

A close-up photograph of a light green grasshopper clinging vertically to a thin, textured plant stem. The background is a soft-focus green, suggesting a natural, outdoor setting.

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# Chapter 11

## How Genes Are Controlled

PowerPoint Lectures

***Campbell Biology: Concepts & Connections, 8th Edition, Global Edition***

REECE • TAYLOR • SIMON • DICKEY • HOGAN

Lecture by Edward J. Zalisko

# Introduction

- Cloning is the creation of an individual by asexual reproduction.
- The ability to clone an animal from a single cell demonstrates that every adult body cell
  - contains a complete genome that is
  - capable of directing the production of all the cell types in an organism.
- Cloning has been attempted to save endangered species.
- However, cloning
  - does not increase genetic diversity
  - may trivialize the tragedy of extinction and detract from efforts to preserve natural habitats.

新寵物誕生！農委會育成黑色蠶寶寶「黑旋風」  
2018-05-10 聯合報  
利用豐富的種原庫，經多年雜交選育



- Well-preserved animals that have been dead for decades may be cloned using closely related animals as surrogates.
- Scientists have cloned a banteng (2003) (**Frozen tissue**, died at 1980), an endangered species of cattle native to Indonesia. As of 2013, it remains a healthy inhabitant of the San Diego Zoo.
- The development of different types of cells depends on turning on and off different genes in different cells—the control of gene expression.

2018.1 Cloned monkey, China



Zhong Zhong, one of the cloned macaque monkeys.  
<https://www.nature.com/articles/d41586-018-01027-z>

1. Identical genetic background; 2. Disease model



The cost? ~ \$50,000 USD



# A clone → Same dog?

Different mitochondrial DNA  
from its genetic donor,  
slightly less related than  
identical twins.

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Preserving Your Pets

Buddy

While we understand a special pet may be irreplaceable, we also understand the joy and peace of mind that comes from knowing one day you may be able to have a genetic twin of your beloved pet. The possibility of recreating the genetics of your amazing pet is now available through our Genetic Preservation service.

ViaGen offers Genetic Preservation for pets, for a cost of \$1600. Once you place an order, we will ship a biopsy kit to your veterinarian. The biopsy kit contains all the necessary tools and shipping material and your veterinarian will return the kit to us with small biopsy samples taken from your pet. The biopsy procedure is a simple process and

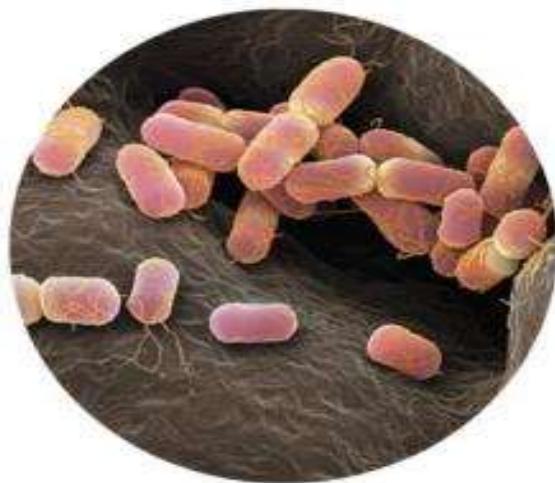
OUR SERVICES

Overview  
Cloning  
Genetic Preservation  
Pets

Two of **Barbra Streisand's** dogs, Miss Violet and Miss Scarlett, are clones of her late dog Sammie.

<https://www.nytimes.com/2018/03/02/style/barbra-streisand-cloned-her-dog.html>

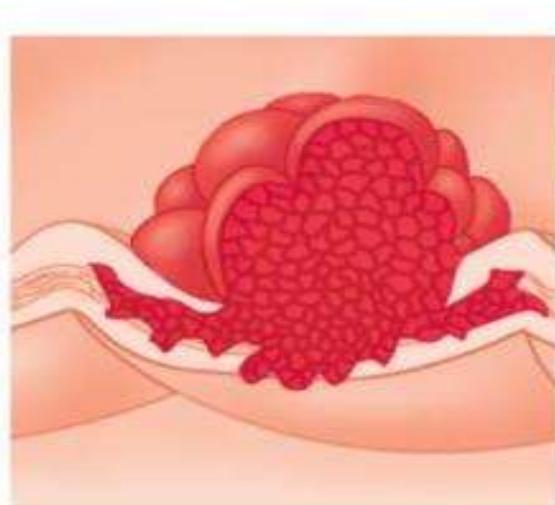
## Chapter 11: Big Ideas



**Control of Gene  
Expression 11.1-11.11**



**Cloning of Plants  
and Animals 11.12-11.15**



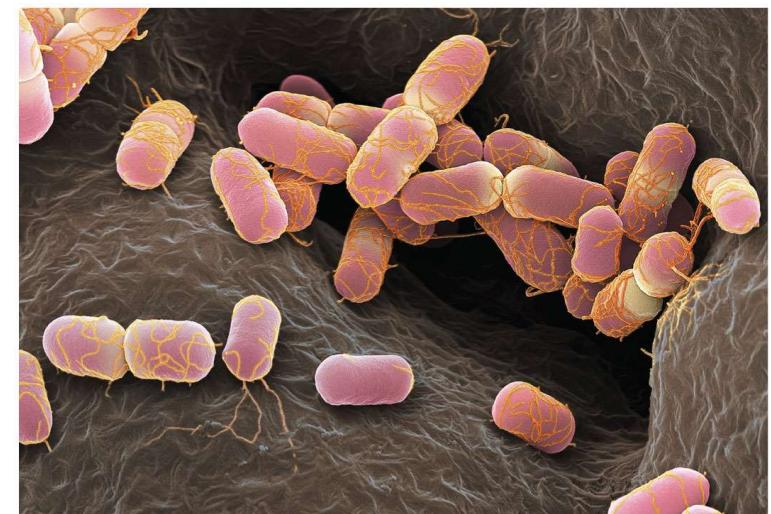
**The Genetic Basis  
of Cancer 11.16-11.19**

# CONTROL OF GENE EXPRESSION

## 11.1 Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- **Gene regulation** is the turning **on and off** of genes.
- **Gene expression** is the overall process of information flow from genes to proteins.
- The control of gene expression allows **cells** to produce specific kinds of proteins when and where they are needed.
- Our earlier understanding of gene control came from the study of *E. coli*. 大腸桿菌
- An **operon** is a cluster of genes with related functions, along with the control sequences.
- With rare exceptions, operons **only** exist in **prokaryotes**.

操作元



## 11.1 Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

乳糖

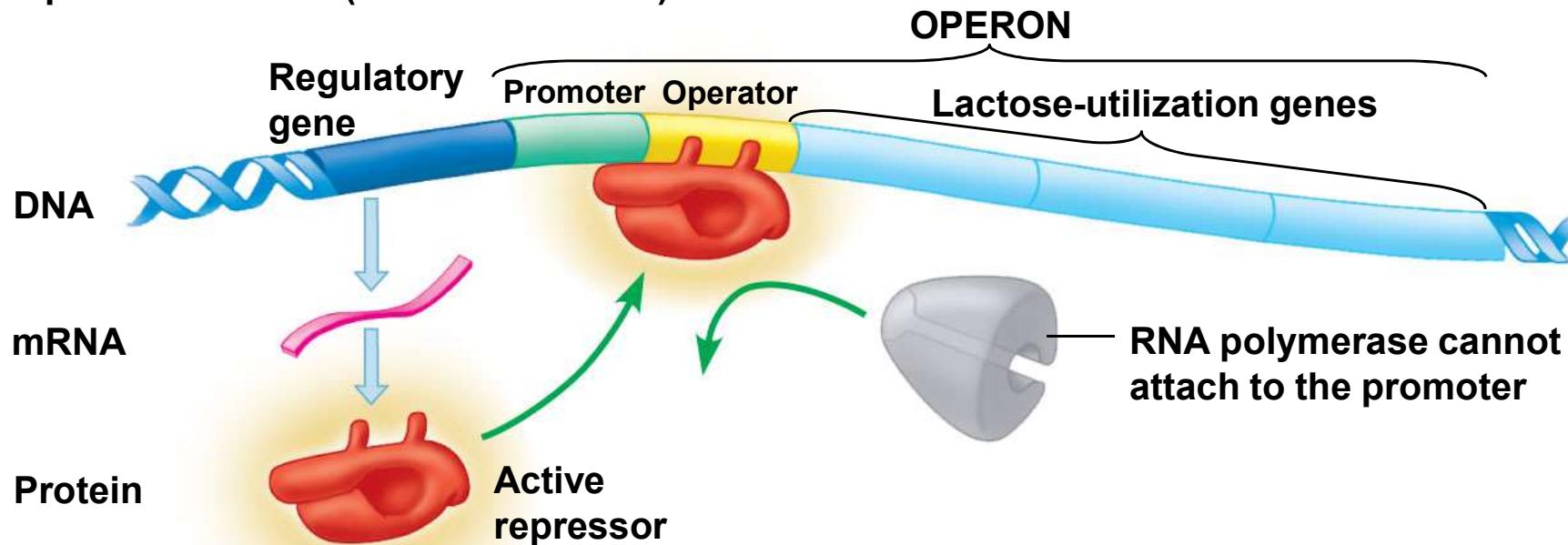
- When an *E. coli* encounters **lactose**, all the enzymes needed for its metabolism are made at once using the lactose operon.
- The lactose (*lac*) operon includes
  1. **three** adjacent lactose-utilization genes,
  2. a **promoter** sequence where RNA polymerase binds and initiates transcription of all three lactose genes, and
  3. an **operator** sequence where a **repressor** can bind and block RNA polymerase action.

## 11.1 Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

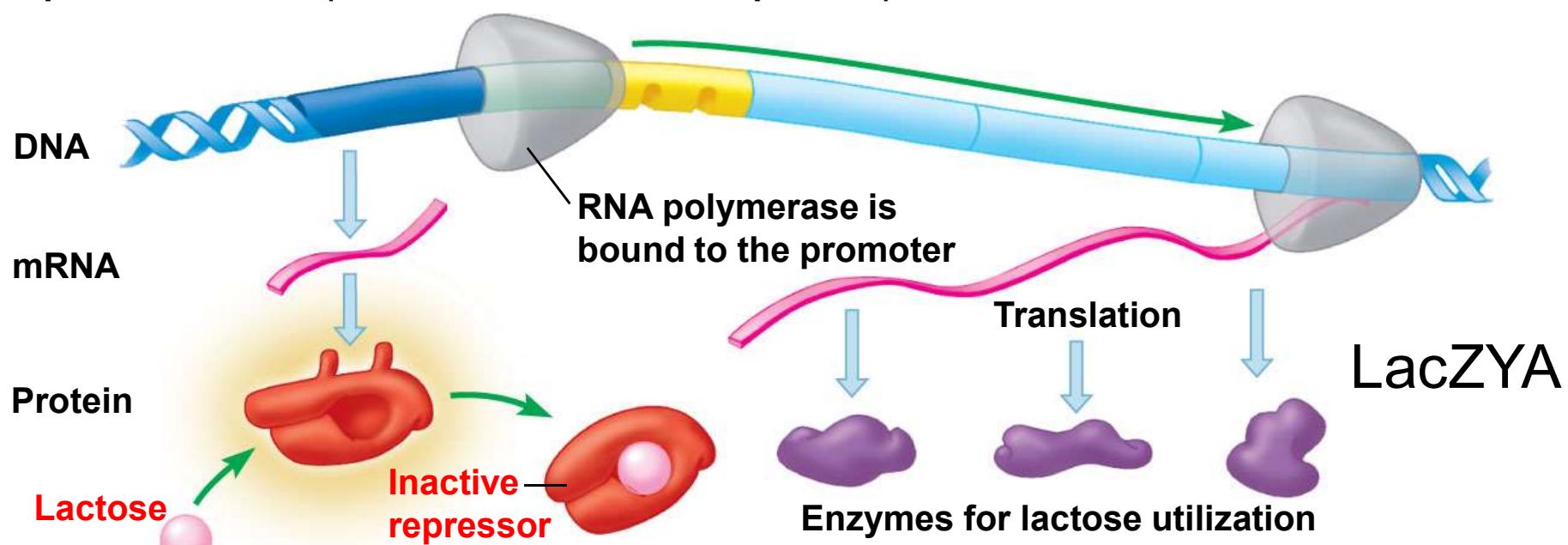
- *E. coli* uses three enzymes to take up and start metabolizing lactose only when lactose is present.
- The genes coding for these three enzymes are
  - located next to each other and
  - regulated as a single unit.
- Regulation of the *lac* operon
  - A **regulatory gene**, located outside the operon, codes for a **repressor protein**.
  - In the absence of lactose, the repressor binds to the operator and prevents RNA polymerase action.
  - Lactose inactivates the repressor, so
    - the operator is unblocked,
    - RNA polymerase can bind to the promoter, and
    - all three genes of the operon are transcribed.

Figure 11.1B

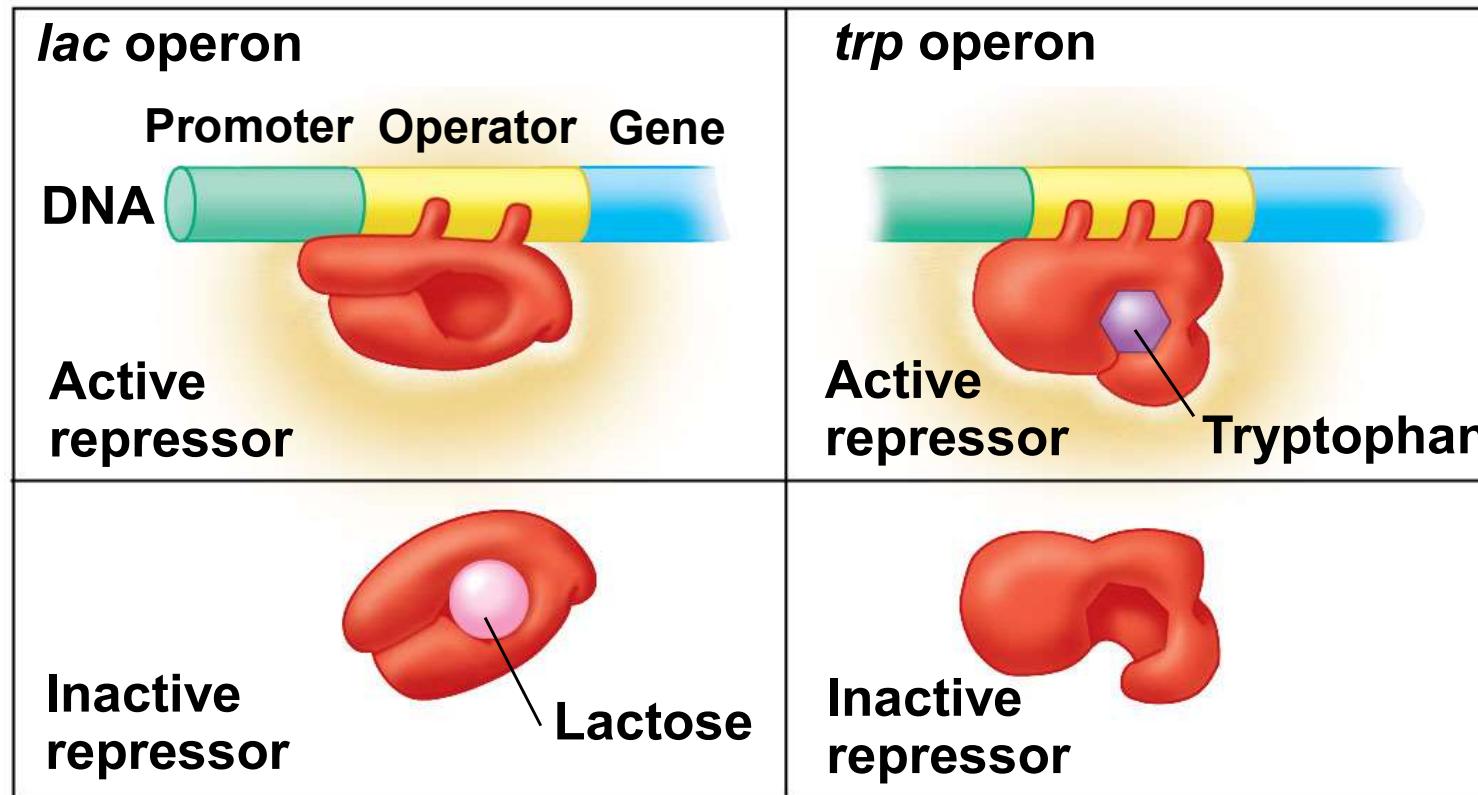
**Operon turned off (lactose is absent):**



**Operon turned on (lactose inactivates the repressor):**



# 11.1 Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes



## 11.1 Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- There are two types of repressor-controlled operons.
  - The *lac* operon is an example of an inducible operon that is usually turned off but can be stimulated (**induced**) by a molecule—in this case, by lactose.
  - The *trp* operon is an example of a repressible operon that is normally turned on but can be inhibited (**repressed**) when a specific molecule (such as amino acid tryptophan) is present in abundance.
- Another type of operon control involves **activators**, proteins that turn operons on by
  - binding to DNA and
  - stimulating gene transcription.
- Activators help control a wide variety of operons.

