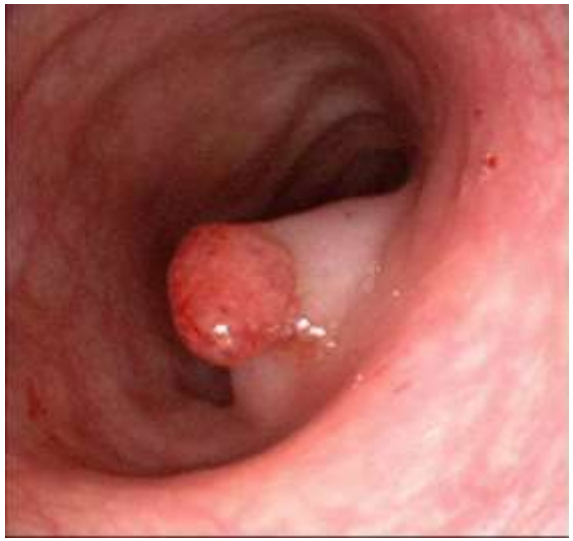
Small benign growth (polyp)

A multistep model for the development of colorectal cancer

2 **Activation of *ras* oncogene**



3 **Loss of tumor-suppressor gene *DCC***

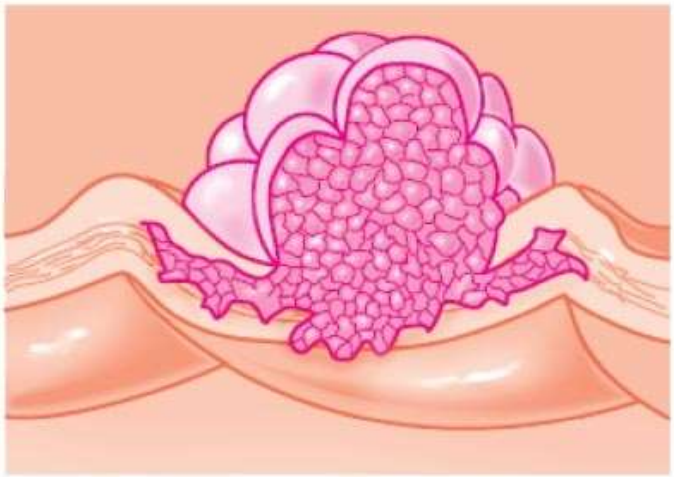


Larger benign growth (adenoma)

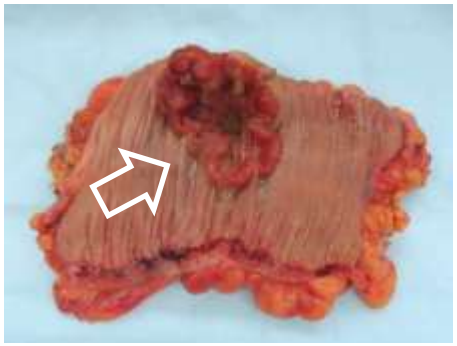
A multistep model for the development of colorectal cancer

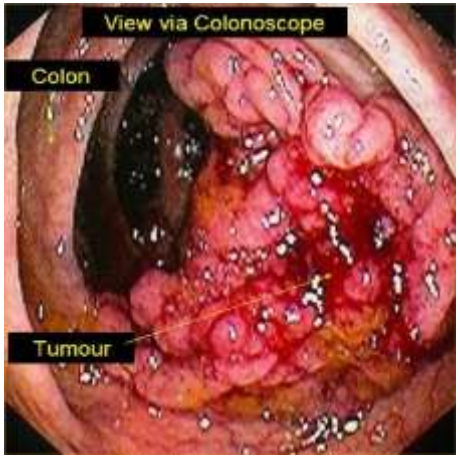
4 **Loss of tumor-suppressor gene *p53***

5 **Additional mutations**



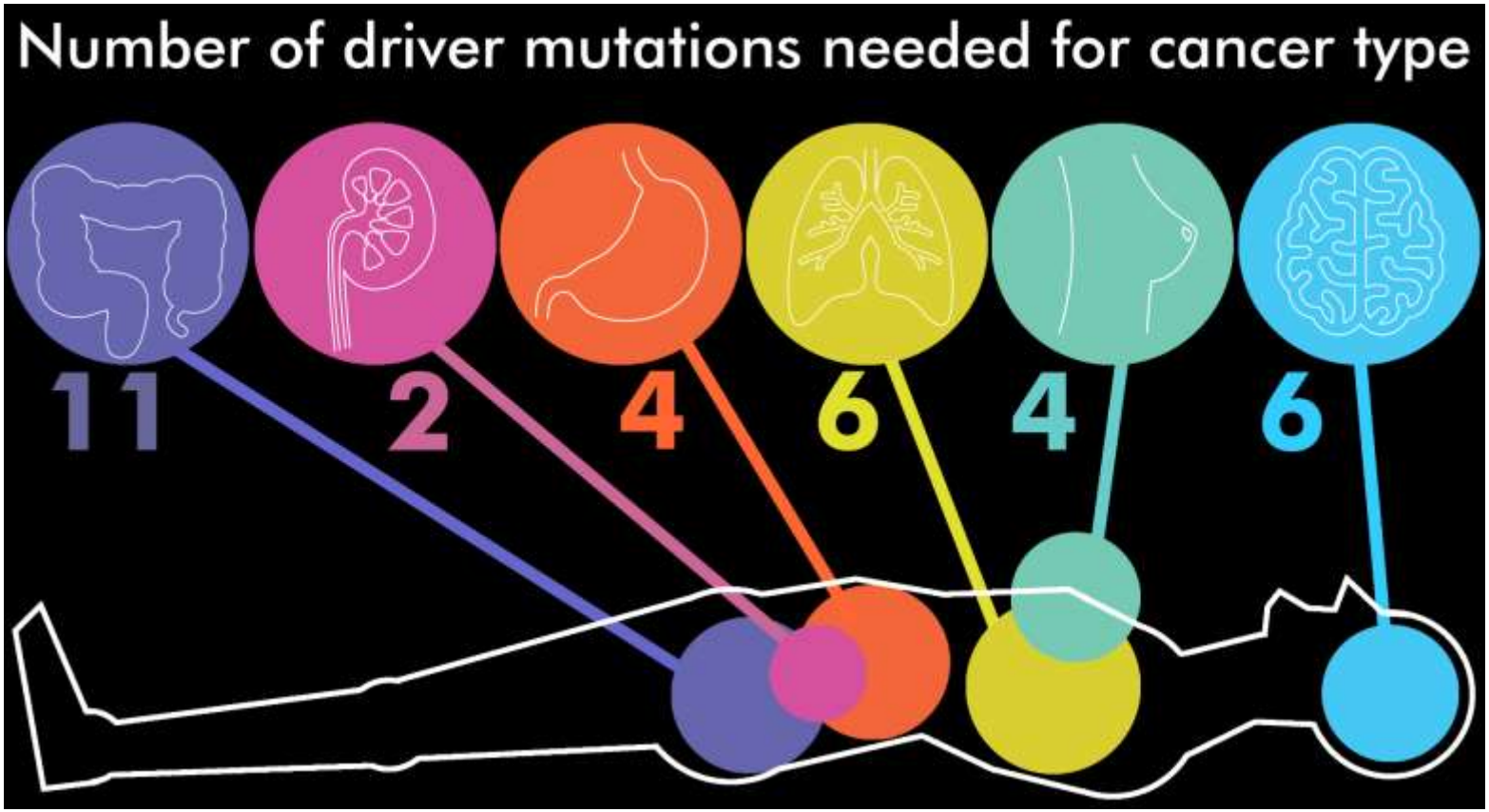
Malignant tumor (carcinoma)





In addition to mutations and genetic alternations, a number *tumor viruses* can cause cancer in various animals, including humans.