## 11.2 Chromosome structure and chemical modifications can affect gene expression

- **Differentiation** 分化
  - involves cell **specialization**, in structure and function, and
  - is controlled by turning specific sets of genes on or off.
- **Almost** all of the cells in an organism contain an identical genome.
- The differences between cell types are
  - **not** due to the presence of different genes but instead
  - due to **selective** gene expression.

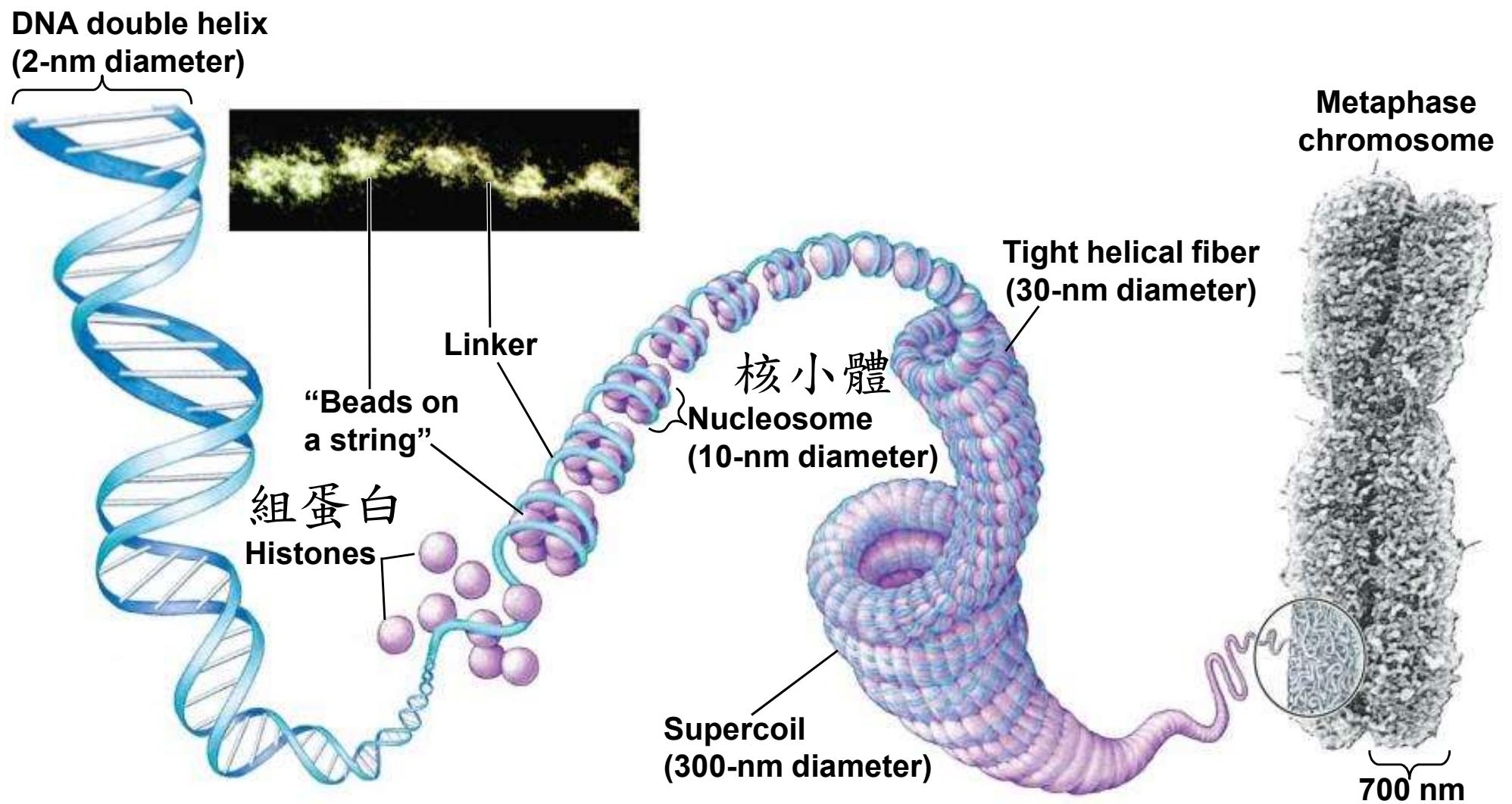
## 11.2 Chromosome structure and chemical modifications can affect gene expression

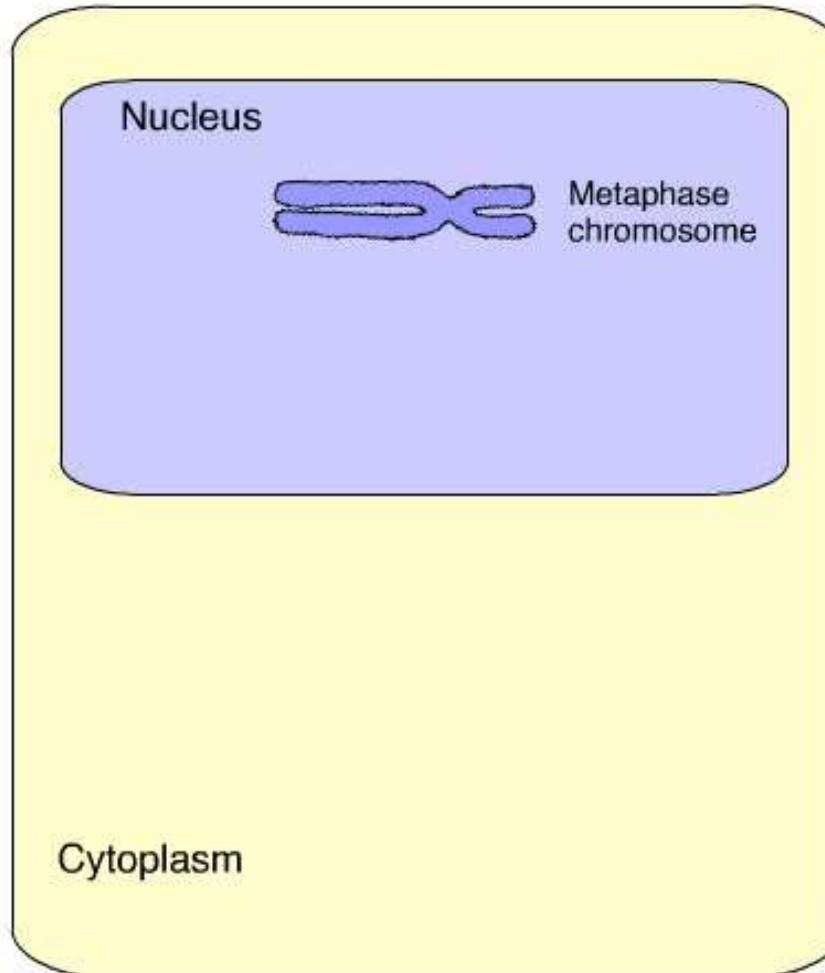
- Eukaryotic chromosomes undergo multiple levels of folding and coiling, called **DNA packing**.
  - **Nucleosomes** are formed when DNA is wrapped around **histone** proteins.
    - This packaging gives a “beads on a string” appearance.
    - Each nucleosome bead includes DNA plus eight histones.
    - Stretches of DNA, called linkers, join consecutive nucleosomes.
  - At the next level of packing, the **beaded string** is wrapped into a tight helical fiber.
  - This fiber coils further into a thick **supercoil**.
  - Looping and folding can further **compact** the DNA.

## 11.2 Chromosome structure and chemical modifications can affect gene expression

- DNA packing can **prevent gene expression** by preventing RNA polymerase and other transcription proteins from contacting the DNA.
- Cells seem to use higher levels of packing for long-term inactivation of genes.
- Highly compacted chromatin, found in varying regions of interphase chromosomes, is generally **not expressed** at all.

Figure 11.2A



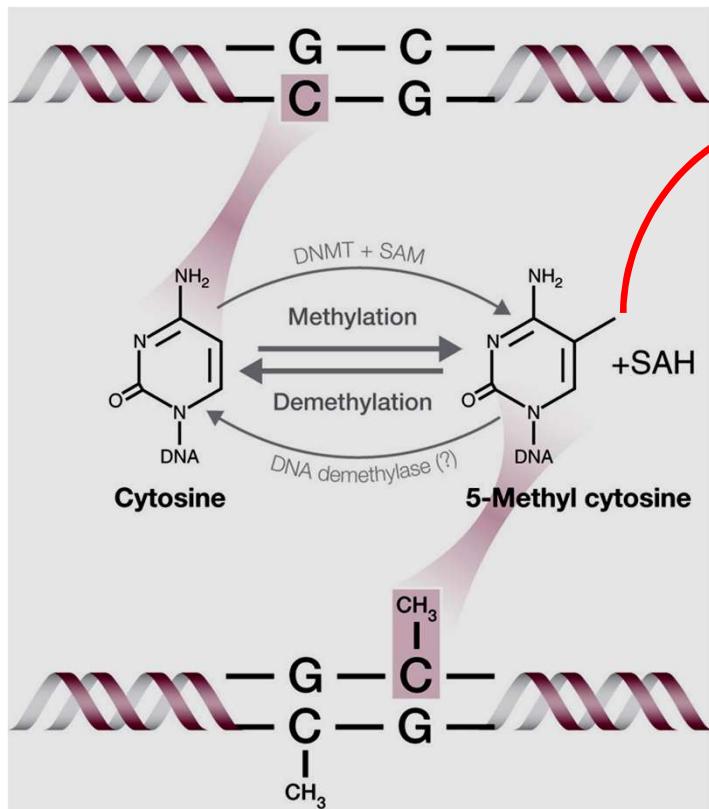


Animation: DNA Packing  
Right click on animation / Click play

## 11.2 Chromosome structure and chemical modifications can affect gene expression

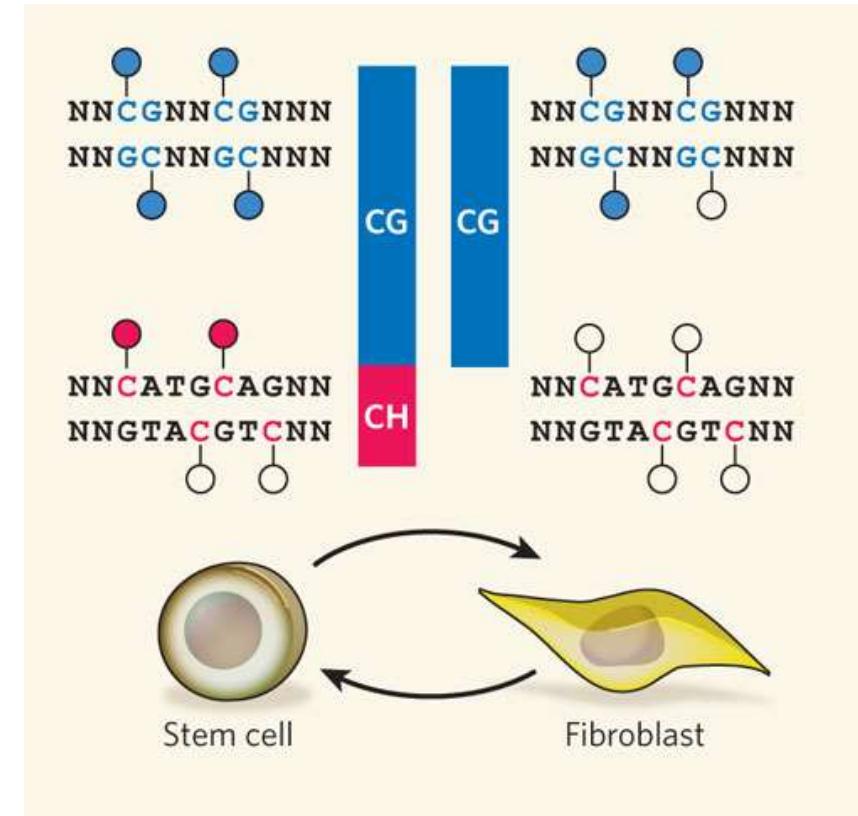
- Chemical modification of DNA bases or histone proteins can result in **epigenetic** inheritance. 表觀遺傳
  - Certain enzymes can add a **methyl group** to DNA bases, without changing the sequence of the bases.
  - Individual genes are usually more methylated in cells in which the genes are not expressed. Once methylated, genes usually stay that way **through successive cell divisions** in an individual.
  - Removal of the extra methyl groups can turn on some of these genes.
  - Inheritance of traits transmitted by mechanisms not directly involving the nucleotide sequence is called **epigenetic inheritance**. These modifications **can be reversed** by processes not yet fully understood.

# Epigenetics: reversible regulation of gene regulation without permanent DNA sequence change; 1. DNA Methylation, 2. Histone modification; 3. RNA regulation



Methyl group: -CH<sub>3</sub>

<http://www.promega.com/resources/product-guides-and-selectors/protocols-and-applications-guide/epigenetics/>



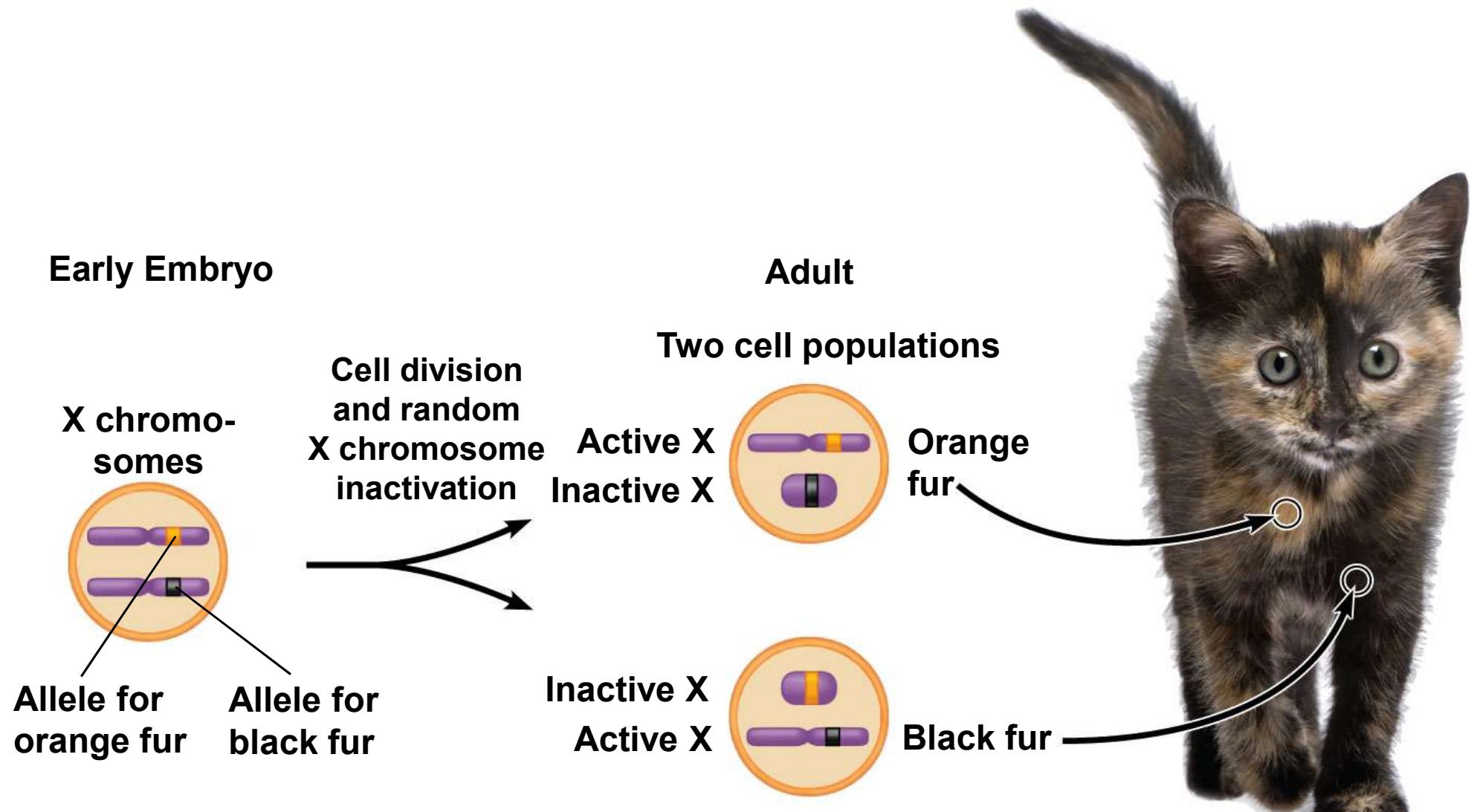
In stem cells, regions of DNA with CpG methylation (blue) are mostly uniformly methylated, whereas this modification is more heterogeneous in fibroblasts. **Non-CpG methylation** (red), which occurs primarily at CA nucleotides, is detected **only in stem cells**, yet is asymmetric and more scarce and patchy than CpG methylation. If fibroblasts are converted to induced pluripotent stem cells they regain non-CpG methylation. Filled circles, methylated cytosines; unfilled circles, unmethylated cytosines. H stands for A, C or T; N stands for any nucleotide. *Nature* **462**, 296-297(19 November 2009)

## 11.2 Chromosome structure and chemical modifications can affect gene expression

### ■ X-chromosome inactivation

- In female mammals, **one of the two X chromosomes** is highly compacted and **transcriptionally inactive**.
- Either the maternal or paternal chromosome is **randomly** inactivated.
- Inactivation occurs early in **embryonic development**, and all cellular **descendants** have the same inactivated chromosome.
- An inactivated X chromosome is called a **Barr body**.
- Tortoiseshell fur coloration is due to inactivation of X chromosomes in heterozygous female cats.

Figure 11.2B



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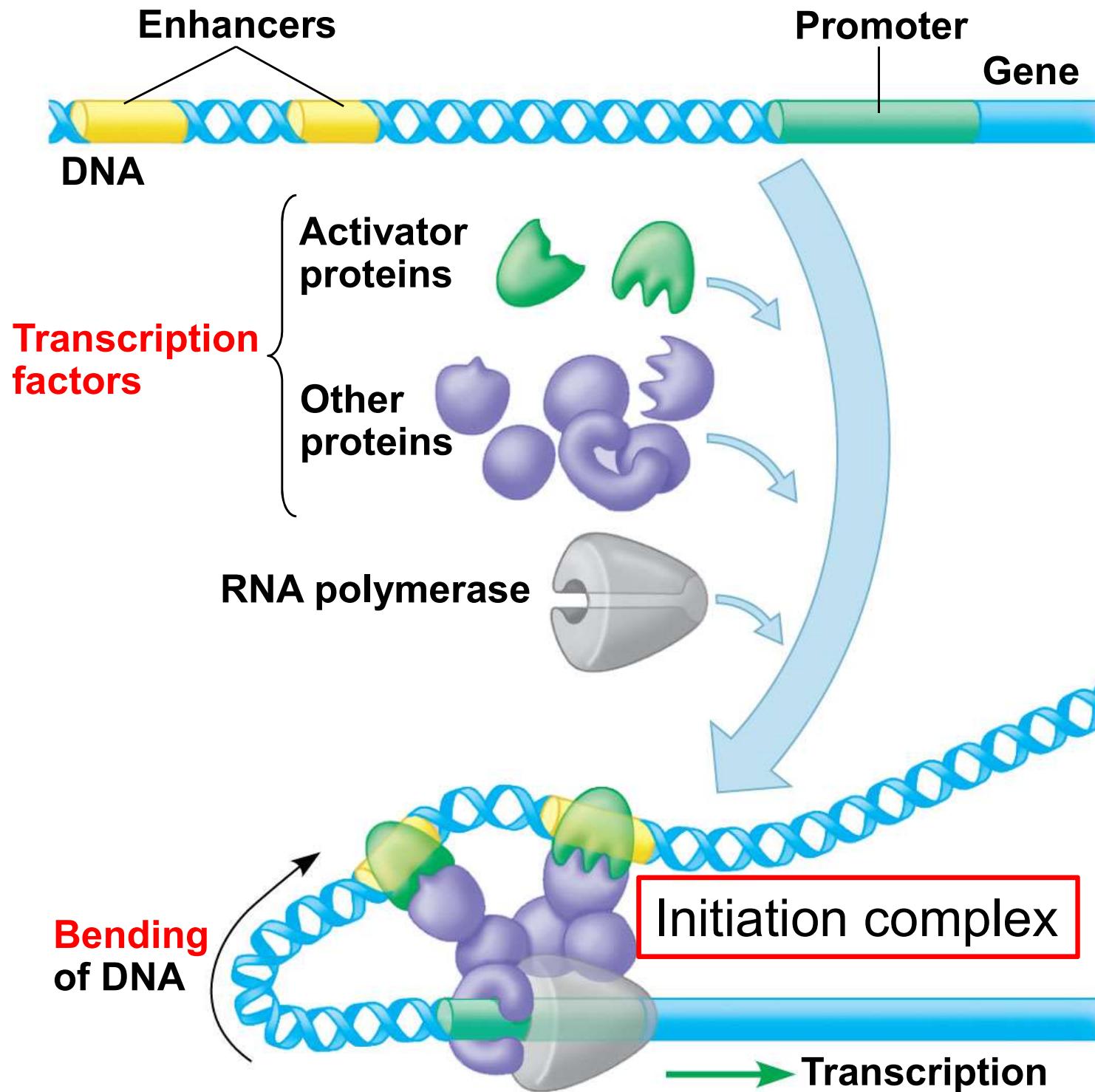
## 11.3 Complex assemblies of proteins control eukaryotic transcription

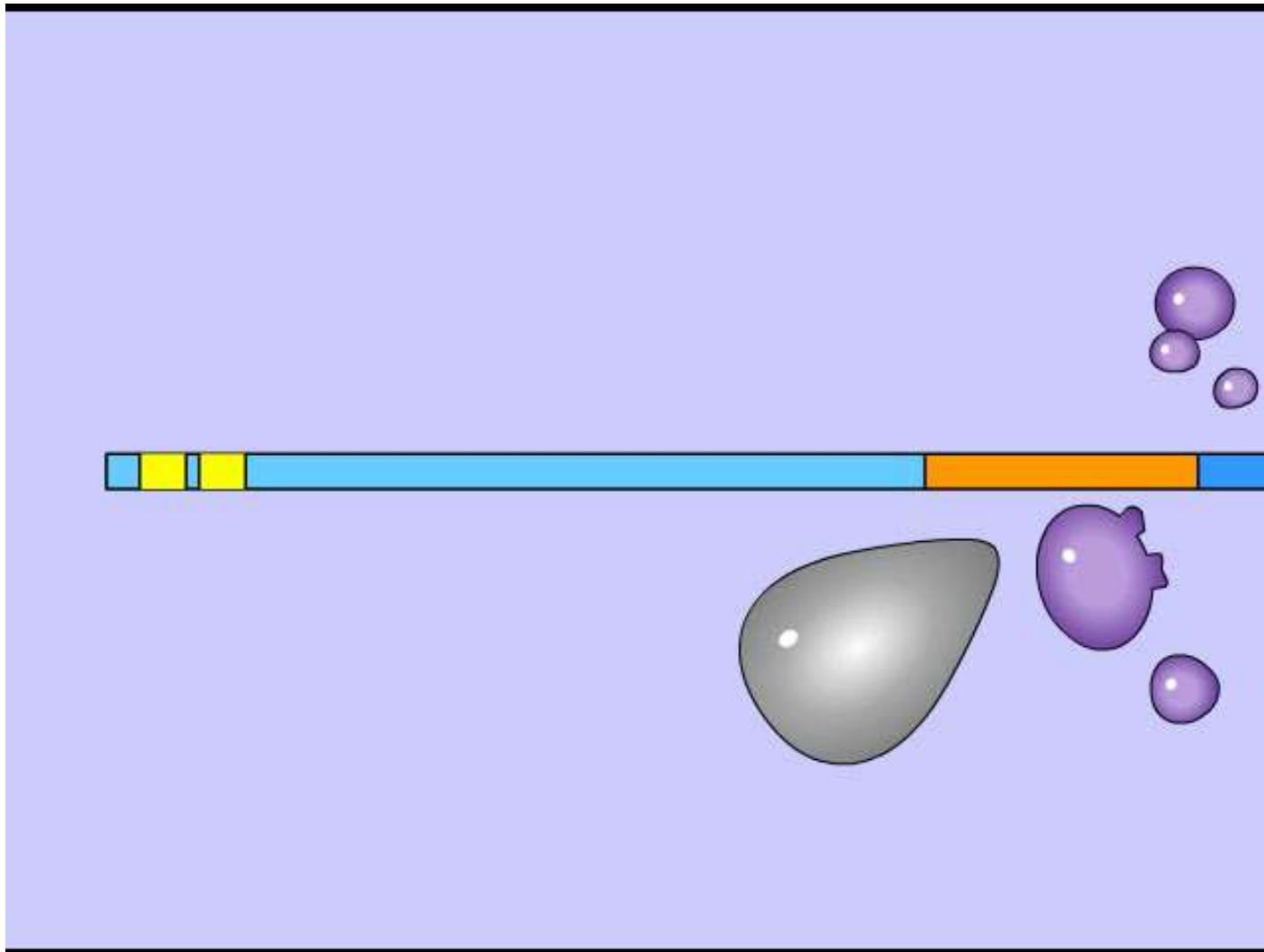
- Prokaryotes and eukaryotes employ **regulatory proteins** (activators and repressors) that
  - bind to specific segments of DNA and
  - either promote or block the binding of RNA polymerase, turning the transcription of genes on and off.
- In eukaryotes, **activator proteins** seem to be more important than repressors. Thus, the default state for most genes seems to be off.
- A typical plant or animal cell needs to turn on and transcribe only a small percentage of its genes.

## 11.3 Complex assemblies of proteins control eukaryotic transcription

- Eukaryotic RNA polymerase requires the assistance of proteins called **transcription factors**.
- Transcription factors include
  - **activator proteins**, which bind to DNA sequences called **enhancers** and initiate gene transcription. The binding of the activators leads to **bending** of the DNA.
  - Other transcription factor proteins interact with the bound activators, which then collectively bind as a complex at the gene's promoter.
- RNA polymerase then attaches to the promoter and transcription begins.

Figure 11.3





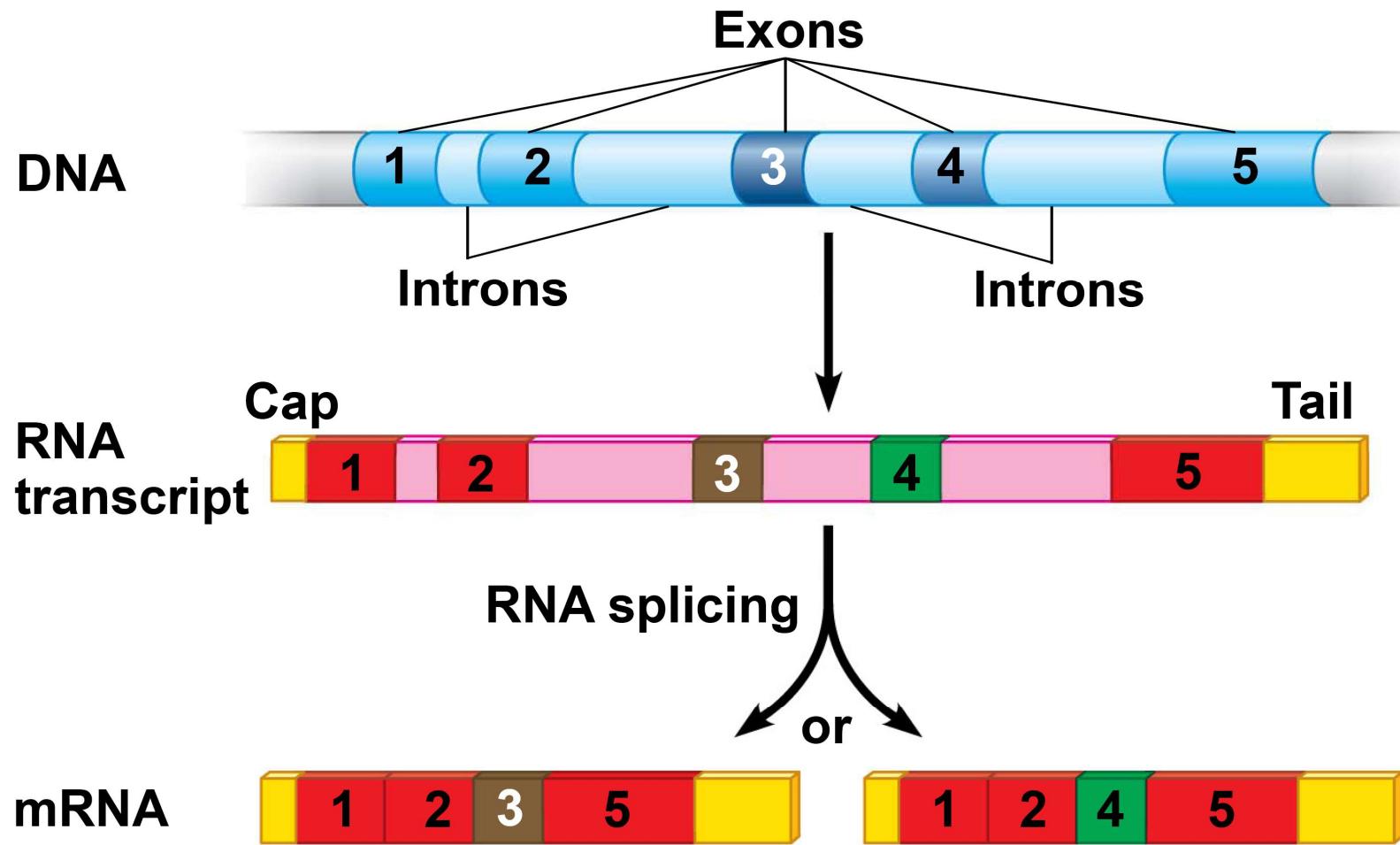
Animation: Initiation of Transcription  
Right click on animation / Click play