Recent study: **1 to 10 mutations are needed to drive cancer**



The number of mutations driving cancer varies considerably across different cancer types. Cancers develop by natural selection, acting on the mutations that accumulate in the cells of our bodies over time. Strikingly, mutations are usually well-tolerated by cells in the body. Many driver genes have not yet been identified and they will be the target for further searching in the future. This increasingly precise understanding of the underlying changes that result in cancer provides the foundation for the discovery and use of targeted therapies that treat the disease.

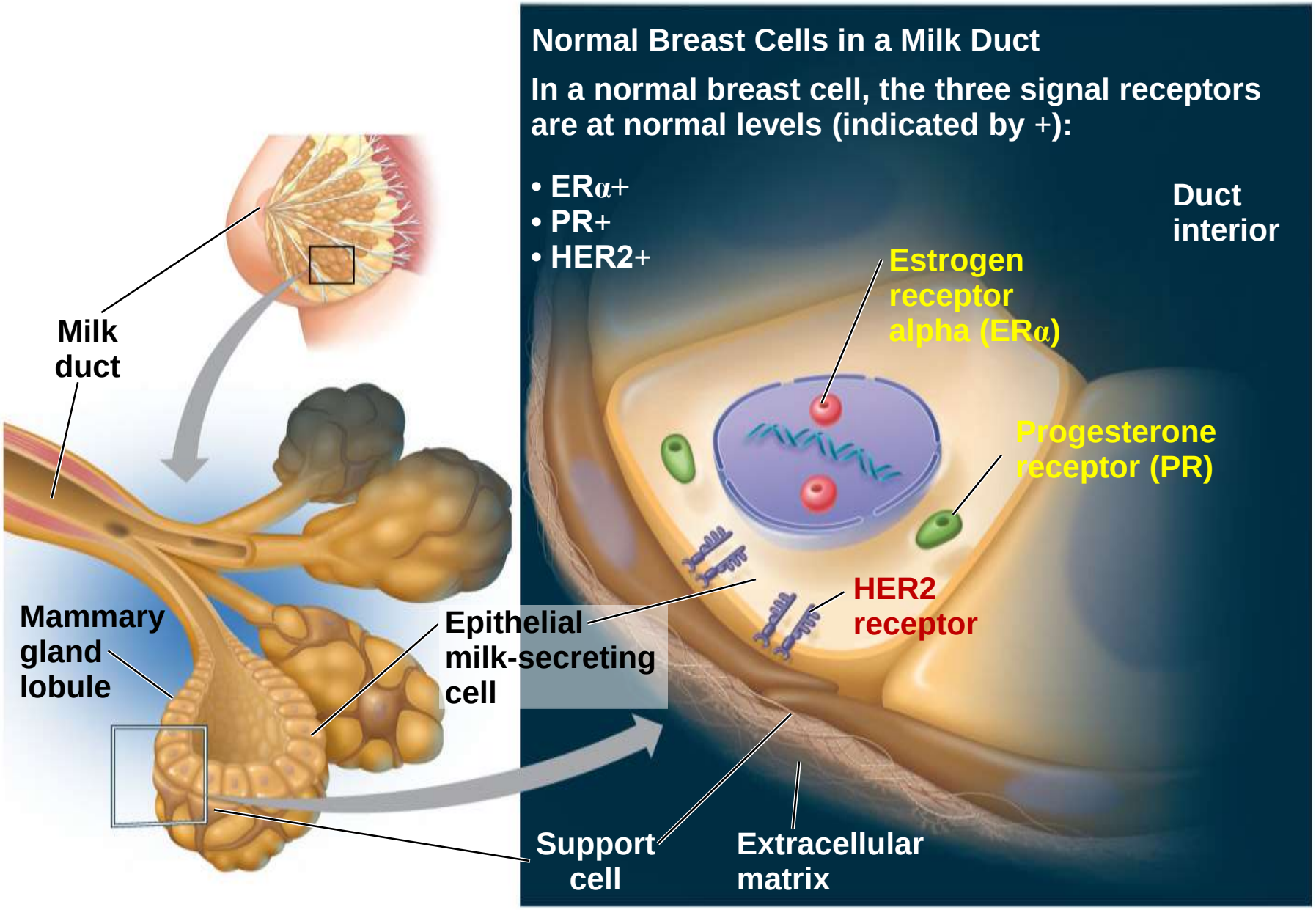
Martincorena et al. (*Cell, 2017*) Universal patterns of selection in cancer and somatic tissues.

Genomics, Cell Signaling, and Cancer

A research scientist examines DNA sequencing data from breast cancer samples.

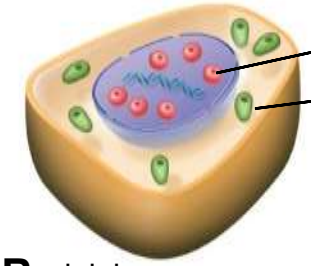
Figure 18.27b

MAKE CONNECTIONS: Genomics, Cell Signaling, and Cancer



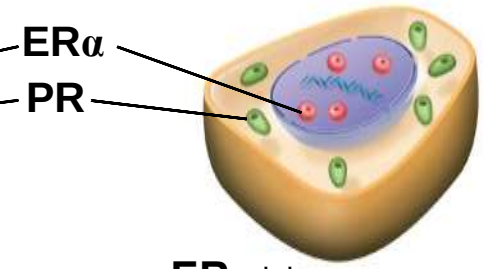
MAKE CONNECTIONS: Genomics, Cell Signaling, and Cancer

Luminal A



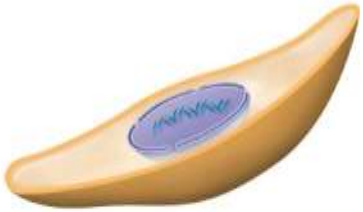
- ERα+++
- PR++
- HER2–
- **40% of breast cancers**
- Best prognosis

Luminal B



- ERα++
- PR++
- HER2– (shown here); some HER2++
- 15–20% of breast cancers
- Poorer prognosis than luminal A subtype

Basal-like

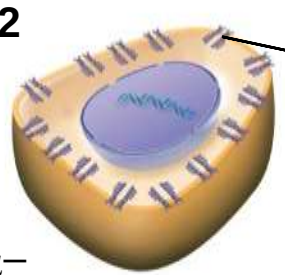


- ERα–
- PR–
- HER2–

Triple Negative

- 15–20% of breast cancers
- **More aggressive; poorer prognosis than other subtypes**

HER2



- ERα–
- PR–
- HER2++
- 10–15% of breast cancers
- Poorer prognosis than luminal A subtype