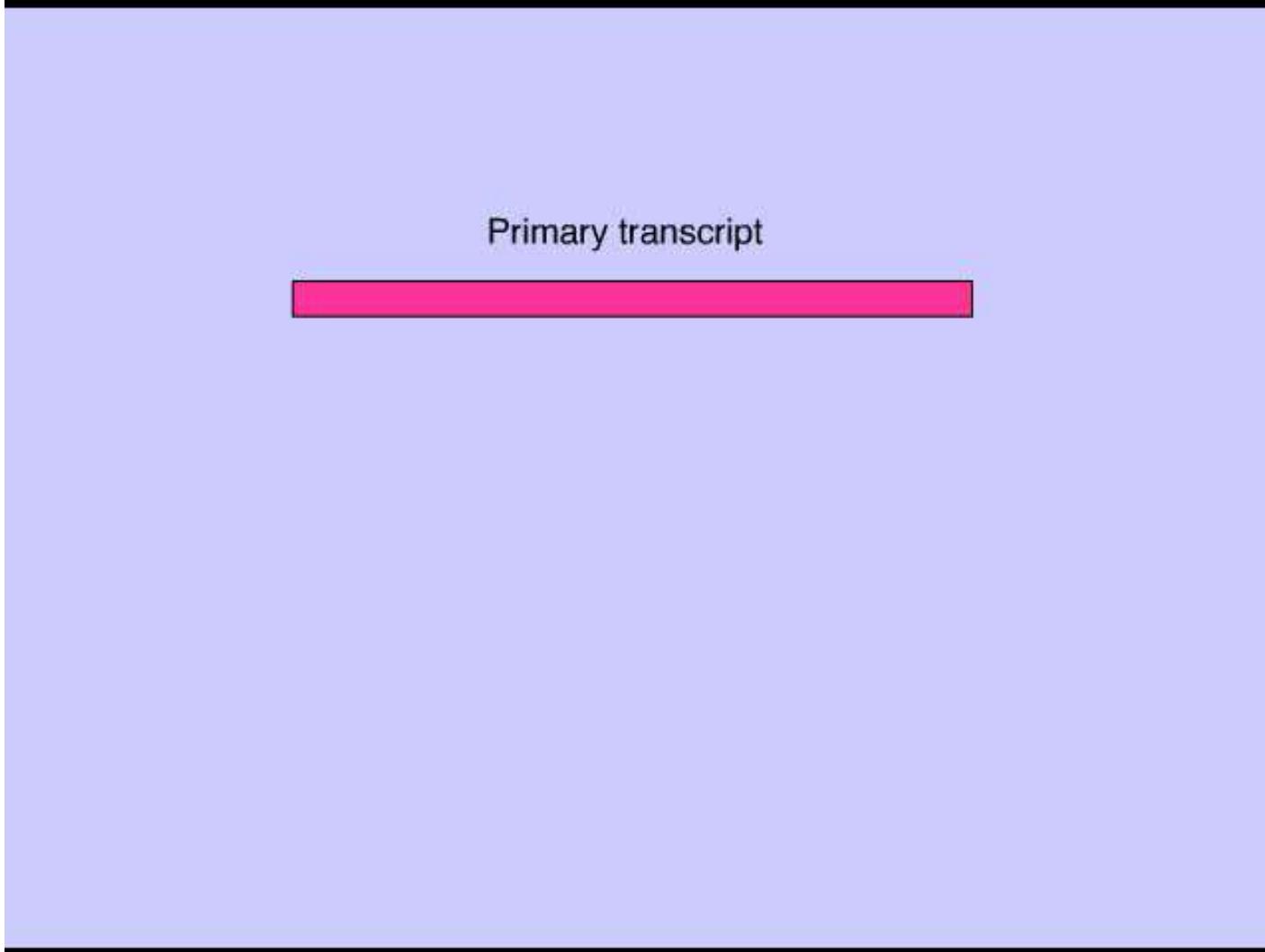
## 11.3 Complex assemblies of proteins control eukaryotic transcription

- **Silencers** are repressor proteins that
  - may bind to DNA sequences and
  - inhibit transcription.
- Coordinated gene expression in eukaryotes often depends on the association of a specific **combination** of control elements with every gene of a particular metabolic pathway.

## 11.4 Eukaryotic RNA may be spliced in more than one way

- **Alternative RNA splicing**
  - produces different mRNAs from **the same transcript**,
  - results in the production of more than one polypeptide from the same gene, and
  - In humans, more than 90% of protein-coding genes appear to undergo alternate splicing.



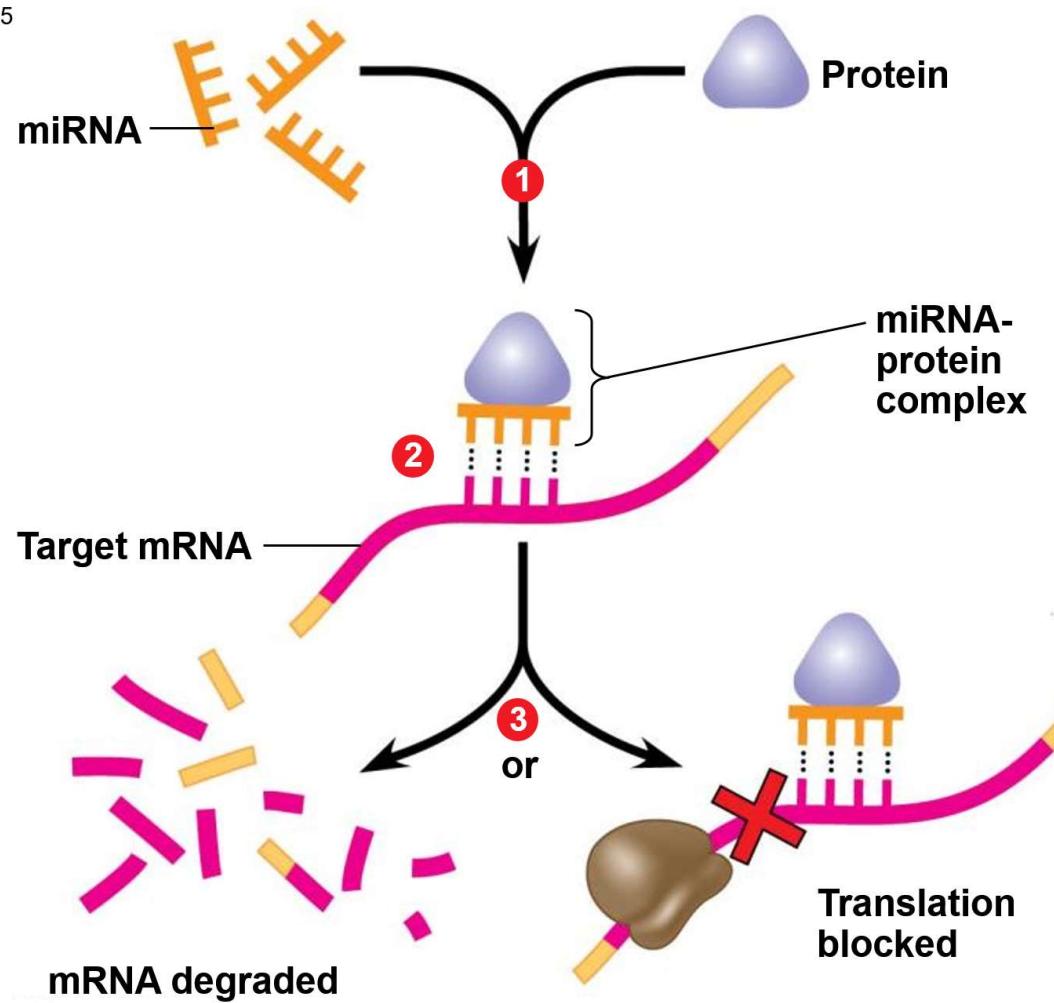


Primary transcript

Animation: RNA Processing  
Right click on animation / Click play

## 11.5 Small RNAs play multiple roles in controlling gene expression

- Only about **1.5%** of the human genome codes for proteins.  
(This is also true of many other multicellular eukaryotes.)
- Another small fraction of DNA consists of genes for **ribosomal RNA and transfer RNA**.
- A flood of recent data suggests that a significant amount of the remaining genome is transcribed into functioning but **non-protein-coding RNAs**, including a variety of **small RNAs**.
- **microRNAs (miRNAs)** can bind to **complementary** sequences on **mRNA** molecules either (1993)
  - degrading the target mRNA or
  - blocking its translation.
- **RNA interference (RNAi)** is the use of miRNA to artificially control gene expression by injecting miRNAs into a cell to turn off a specific gene sequence.



**Andrew Z. Fire   Craig C. Mello**  
 The Nobel Prize in  
 Physiology or Medicine  
 2006 was awarded jointly to  
 Andrew Z. Fire and Craig C.  
 Mello "for their discovery of  
*RNA interference - gene  
 silencing by double-  
 stranded RNA*"

RNAi therapeutic	Type of cancer targeted	Targets	Sponsors	Clinical trial status
CEQ508	Familial adenomatous polyposis	$\beta$ -Catenin	MDRNA, Inc.	Active, phase I
ALN-PLK1	Liver tumors	PLK1	Alnylam Pharm.	Active, phase I
FANG	Solid tumors	Furin	Gradalis, Inc.	Active, phase II
CALAA-01	Solid tumors	RRM2	Calando Pharm.	Active, phase I
SPC2996	Chronic myeloid leukemia	BCL-2	Santaris Pharm.	Ongoing, phase I, II
ALN-VSP02	Solid tumours	VEGF, kinesin spindle protein	Alnylam Pharm.	Active, phase I
NCT00672542	Metastatic melanoma	LMP2, LMP7, and MECL1	Duke university	Active, phase I
Atu027	Advanced, recurrent or metastatic solid malignancies	PKN3	Silence therapeutics	Active, phase I

VEGF=Vascular endothelial growth factor; RNAi=RNA interference



# US approves first RNA interference drug 2018/8/16

<https://www.chemistryworld.com/news/us-approves-first-rna-interference-drug/3009385.article>

To treat hereditary transthyretin amyloidosis – a rare, progressive and often fatal disease; neuropathy  
A mutation in patients with this hereditary disease makes a toxic form of transthyretin protein that is deposited in the heart and peripheral nerves. Patisiran silences this gene using short pieces of double-stranded RNA that target and destroy the sequence of messenger RNA (mRNA) that encodes for manufacturing the protein.

## 激戰! 輝瑞公佈治療TTR類澱粉沉積三期正面數據 仍暫時不敵競爭者Alnylam (值得閱讀案例)

日期 : 2018/8/29 作者 : 江欣盈綜合外電 罕見疾病 、 輝瑞 Pfizer

今年四月中Genet曾為各位報導老大哥輝瑞 ( Pfizer ) 因應威而剛到期的另尋他路，當時提到其中一個暢銷藥未來之星就是治療罕見心臟疾病—**家族性澱粉樣多發性神經病變 ( transthyretin amyloid cardiomyopathy )** 所引起的心肌病變—的新藥tafamidis。現在輝瑞再度公佈tafamidis三期正面數據，就在對手Alnylam剛拿到同一適應症（也是公司第一張）藥證patisiran ( Onpattro™ ) 之際。

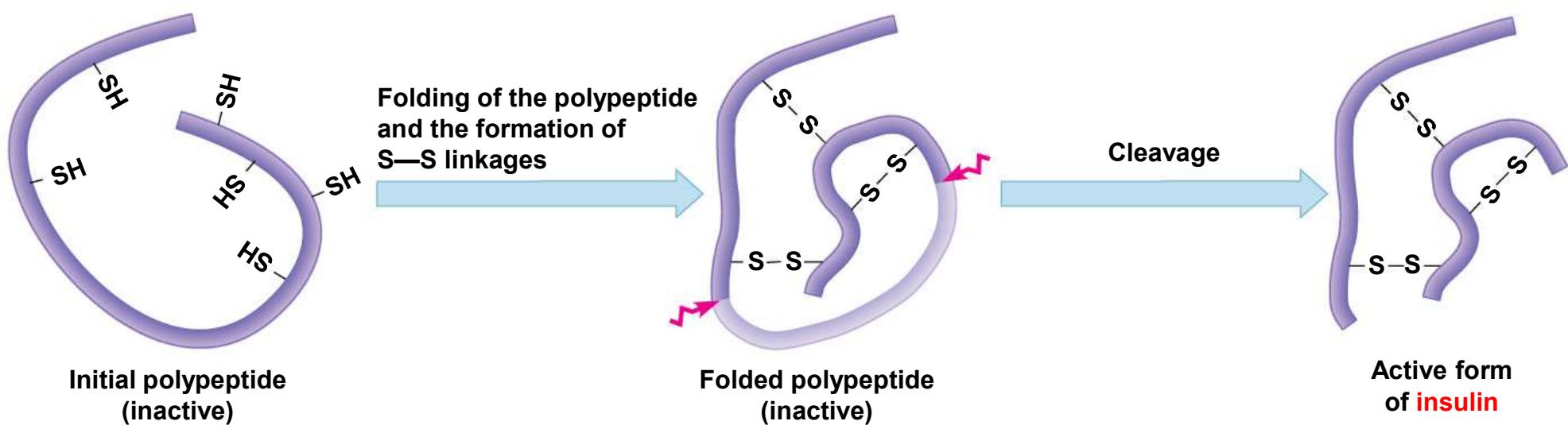
<http://www.genetinfo.com/investment/featured/item/19408.html?limitstart=0>

延伸閱讀: 威而剛專利謝幕！輝瑞另尋他路：老大哥的生存之道

延伸閱讀: 《FDA》中止和逆轉疾病! 通過第一張RNAi藥證 Alnylam苦盡甘來獨占鰲頭

## 11.6 Later stages of gene expression are also subject to regulation

- After mRNA is fully processed and transported to the cytoplasm, gene expression can still be regulated by
  - breakdown of mRNA,
  - initiation of translation,
  - protein activation, and
  - protein breakdown.