Figure 18.27c

Figure 18.27da

HER2 Receptor Signaling

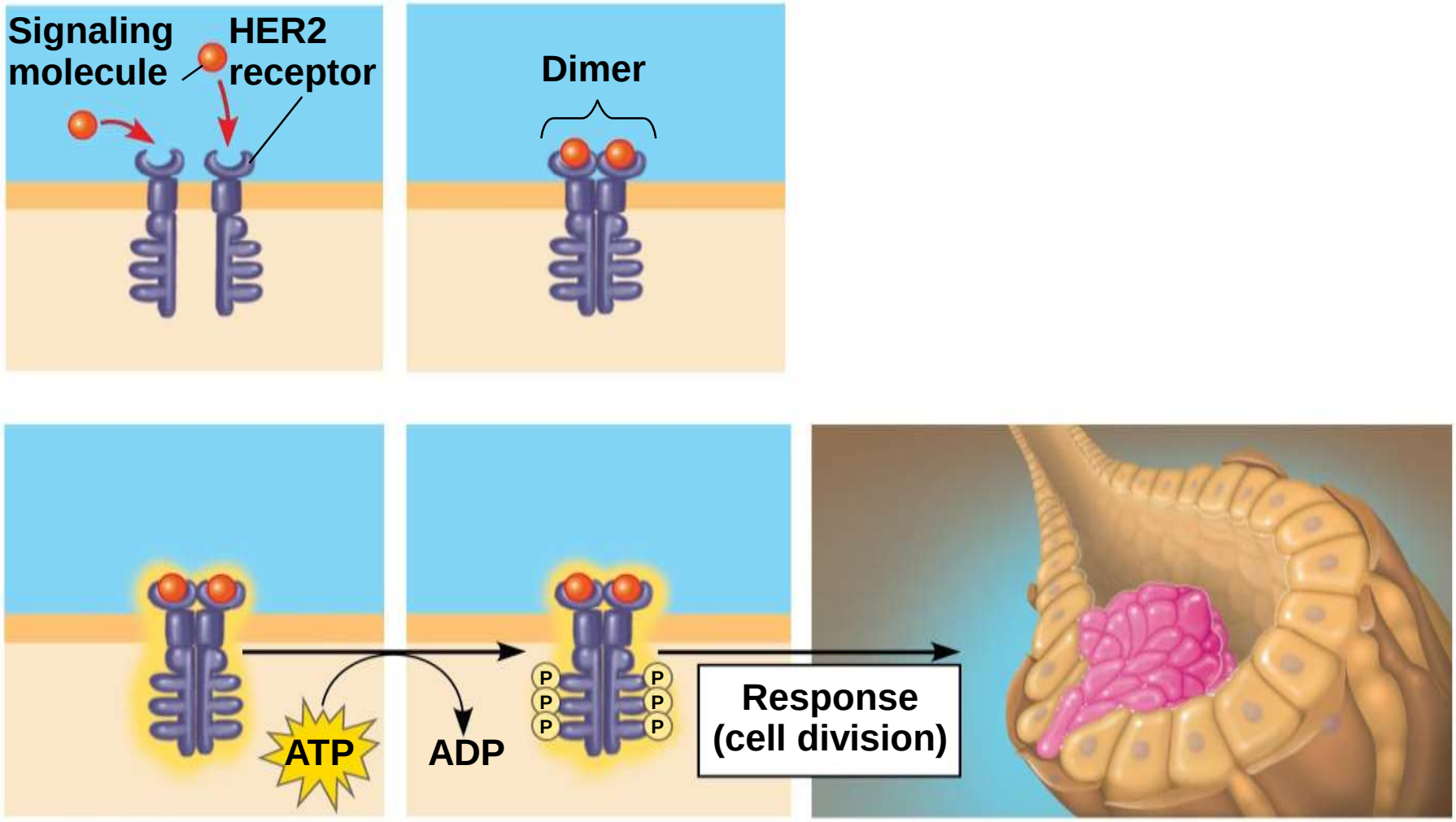
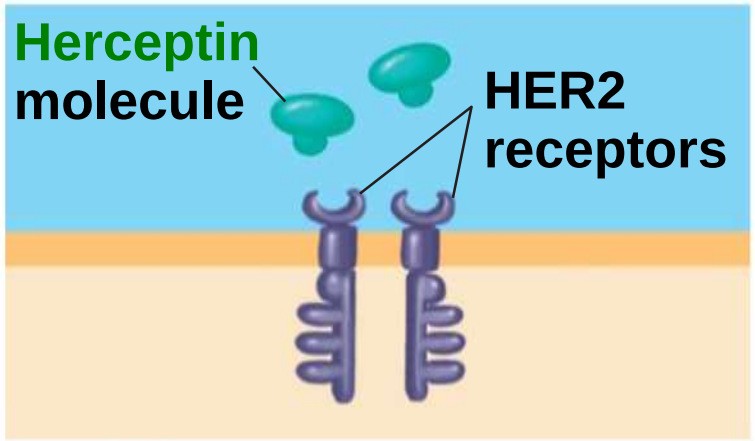
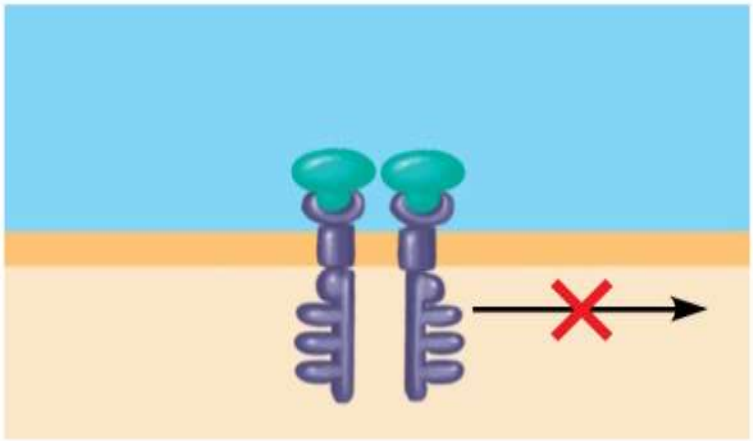


Figure 18.27db

Treatment with Herceptin for the HER2 subtype



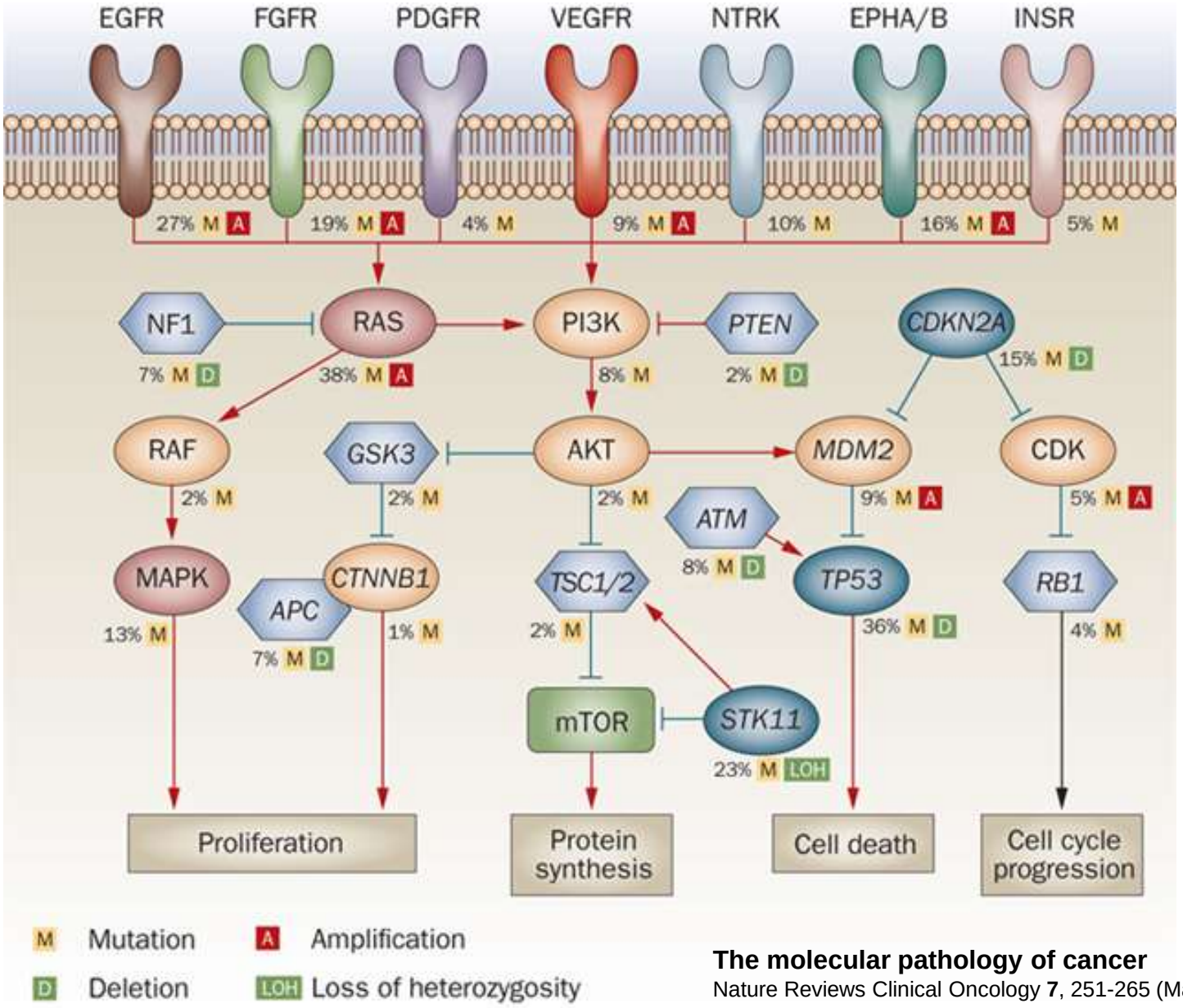


Cancer Cell Division **Inhibited**

Herceptin is a monoclonal antibody used to treat HER2 positive breast cancer.

補充: Important mutated signaling pathways in lung adenocarcinomas.

Anti-cancer drug targets



The molecular pathology of cancer
Nature Reviews Clinical Oncology **7**, 251-265 (May 2010)

Inherited Predisposition and Other Factors Contributing to Cancer

- Individuals can **inherit** oncogenes or mutant alleles of tumor-suppressor genes
  - Inherited mutations in the tumor-suppressor gene *adenomatous polyposis coli* (APC gene) are common in individuals with colorectal cancer
  - Mutations in the BRCA1 or BRCA2 gene are found in at least half of inherited breast cancers , and tests using DNA sequencing can detect these mutations

The Role of Viruses in Cancer

- A number of tumor viruses can also cause cancer in humans and animals
  - Epsterin-Barr (EB) virus → Burkitt's lymphoma 淋巴瘤

  - Papillomavirus → Cervical cancer
  - HTLV-1 (Human T-cell Lymphotropic Virus, type Ⅰ) → Adult leukemia
- **Mechanism:** Viruses can interfere with normal gene regulation in several ways if they integrate into the DNA of a cell

You should now be able to:

Explain the concept of an operon and the function of the operator, repressor, and corepressor

Explain the adaptive advantage of grouping bacterial genes into an operon

Explain how repressible and inducible operons differ and how those differences reflect differences in the pathways they control

- Explain how DNA methylation and histone acetylation affect chromatin structure and the regulation of transcription
- Define control elements and explain how they influence transcription
- Explain the role of promoters, enhancers, activators, and repressors in transcription control

- Explain how eukaryotic genes can be coordinately expressed
- Describe the roles played by small RNAs on gene expression
- Explain why determination precedes differentiation
- Describe two sources of information that instruct a cell to express genes at the appropriate time

- Explain how maternal effect genes affect polarity and development in *Drosophila* embryos
- Explain how mutations in tumor-suppressor genes can contribute to cancer
- Describe the effects of mutations to the *p53* and *ras* genes

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NIH Record

Embargoed for Release: Wednesday, September 4, 2013, 10 a.m. EDT

NIH program explores the use of genomic sequencing in newborn healthcare

Can sequencing of newborns' genomes provide useful medical information beyond what current newborn screening already provides? Pilot projects to examine this important question are being funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health. Awards of $5 million to four grantees have been made in fiscal year 2013 under the Genomic Sequencing and Newborn Screening Disorders research program. The program will be funded at $25 million over five years, as funds are made available.

Institute/Center

National Human Genome Research Institute (NHGRI)