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Longer-lived mRNA

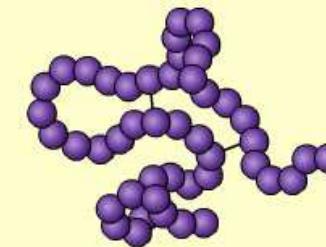
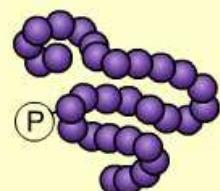
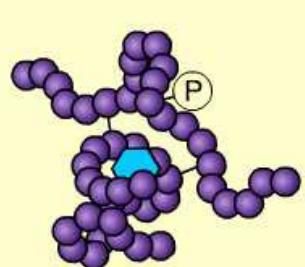


Shorter-lived mRNA

Animation: Blocking Translation  
Right click on animation / Click play

Animation: mRNA Degradation  
Right click on animation / Click play

**UTR: untranslated region**



Polypeptide

Animation: Protein Degradation

Ubiquitin  
Proteosome

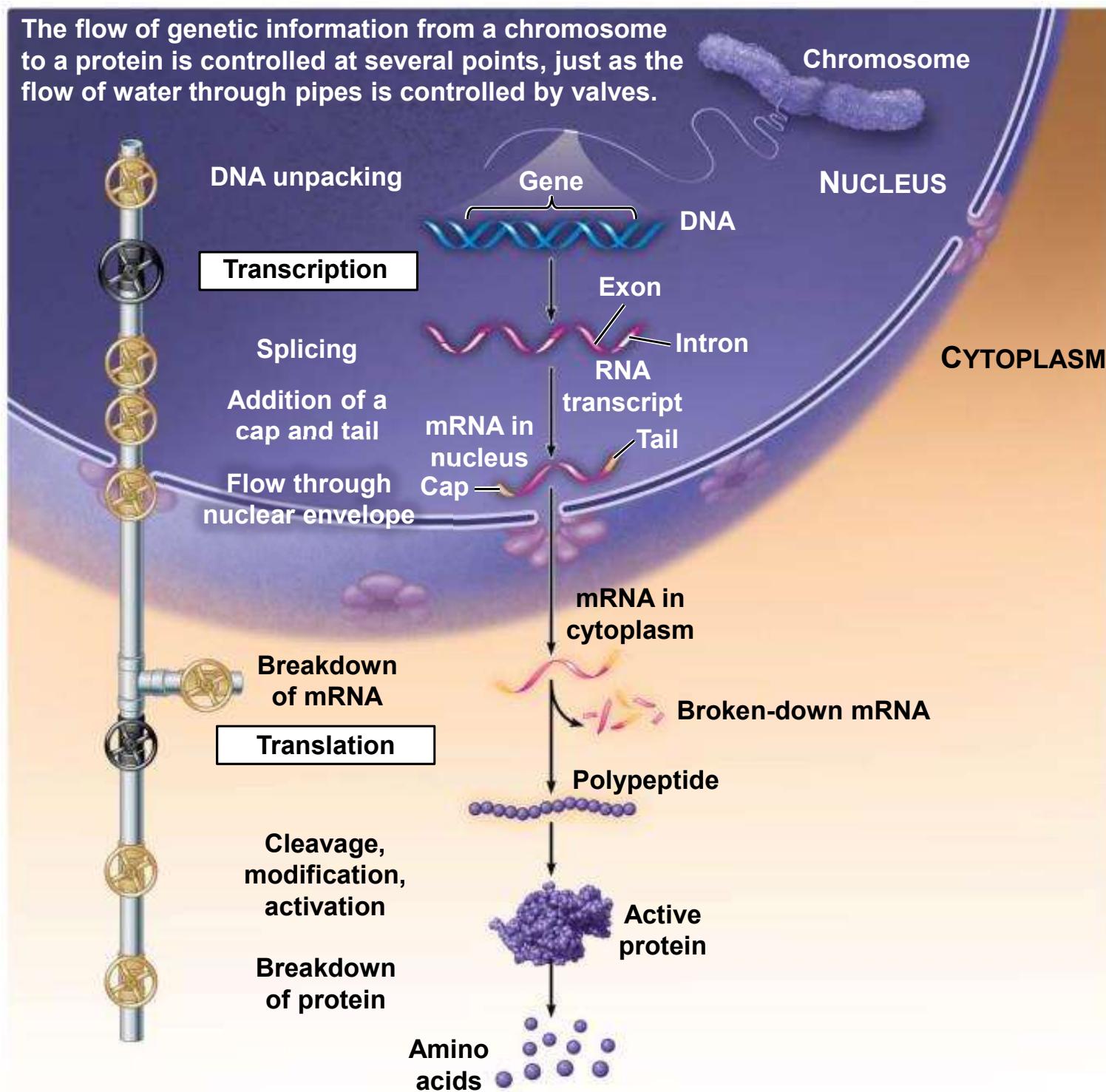
Animation: Protein Processing

Phosphorylation

## 11.7 Multiple mechanisms regulate gene expression in eukaryotes

- **Multiple control points** exist where gene expression in eukaryotes can be
  - turned on or off or
  - speeded up or slowed down.
- Although many control points are shown, only a few of them may be important for any particular protein.
- These control points are like a series of pipes carrying water from your local water supply to a faucet in your home. Valves in this series of pipes are like the control points in gene expression.

Figure 11.7-8



## 11.7 Multiple mechanisms regulate gene expression in eukaryotes

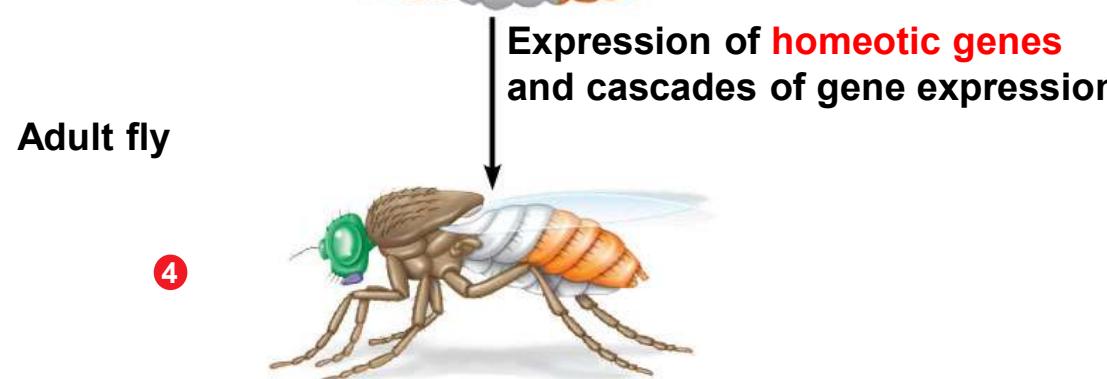
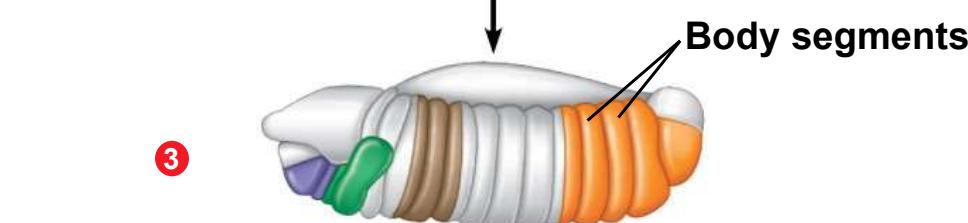
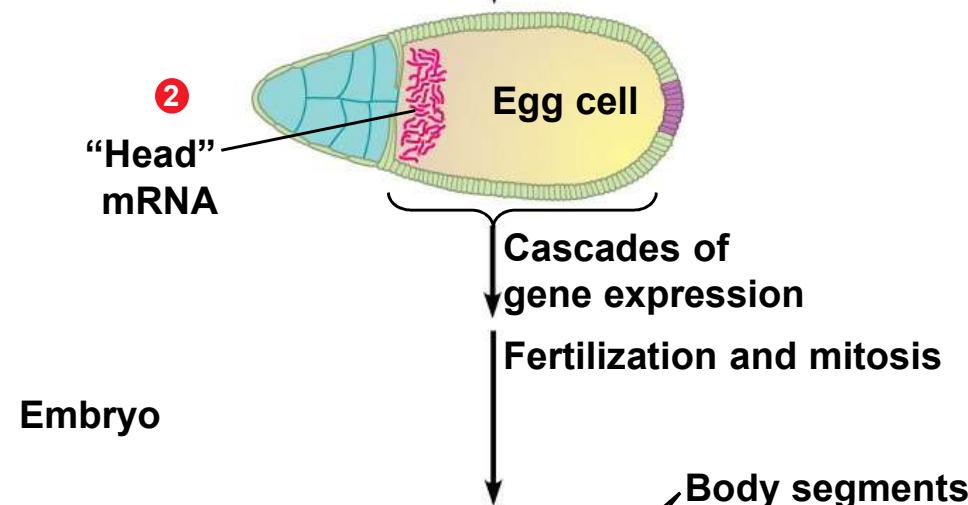
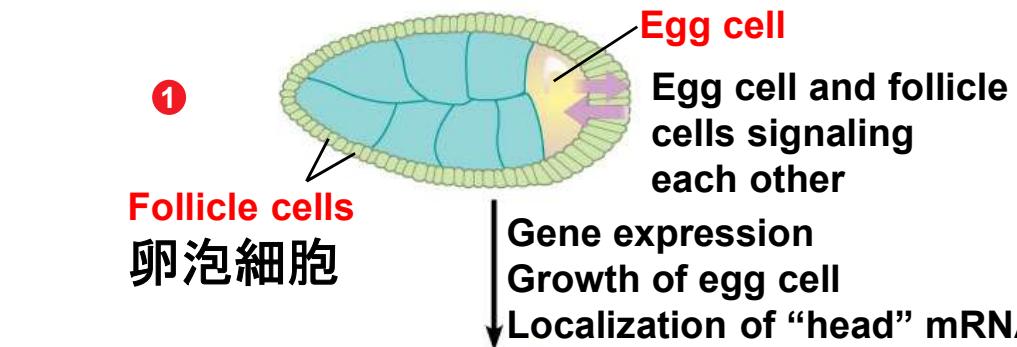
- These control points include:
  1. chromosome changes and DNA unpacking,
  2. control of transcription,
  3. control of RNA processing including the
    - addition of a cap and tail and
    - splicing,
  4. flow through the nuclear envelope,
  5. breakdown of mRNA,
  6. control of translation, and
  7. control after translation including
    - cleavage/modification/activation of proteins and
    - breakdown of protein.

At cell level

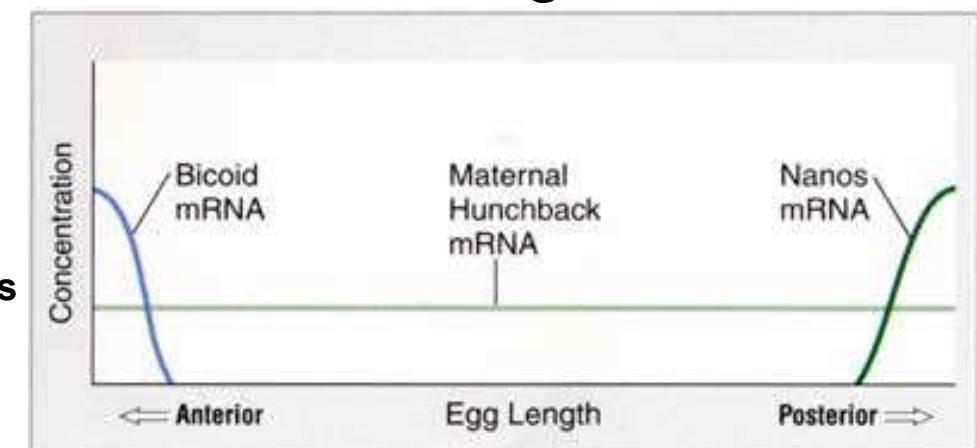
## 11.8 Cell signaling and cascades of gene expression direct animal development

- Early research on gene expression and embryonic development came from studies of a fruit fly.
- Research on fruit flies and other developmental mutants, such as a mutant fly with two legs where its antennae should be, has led to the identification of many of the genes that program development in the normal fly.
  1. **Orientation** of the head-to-tail, top-to-bottom, and side-to-side **axes** are determined by early genes in the egg that produce proteins and **maternal mRNAs**.
  2. **Segmentation** of the body is influenced by cascades of proteins that diffuse through the cell layers. 同源異型基因
  3. Adult features develop under the influence of **homeotic genes**, master control genes that determine the anatomy of the parts of the body.

## Egg cell within ovarian follicle

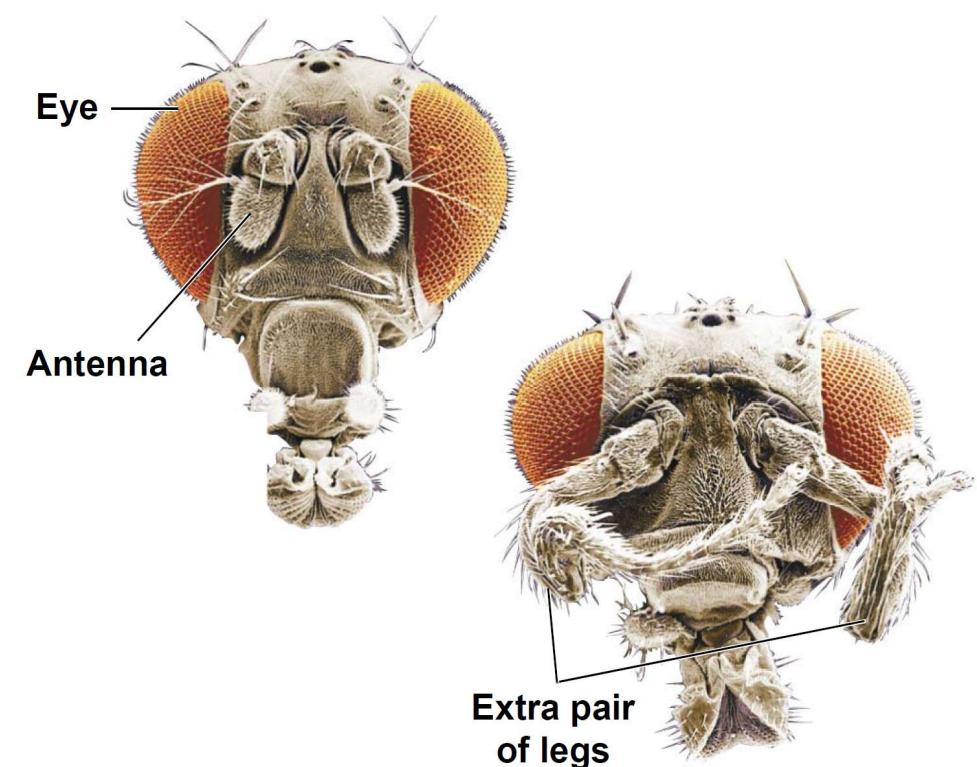
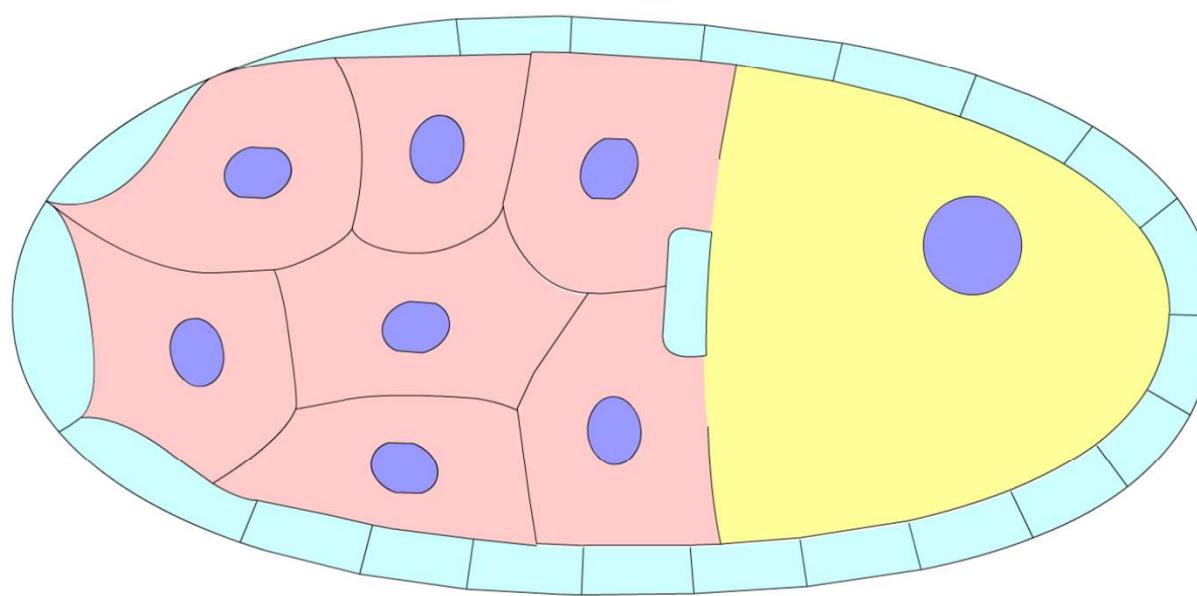


## Bicoid gradient Nano gradient

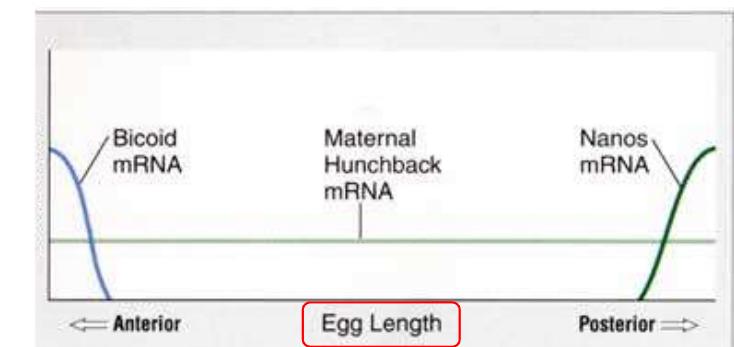


<http://scienceblogs.com/pharyngula/2006/07/10/bicoid-nanos-and-bricolage/>

Animation: Development of Head-Tail Axis in Fruit Flies  
Right click on animation / Click play



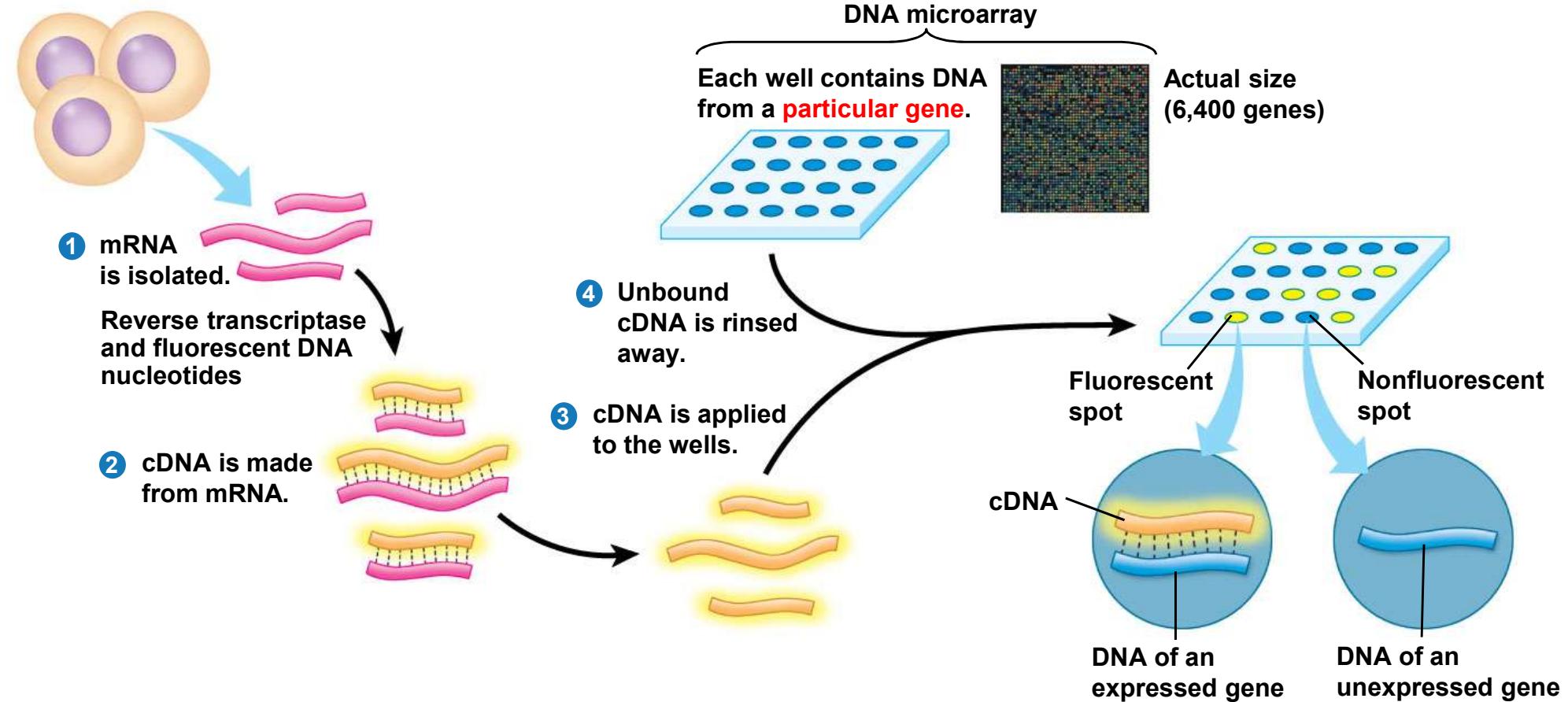
Bicoid gradient  
Nano gradient



## 11.9 Scientists use DNA microarrays test for the transcription of many genes at once

- Genome-wide expression studies are made possible by **DNA microarrays**. 微陣列系統、生物晶片
- A DNA microarray: consist of a glass or plastic surface with tiny amounts of thousands of different kinds of single-stranded DNA fragments attached to microscopic wells in a tightly spaced array, or grid.
  - is used to test for transcription in the following way:
    - mRNA from a specific cell type is isolated,
    - fluorescent cDNA is produced from the mRNA,
    - cDNA is applied to the microarray,
    - unbound cDNA is washed off, and
    - complementary cDNA is detected by fluorescence.

Figure 11.9



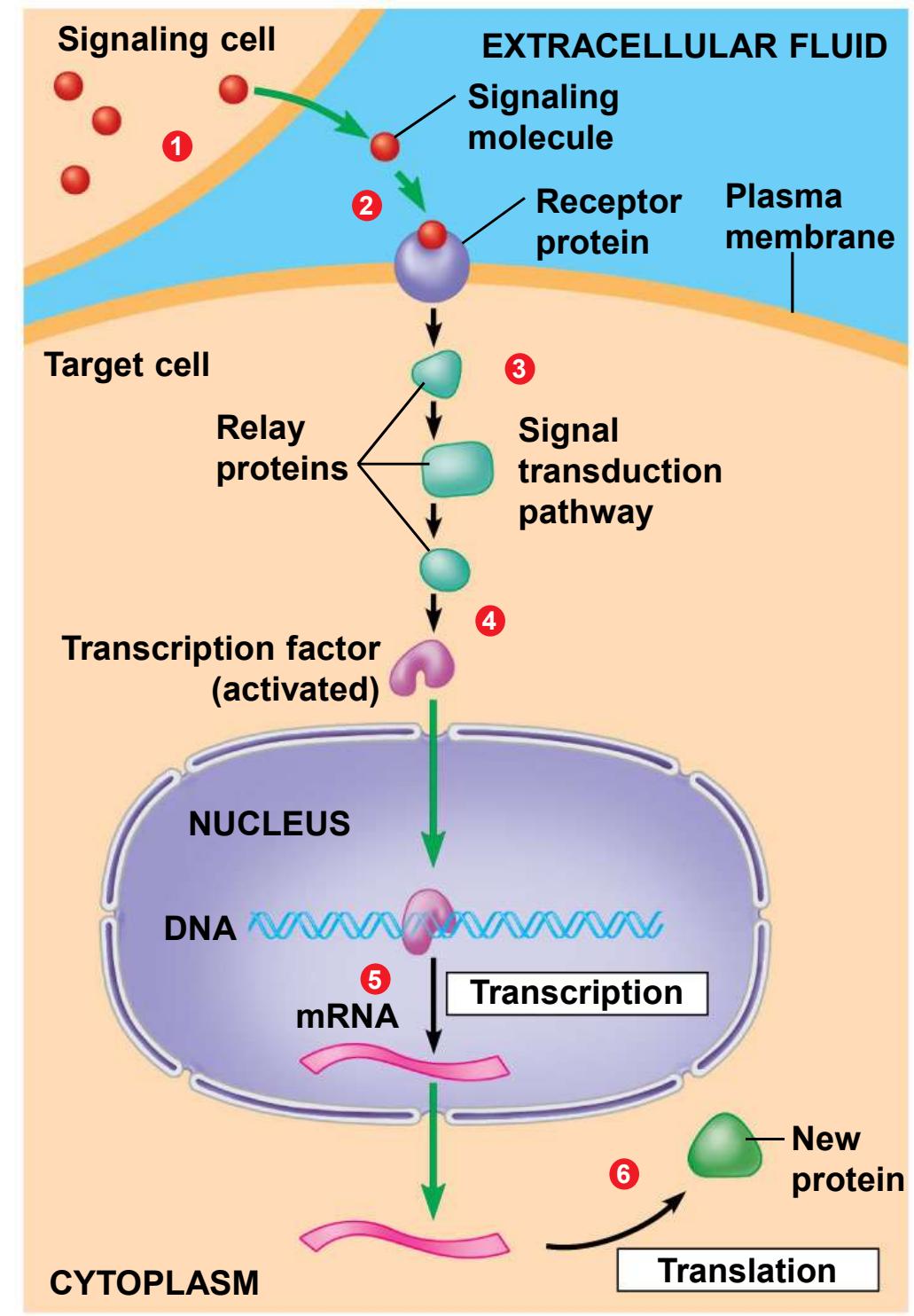
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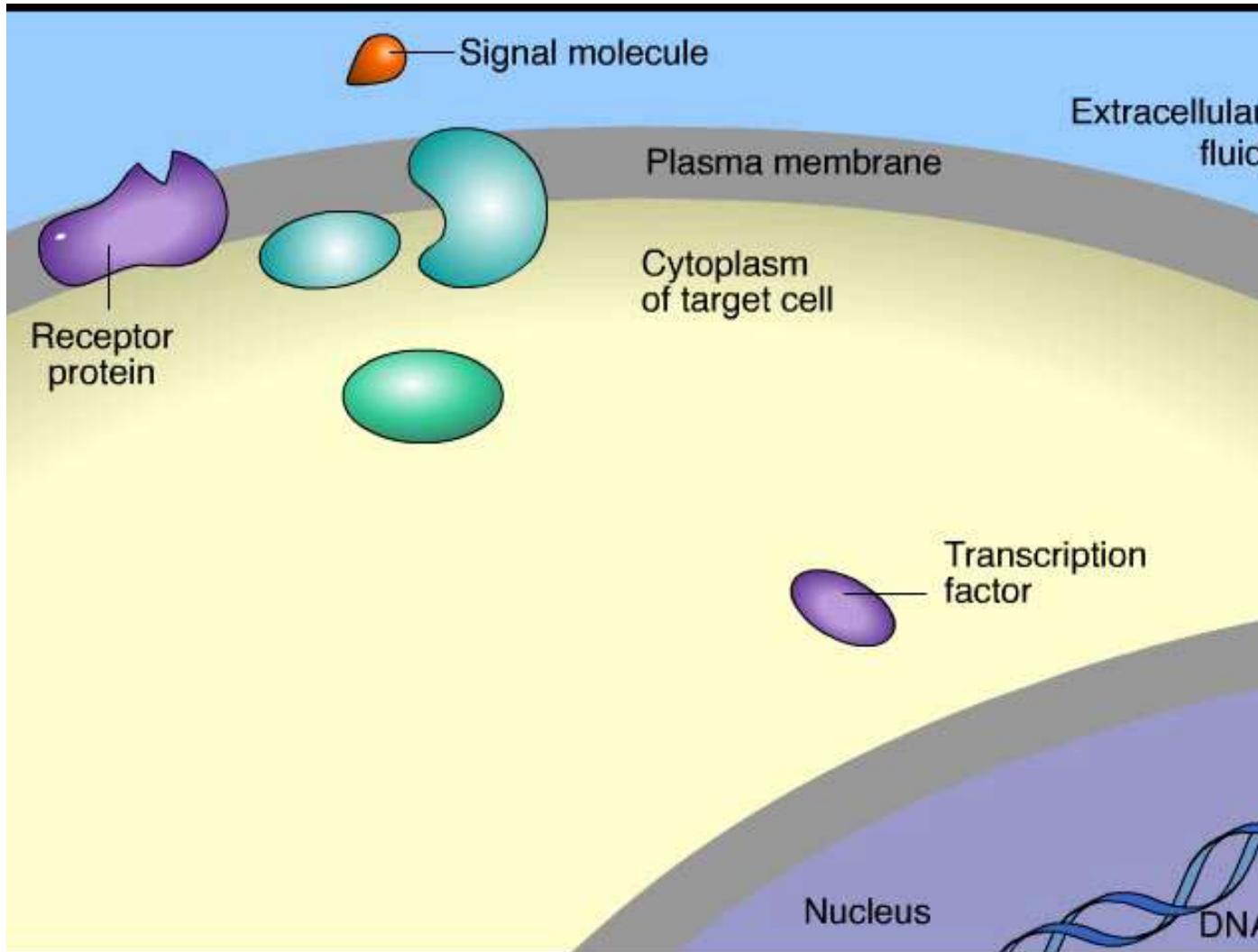
- DNA microarrays are a potential boon to medical research.
  - A study showed that DNA microarray data can **classify** different types of leukemia, helping to identify which chemotherapies will be most effective.
  - Some oncologists predict that DNA microarrays will usher in a new era in which medical treatment is **personalized** to each patient
  - DNA microarrays also reveal general **profiles of gene expression** over the lifetime of an organism.

SAN FRANCISCO, April 17, 2019 /PRNewswire/ -- The global DNA & gene chip market size is expected to reach USD 10.7 billion by 2025, according to a new report by Grand View Research, Inc., at an 11.4% CAGR during the forecast period. DNA and gene chips have gained much success in providing high throughput capabilities for comprehensive genome studies to enhance disease knowledge and target them. This technology has emerged as a valuable and promising solution across various aspects of disease management. These factors have been driving the market.

## 11.10 Signal transduction pathways convert messages received at the cell surface to responses within the cell

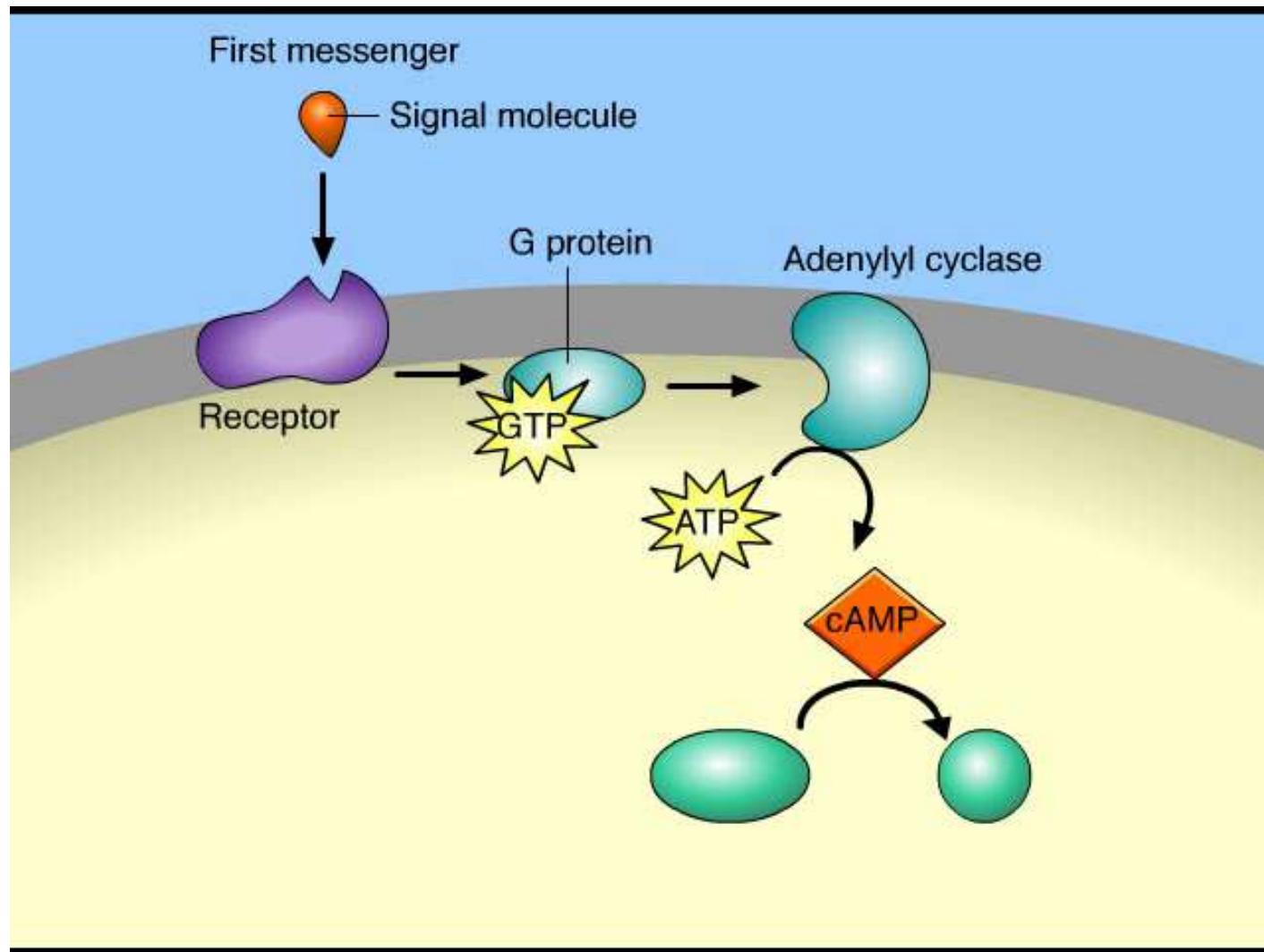
- A **signal transduction pathway** is a series of molecular changes that convert a signal on the target cell's surface to a specific response within the cell.
- Signal transduction pathways are crucial to many cellular functions.