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Contact

Steven Benowitz
301-451-8325

Robert Bock
301-496-5133

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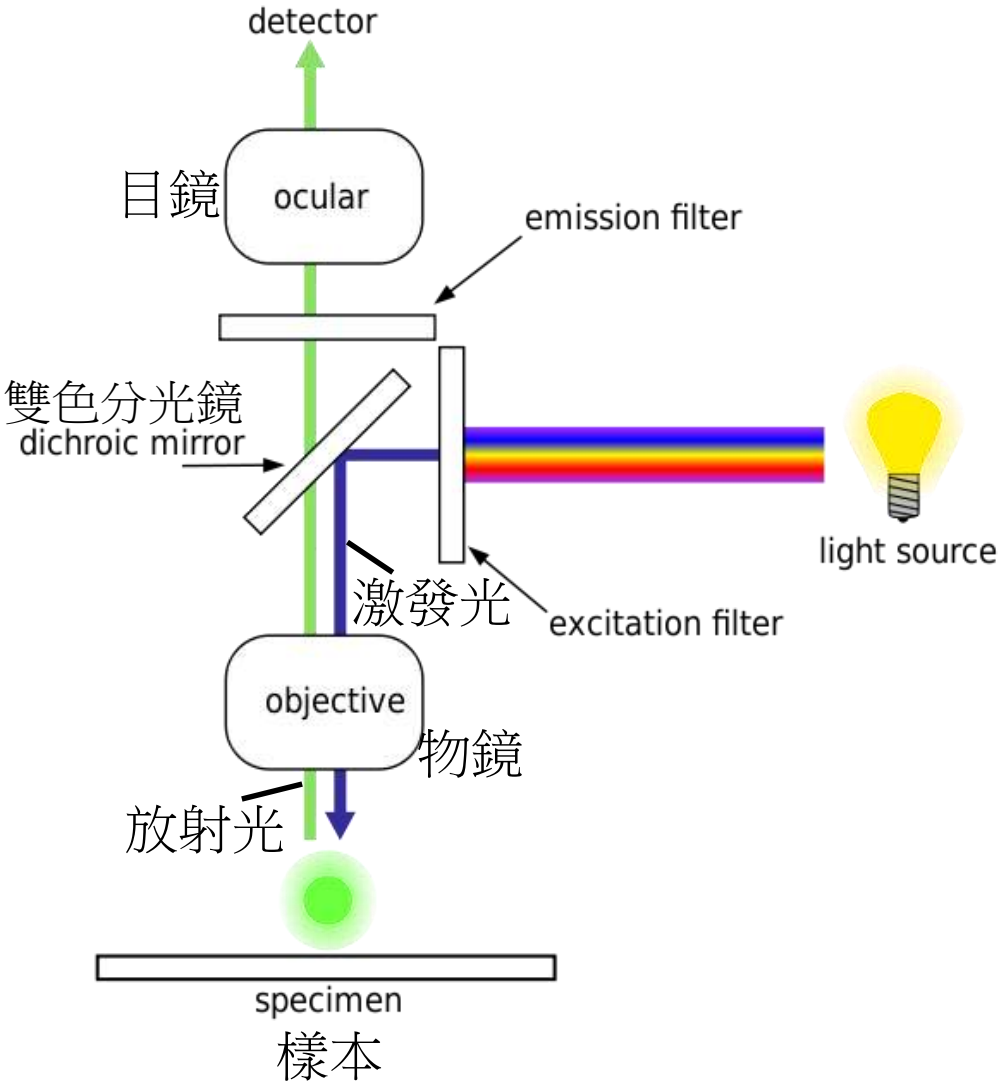
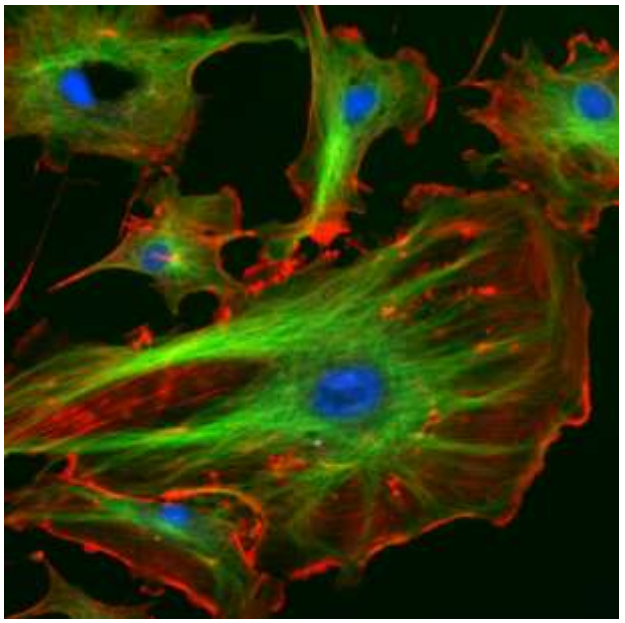
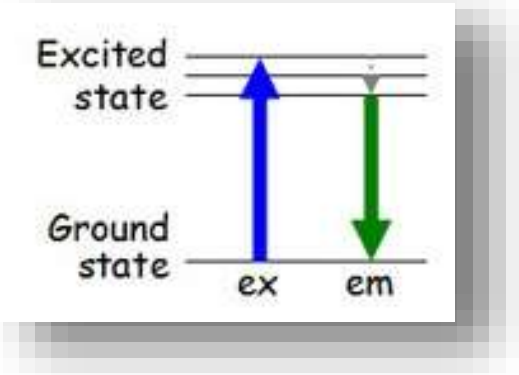
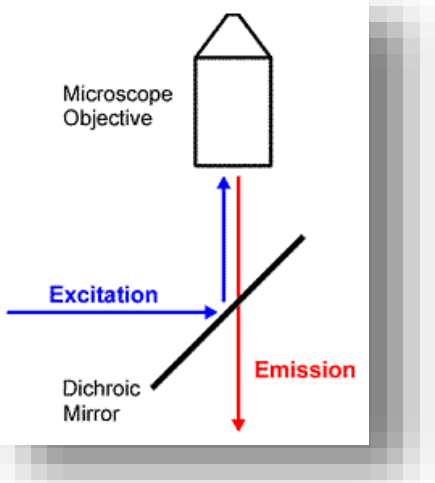
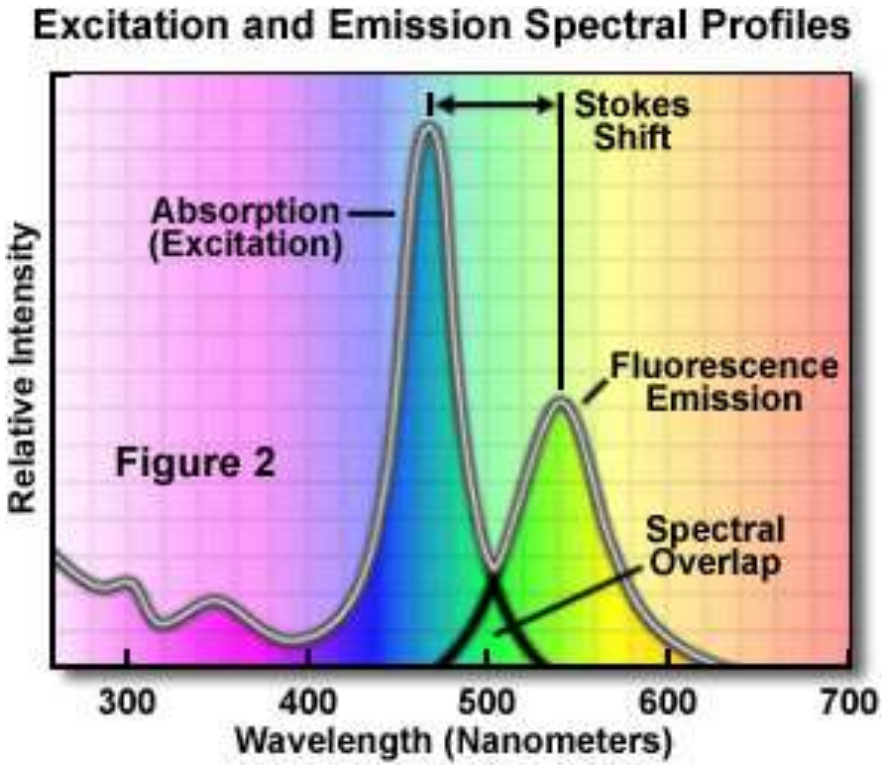
Fluorescent Microscope