# Chemical signal Reception Transduction Response

Animation: Overview of Cell Signaling  
Right click on animation / Click play



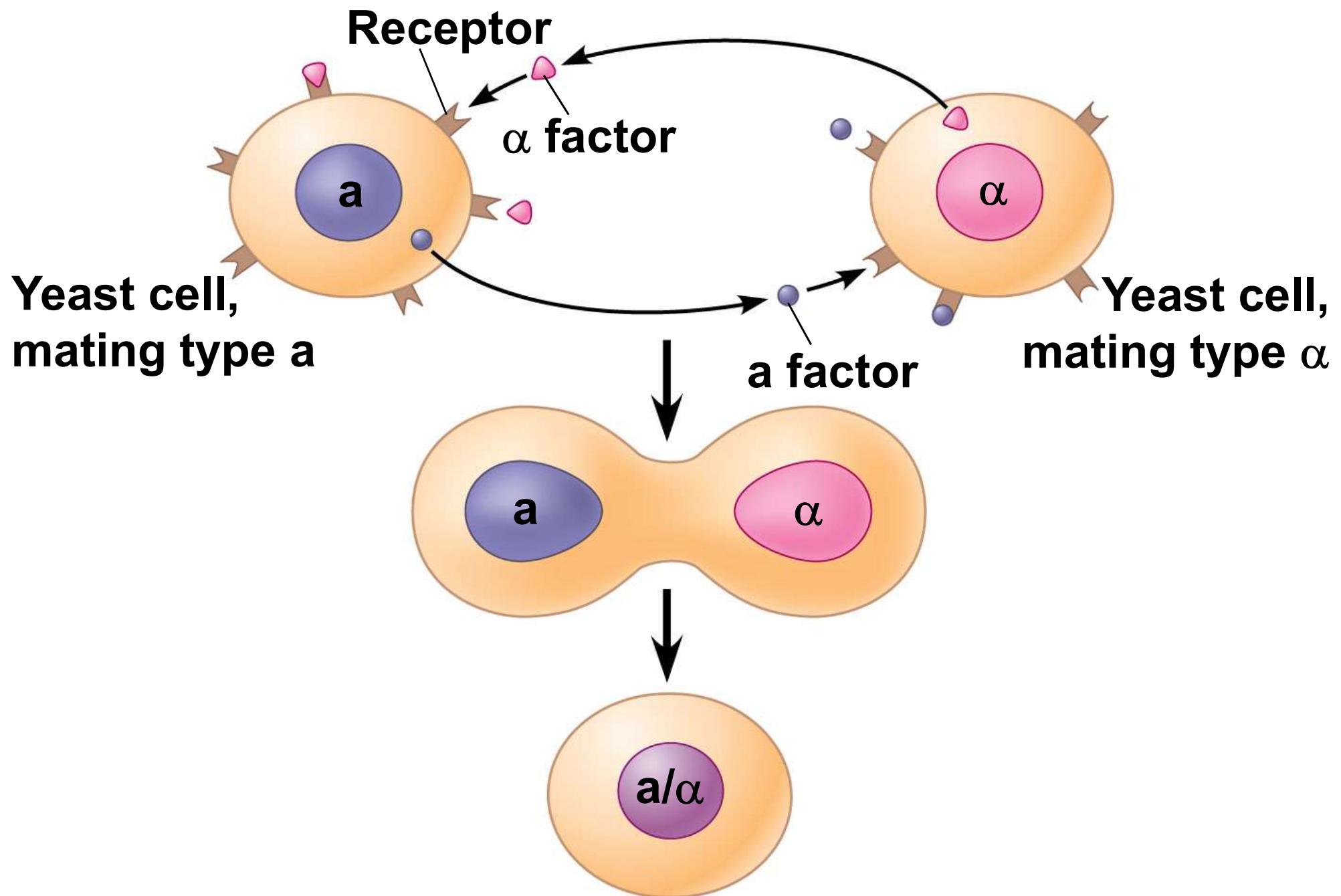
**Multi-step transduction pathway**  
 First messenger  
 Second messenger  
 G-protein  
 Receptor protein kinase  
 Epinephrine  
 Adenylyl cyclase  
 ATP to cAMP (cyclic)  
 Phospholipase C (PLC)  
 $\text{IP}_3$   
 Signal amplification

Animation: Signal Transduction Pathways  
 Right click on animation / Click play

## 11.11 Cell-signaling systems appeared early in the evolution of life

- In the yeast used to make bread, beer, and wine, mating is controlled by a signal transduction pathway.
- These yeast cells identify their mates by chemical signaling.
- Yeast have two mating types: **a** and **α**.
  - Each produces a chemical factor that binds to receptors on cells of the opposite mating type.
  - Binding to receptors triggers growth toward the other cell and **fusion**.
- Early versions of the cell-signaling mechanisms used today evolved well before the first multicellular creatures appeared on Earth.

Figure 11.11



# **CLONING OF PLANTS AND ANIMALS**

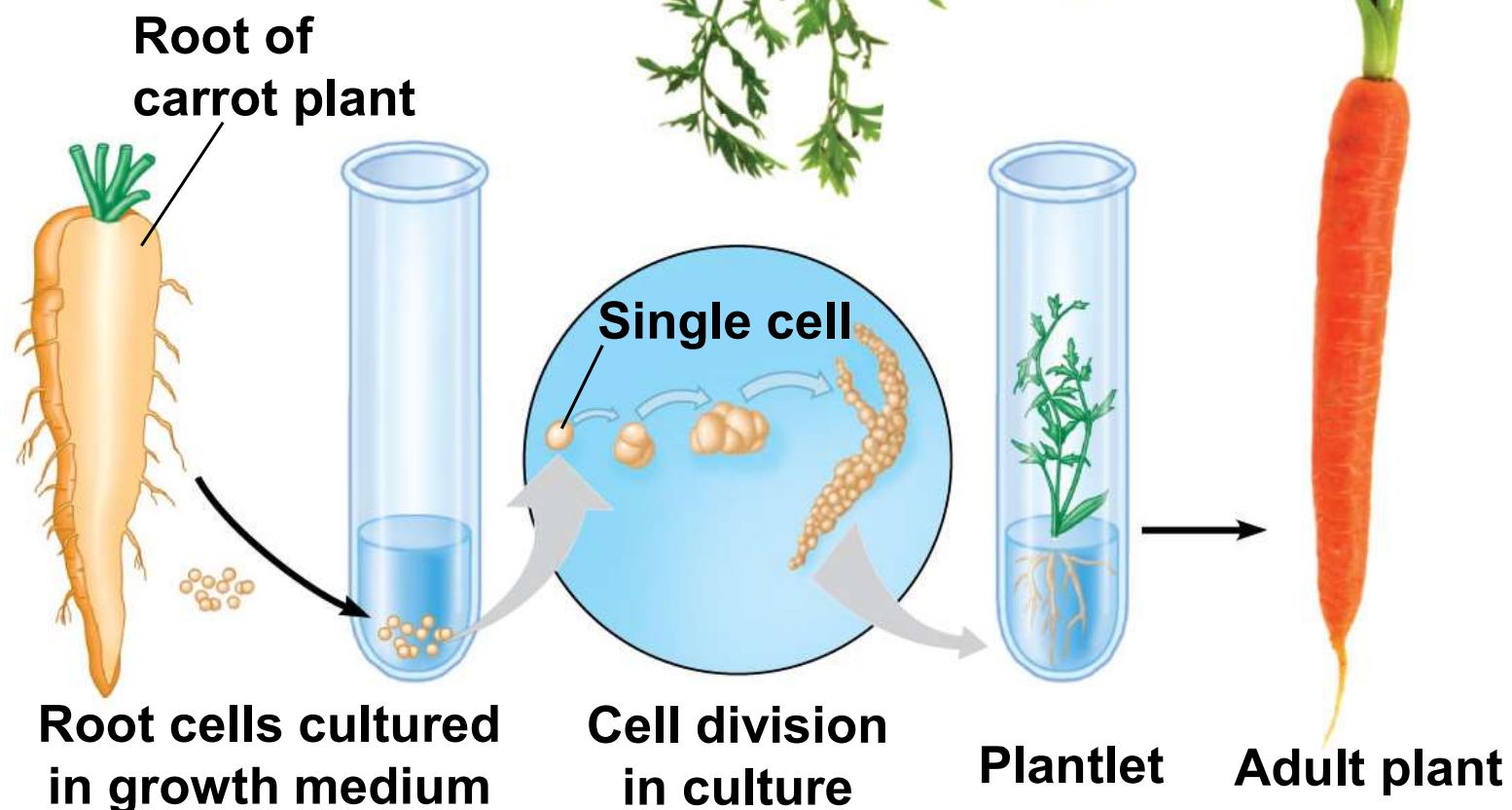
## 11.12 Plant cloning shows that differentiated cells may retain all of their genetic potential

- Most cells express only a small percentage of their genes.
  - If all genes are still present but some are turned off, have the unexpressed genes become **permanently disabled**?
  - Or do all genes (even the unexpressed ones) retain the **potential** to be expressed?
- One way to approach these questions is to determine if a differentiated cell can be stimulated **to generate a whole new organism**.
- In plants, this ability is common.
  - A differentiated plant cell can undergo cell division and give rise to all the tissues of an adult plant.

On a larger scale, the technique described in **Figure 11.12** can be used to produce hundreds or thousands of genetically identical plants from the cells of a single plant.

Such an organism, produced through **asexual reproduction from a single parent**, is called a **clone**.

The term clone refers to an individual created by asexual reproduction.



## 11.12 Plant cloning shows that differentiated cells may retain all of their genetic potential

- In animals, a good indication that differentiation need not impair a cell's genetic potential is the natural process of **regeneration**, the regrowth of lost body parts. 蟒螈
  - When a salamander loses a leg, for example, certain cells in the leg stump **dedifferentiate**, **divide**, and then **redifferentiate**, giving rise to a new leg.
  - Many animals, especially among the invertebrates (sea stars, for example), can regenerate lost parts.

## 11.13 Biologists can clone animals via nuclear transplantation

- Animal cloning can be achieved using **nuclear transplantation**, in this process, the nucleus of an egg cell or zygote is replaced with a nucleus from an adult somatic cell.
  - About 5 days after transplantation, repeated cell divisions form a blastocyst, a hollow ball of about 100 cells.
  - If the animal being cloned is a mammal, the blastocyst is then implanted into the uterus of a surrogate mother.
  - This type of cloning is called **reproductive cloning** because it results in the birth of a new living individual. It was first used in mammals to produce the sheep Dolly (5 July 1996 – 14 February 2003).
  - Researchers have since cloned many other mammals, including mice, cats, horses, cows, mules, pigs, rabbits, ferrets, and dogs.

- Conservation biologists hope that reproductive cloning can be used to restock the populations of **endangered animals**.
  - However, an increasing body of evidence suggests that cloned animals may be **less healthy** than those arising from a fertilized egg.
  - Recent research suggests that the **methylation** of chromatin may be responsible for health problems in cloned animals.
  - Researchers are investigating whether chromatin in a donor nucleus can be **artificially “rejuvenated”** to resemble that of a newly fertilized egg.

Figure 11.13

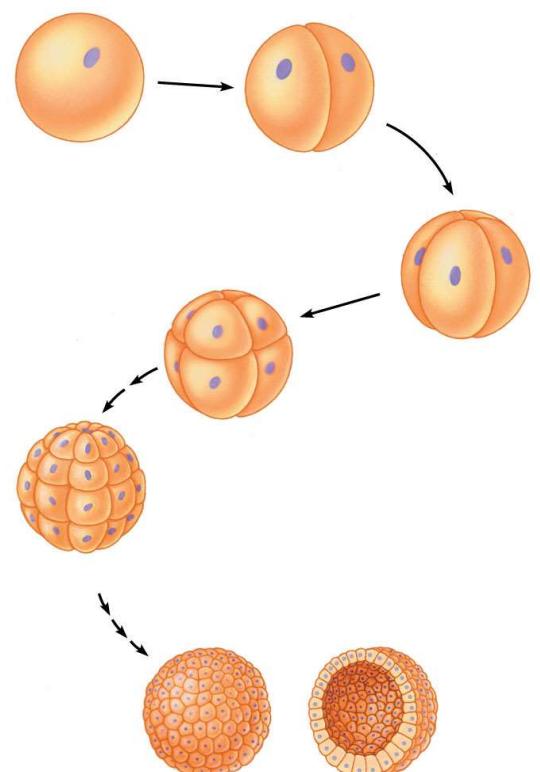
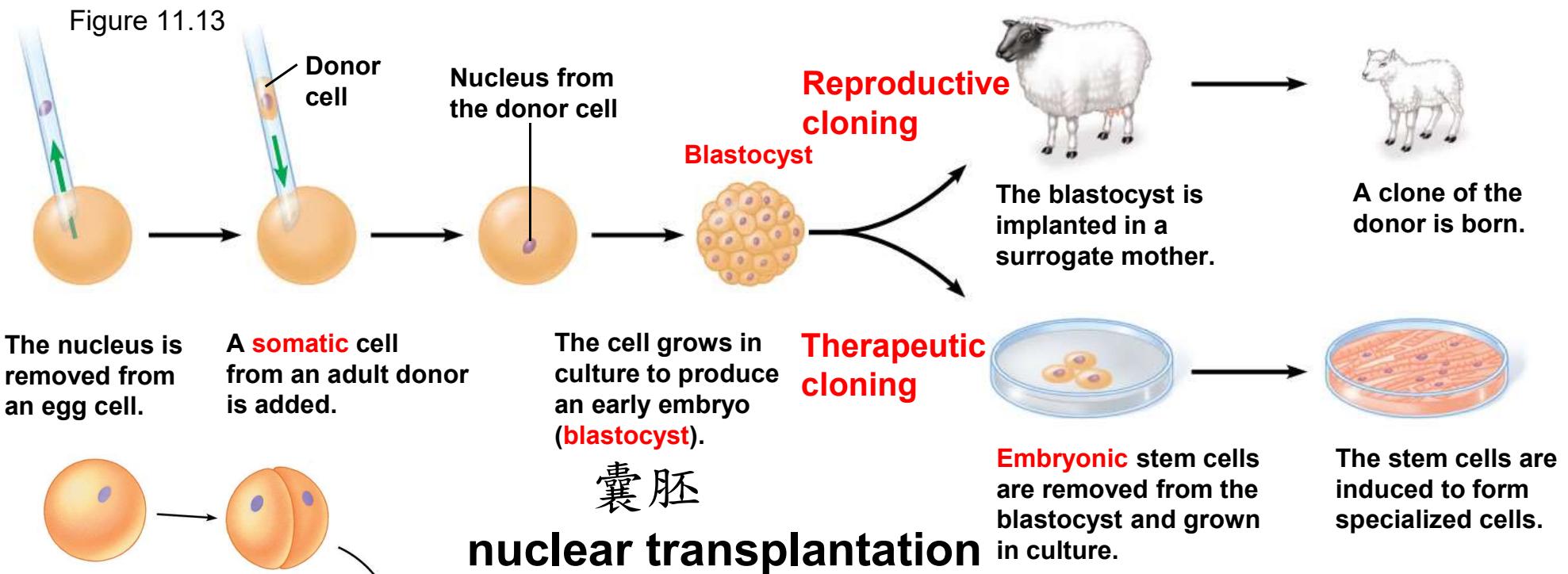
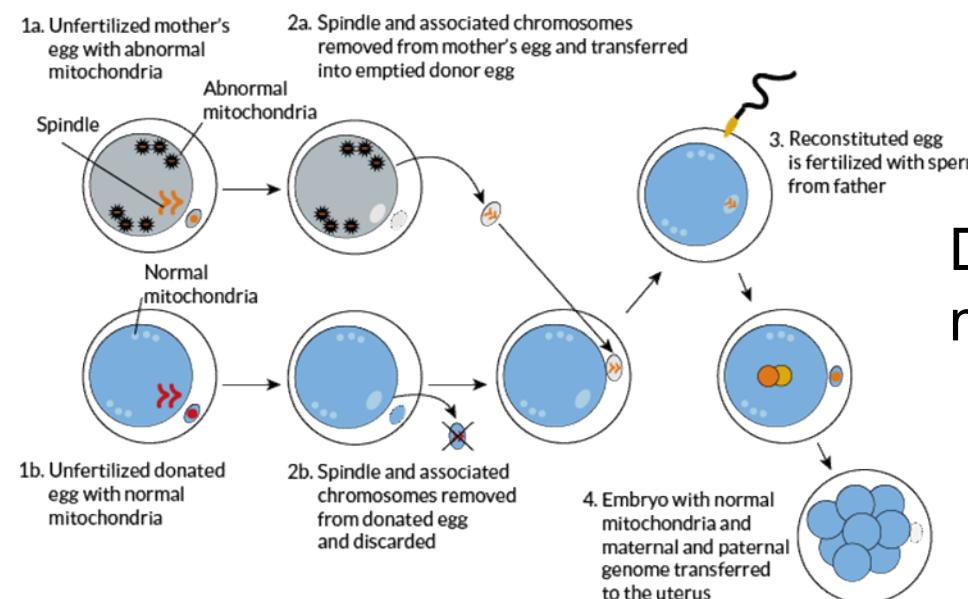