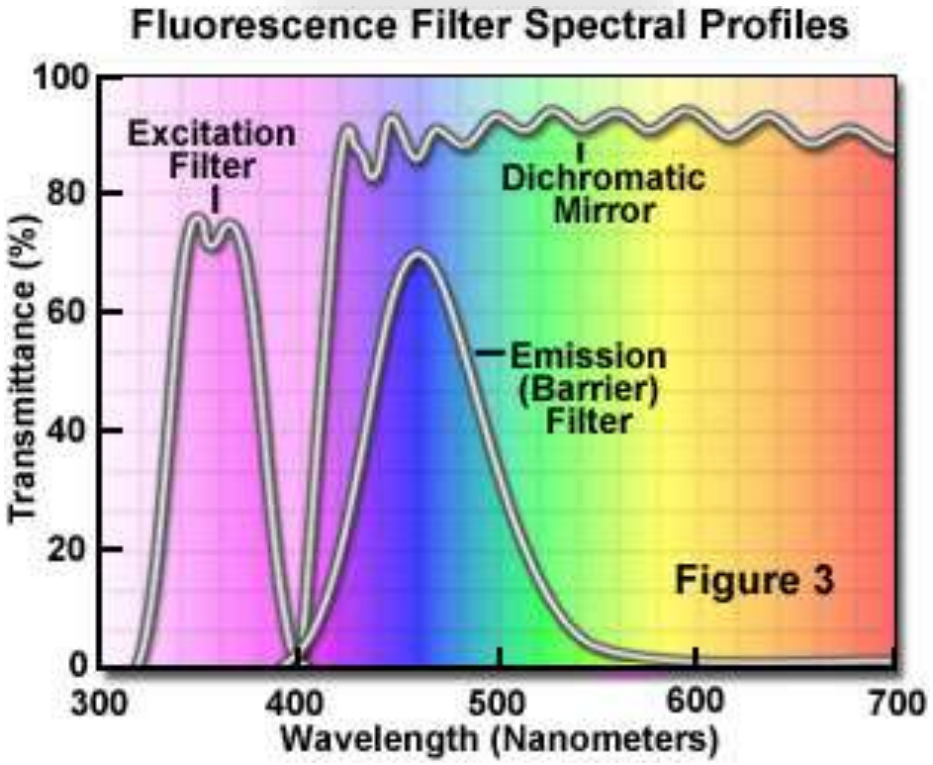










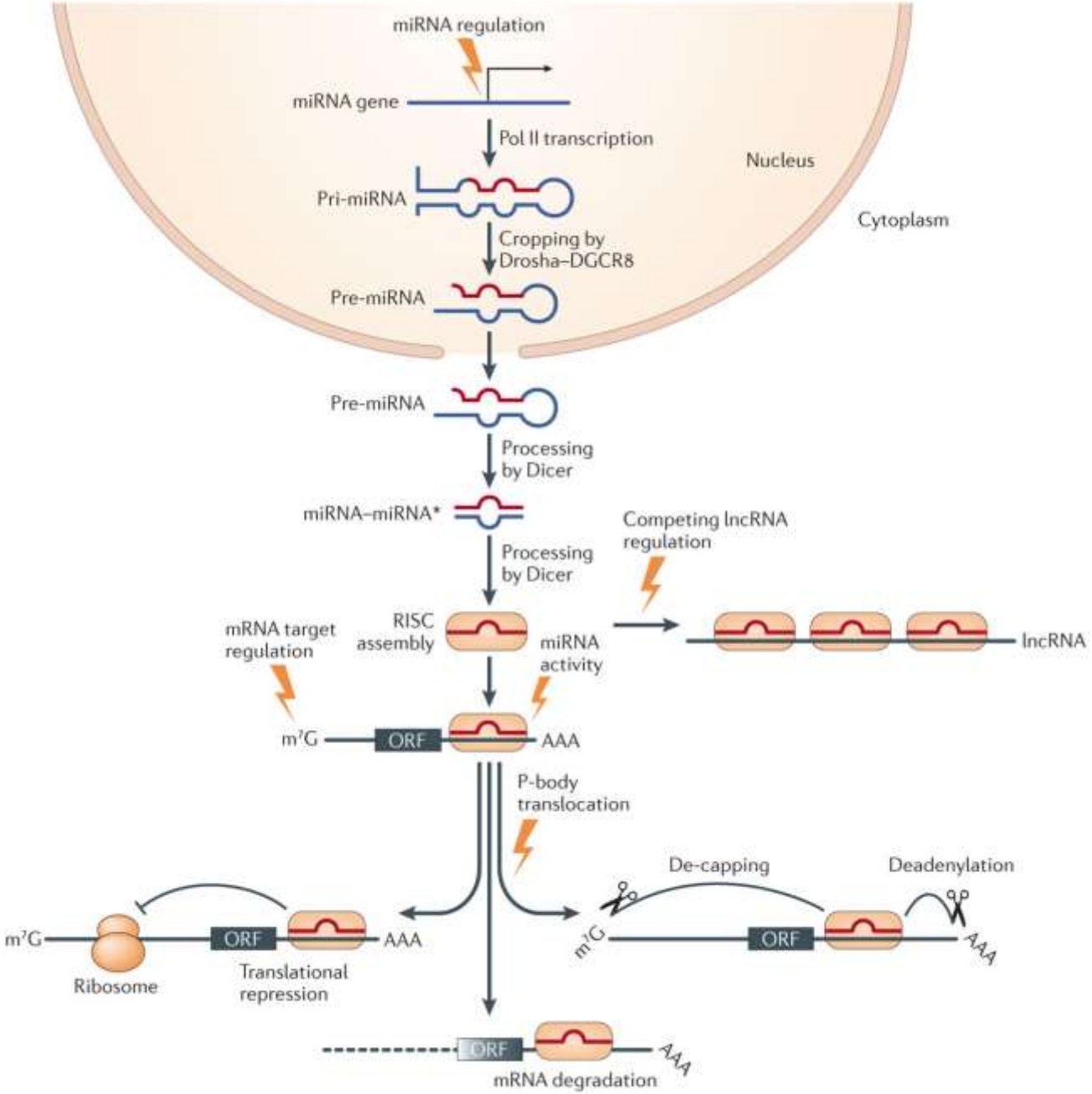


Excitation ,Emission, and Filters

The first mapping of human genome competed in 2003, cost US$2.7 billion. (~新台幣810億)

As of Dec 2012, the cost for an individual's whole-genome sequencing is US$7500 (~新台幣22.5萬) and falling fast.

It is expected one day your genome sequencing could be done as easy to get as a pregnancy test.

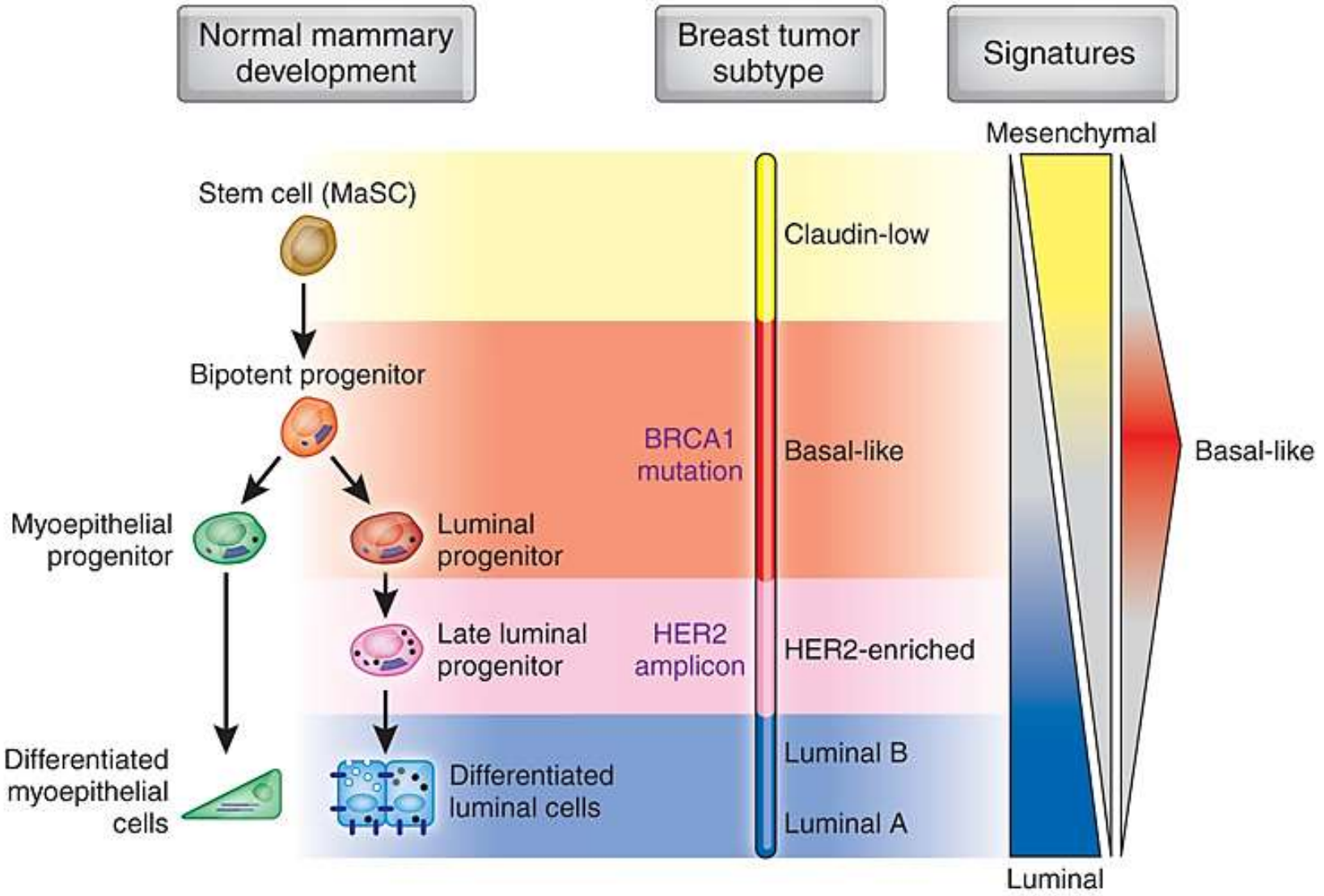


Nature Reviews Drug Discovery **11**, 860-872

Testing for mutations in *BRCA1* and *BRCA2*

High-throughput (高通量) sequencing techniques can sequence many DNA samples at once, as shown here

Model of the human mammary epithelial hierarchy linked to cancer subtype



Mammary development meets cancer genomics Nature Medicine 15, 842 - 844 (2009)

Levels of regulation in bacterial gene expression

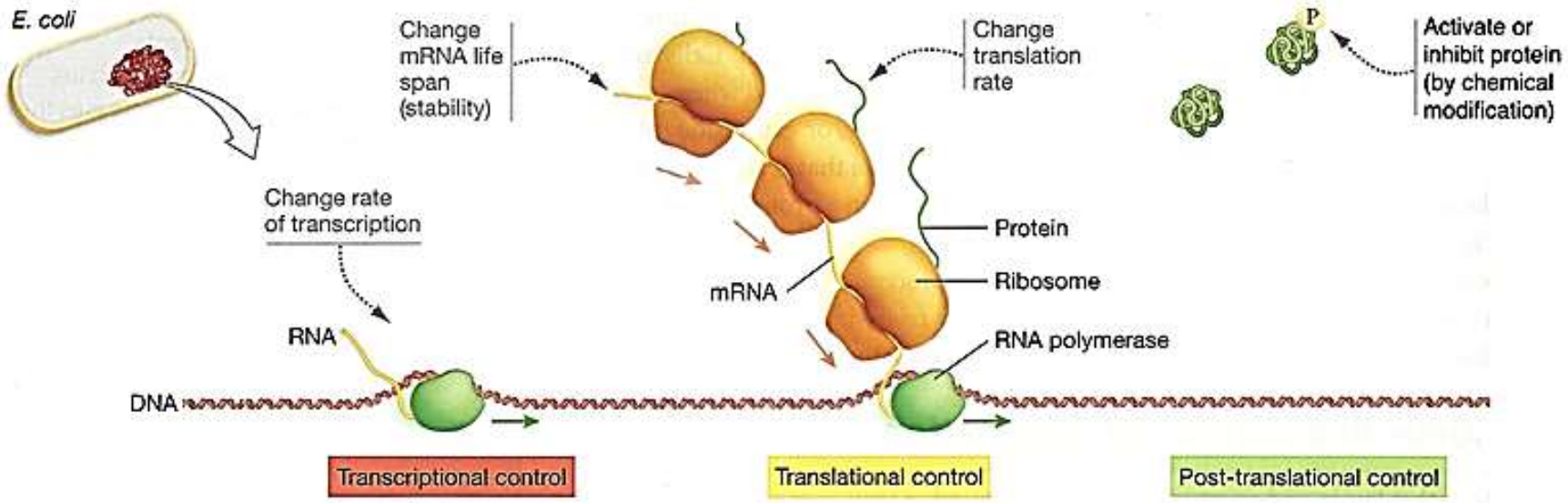


Figure 18.27a

MAKE CONNECTIONS:

Genomics, Cell Signaling, and Cancer

Normal Breast Cells in a Milk Duct

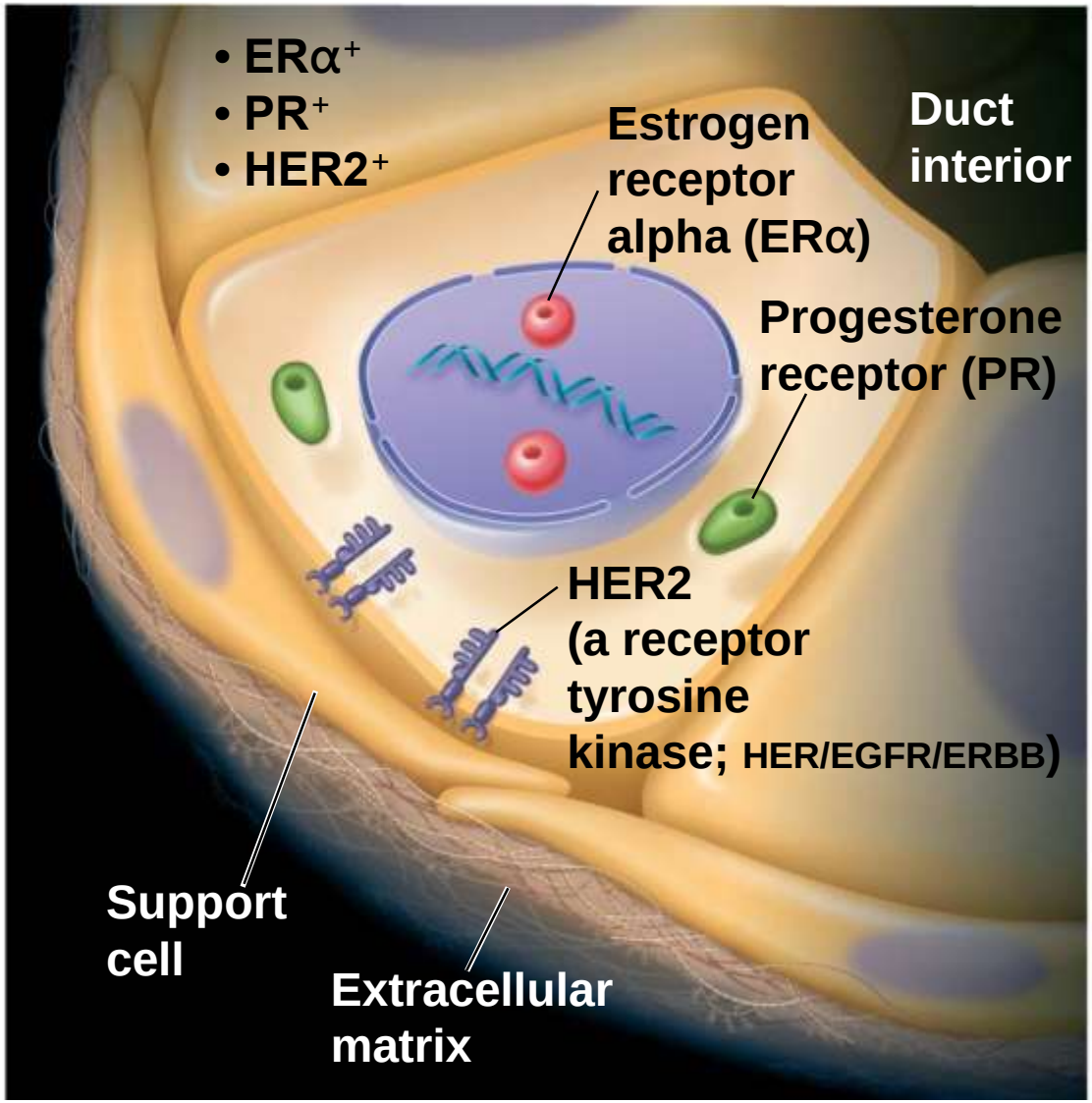
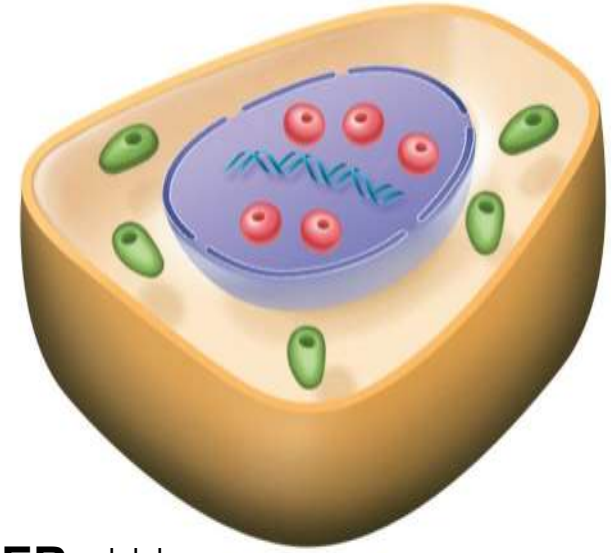


Figure 18.27b

MAKE CONNECTIONS:
Genomics, Cell Signaling, and Cancer

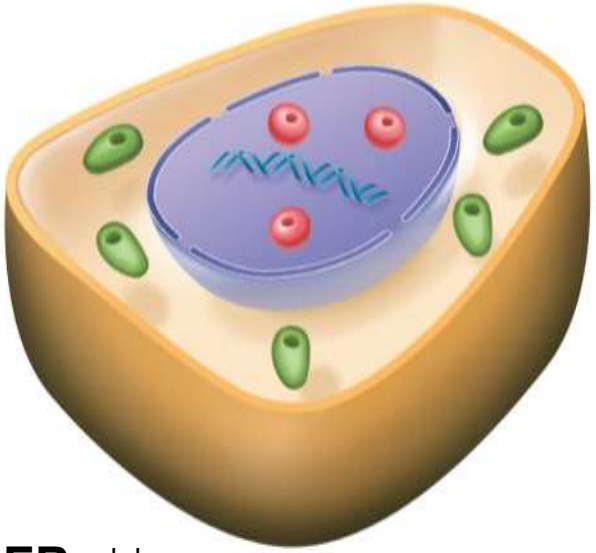
Breast Cancer Subtypes by intrinsic Molecular classification

Luminal A



- ERα^{+++}
- PR^{++}
- HER2^{-}
- 40% of breast cancers
- Best prognosis

Luminal B

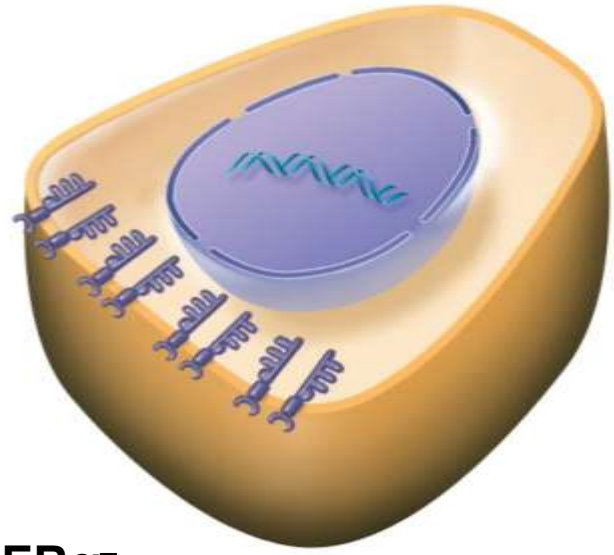


- ERα^{++}
- PR^{++}
- HER2^{-} (shown); some HER2^{++}
- 15–20% of breast cancers
- Poorer prognosis than luminal A subtype

Figure 18.27c

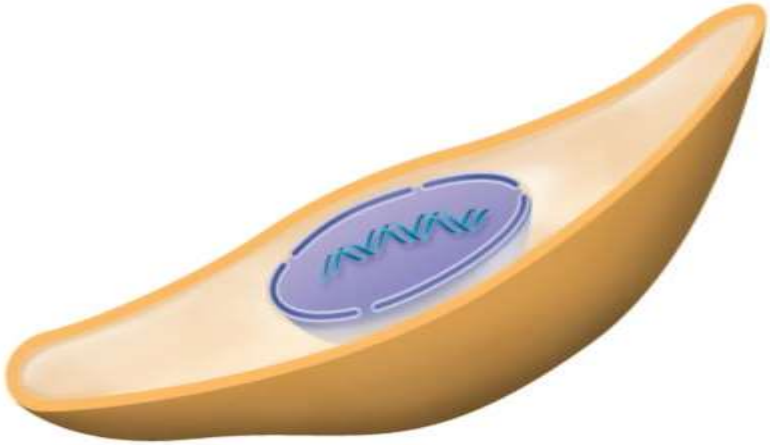
MAKE CONNECTIONS:
Genomics, Cell Signaling, and Cancer
Breast Cancer Subtypes

HER2



- ERα^{-}
- PR^{-}
- HER2^{++}
- 10–15% of breast cancers
- Poorer prognosis than luminal A subtype

Basal-like



- ERα^{-}
- PR^{-}
- HER2^{-}

(triple negative)

- 15–20% of breast cancers
- More aggressive; poorer prognosis than other subtypes

miRNA versus siRNA (補充)

請自主學習

	Occurrence	Configuration	Length	Complementarity to target mRNA	Biogenesis	Action	Function	Clinical uses
miRNA (miRNA)	Occur naturally in plants and animals	Single stranded	19–25 nt	Not exact, and therefore a single miRNA may target up to hundreds of mRNAs	Expressed by genes whose purpose is to make miRNAs, but they regulate genes (mRNAs) other than the ones that expressed them	Inhibit translation of mRNA	Regulators (inhibitors) of genes (mRNAs)	Possible therapeutic uses either as drug targets or as drug agents themselves. Expression levels of miRNAs can be used as potential diagnostic and biomarker tools
Short interfering RNA (siRNA)	Occur naturally in plants and lower animals. Whether or not they occur naturally in mammals is an unsettled question	Double stranded	21–22 nt	100% perfect match, and therefore siRNAs knock down specific genes, with minor off-target exceptions	Regulate the same genes that express them	Cleave mRNA	Act as gene-silencing guardians in plants and animals that do not have antibody-or cell-mediated immunity	siRNAs are valuable laboratory tools used in nearly every molecular biology laboratory to knock down genes. Several siRNAs are in clinical trials as possible therapeutic agents

MicroRNA gets down to business, *Nature Biotechnology* **25**, 631 - 638 (2007)