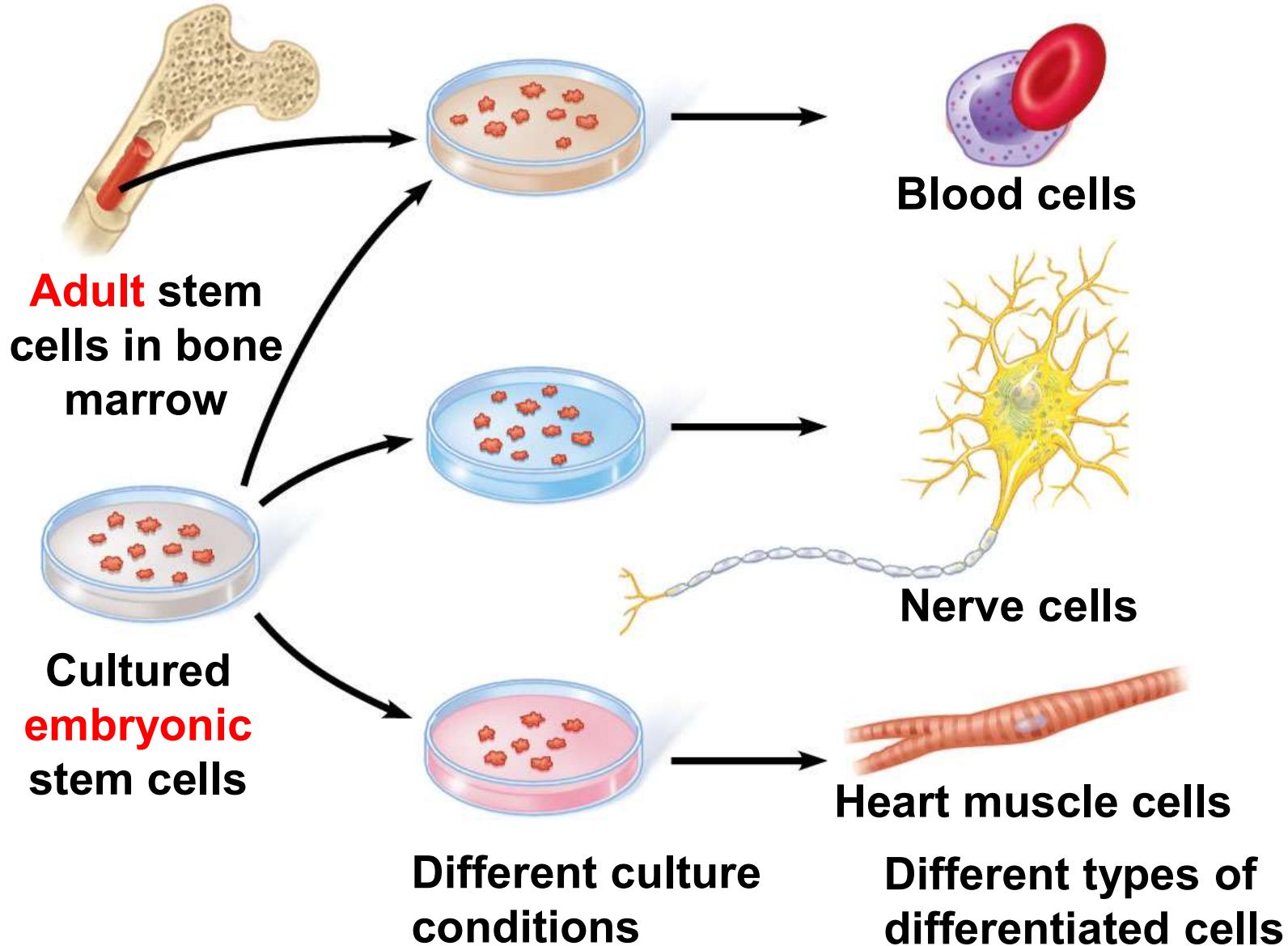
Figure 27.10\_s3



## 11.14 Therapeutic cloning can produce stem cells with great medical potential

- A blastocyst can provide **embryonic stem cells (ES cells)**, which can
  - differentiate in an embryo to give rise to **all the specialized cell types** of the body or
  - divide **indefinitely** when grown in laboratory culture.
- When the goal is to produce embryonic stem cells to use in therapeutic treatments, this process is called **therapeutic cloning**.

Figure 11.15



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## 11.14 Therapeutic cloning can produce stem cells with great medical potential

- Reproductive cloning is used to produce animals with **desirable traits** to
  - produce better agricultural products,
  - produce therapeutic agents, and
  - restock populations of endangered animals.
- Human reproductive cloning raises many **ethical** concerns.



- When grown in laboratory culture, stem cells can
  - divide indefinitely and
  - give rise to many types of differentiated cells.
- The adult body also has stem cells, which serve to replace nonreproducing specialized cells as needed.
- Because **adult stem cells** are farther along the road to differentiation than ES cells, they can give rise to only **a few related types** of cells.
- **Embryonic** stem cells are considered more **promising** than adult stem cells for medical applications.
- The **ultimate aim** of therapeutic cloning is to supply cells for the repair of damaged or diseased organs.

BUT!

TABLE 1: The effects of neurorehabilitation in stem cell transplantation (SCT).

Study	Neurological condition	Methods of SCT	Organism (N)	Results
[42]	chronic ischemic stroke	bone marrow-derived mononuclear stem cells (BM-MNC)	human (N=20)	Neurorehabilitation regime and SCT could increase the release of growth factors: vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) in the microenvironment.
[43]	left thalamic haemorrhagic stroke	autologous bone marrow stem cells	human (case study)	Exercise enhanced the effect of stem cells by helping the mobilization of local stem cells and encouraging angiogenesis. Hence, the concept of neuroregenerative rehabilitation therapy (NRRT) endeavours to combine the impact of neuroregeneration and rehabilitation for a better therapy outcome.
[44]	progressive muscular dystrophy	bone marrow and umbilical cord blood mesenchymal stem cells	human (N=82)	The combination of various therapies: cellular therapies (stem cells) and exercise (neurorehabilitation and neurofacilitation) together yield better outcome than single strategies employed independently.
[45]	muscular dystrophy, spinal cord injury (SCI), cerebral palsy (CP)	autologous bone marrow stem cells	human (N=71)	Stem cells transplantation (SCT) with individually planned neurorehabilitation gave subjective and functional improvement (in 97% of muscular dystrophy cases, in 85% of CP cases), and improvement with respect to muscle strength, urine control, spasticity (all spinal cord injury cases).
[46]	chronic spinal cord injury	neural stem cells	mice (N=80)	The neural stem cell transplantation combined with treadmill training significantly improved spinal cord pathway conduction and increased central pattern generator activity, resulting in significantly improved motor function.
[47]	spinal cord injury (SCI)	human embryonic stem cells (hESC)	human (paraplegic N=136; tetraplegic N=90)	The physiotherapy aided in training of cells and atrophy of limbs, whereas hESC therapy resulted in an overall improvement of the patients with SCI. The hESC therapy along with physiotherapy which addresses the regeneration that is progressing in the patient could herald a new approach in the treatment of SCI.
[48]	spinal cord injury	neural precursors and mesenchymal stem cells	mice (N=44)	The cotransplantation of neural precursors and mesenchymal stem cells can assure a remarkable anatomical and functional recovery following SCI, and such recovery is only partially boosted by enriched environment/exercise.
[49]	spinal cord injury	natural proliferation and phenotypical changes of ependymal cells	rats (N=51)	Physical activity and increased mobility caused the recruitment of progenitors (an increased number of nestin immunoreactive ependymal cells).
[50]	spinal cord injury	autologous bone marrow stem cells ( $CD45^+/CD34^-$ )	rats (N=55)	The combination of bone marrow stem cell therapy ( $CD45^+/CD34^-$ ) and exercise training (swimming) resulted in significant functional improvement in acute spinal cord injury.
[51]	amyotrophic lateral sclerosis (ALS)	foetal stem cells (FSCs)	human (N=30)	Combined treatment of ALS including the individual program with a complex of kinesitherapy, respiratory gymnastics and administration of FSCs suspensions proved to objectively inhibit a progression of ALS over the period from 6 to 18 months from the beginning of treatment and contributes to longer life expectancy among the patients.
[52]	amyotrophic lateral sclerosis (ALS)	autologous bone marrow mononuclear cell (BM-MNC)	Human (case study)	Cellular transplantation along with intensive rehabilitation resulted in slowing of the disease progression, and improvements in neurological symptoms.

N: number of organisms.

# THE GENETIC BASIS OF CANCER

## 11.15 Cancer results from mutations in genes that control cell division

- Cancer is a set of diseases in which the **control mechanisms** that normally limit cellular growth have malfunctioned.
- Scientists have learned that such malfunction is often due to **changes in gene expression**.
- The genes that a cancer-causing virus inserts into a host cell can make the cell cancerous.
  - Such a gene is called an **oncogene** (from the Greek *onco*, tumor).
  - Over the last century, researchers have identified a number of viruses that harbor cancer-causing genes. 人類乳突病毒
  - One example is the human papillomavirus (HPV), which can be transmitted through sexual contact and is associated with several types of cancer, most frequently cervical cancer.

## 11.15 Cancer results from mutations in genes that control cell division

- Mutations in two types of genes can cause cancer.

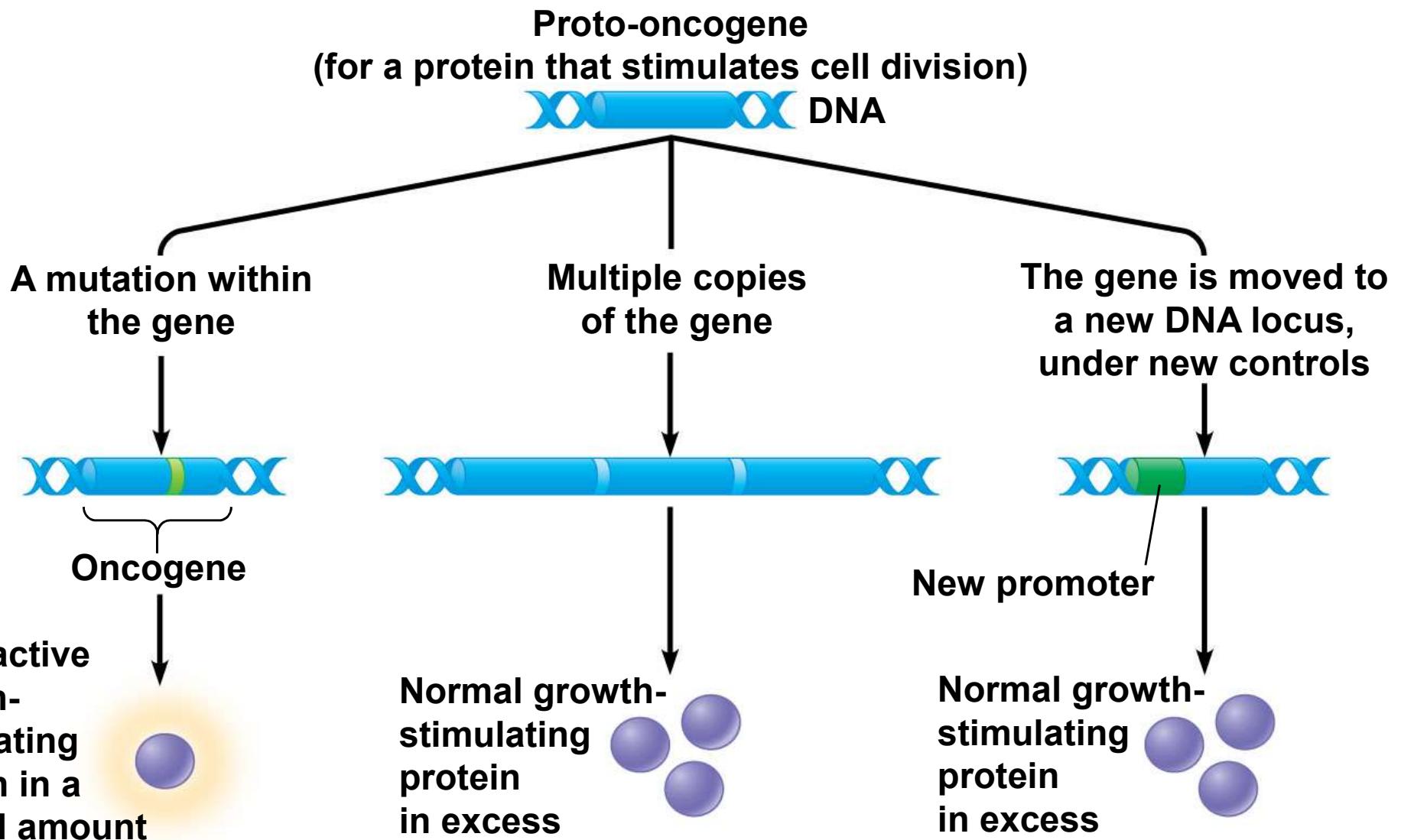
### 1. Oncogenes 致癌基因

- Proto-oncogenes are normal genes that **promote cell division**.
- Mutations to proto-oncogenes create cancer-causing **oncogenes** that often stimulate cell division.

### 2. Tumor-suppressor genes 抑癌基因

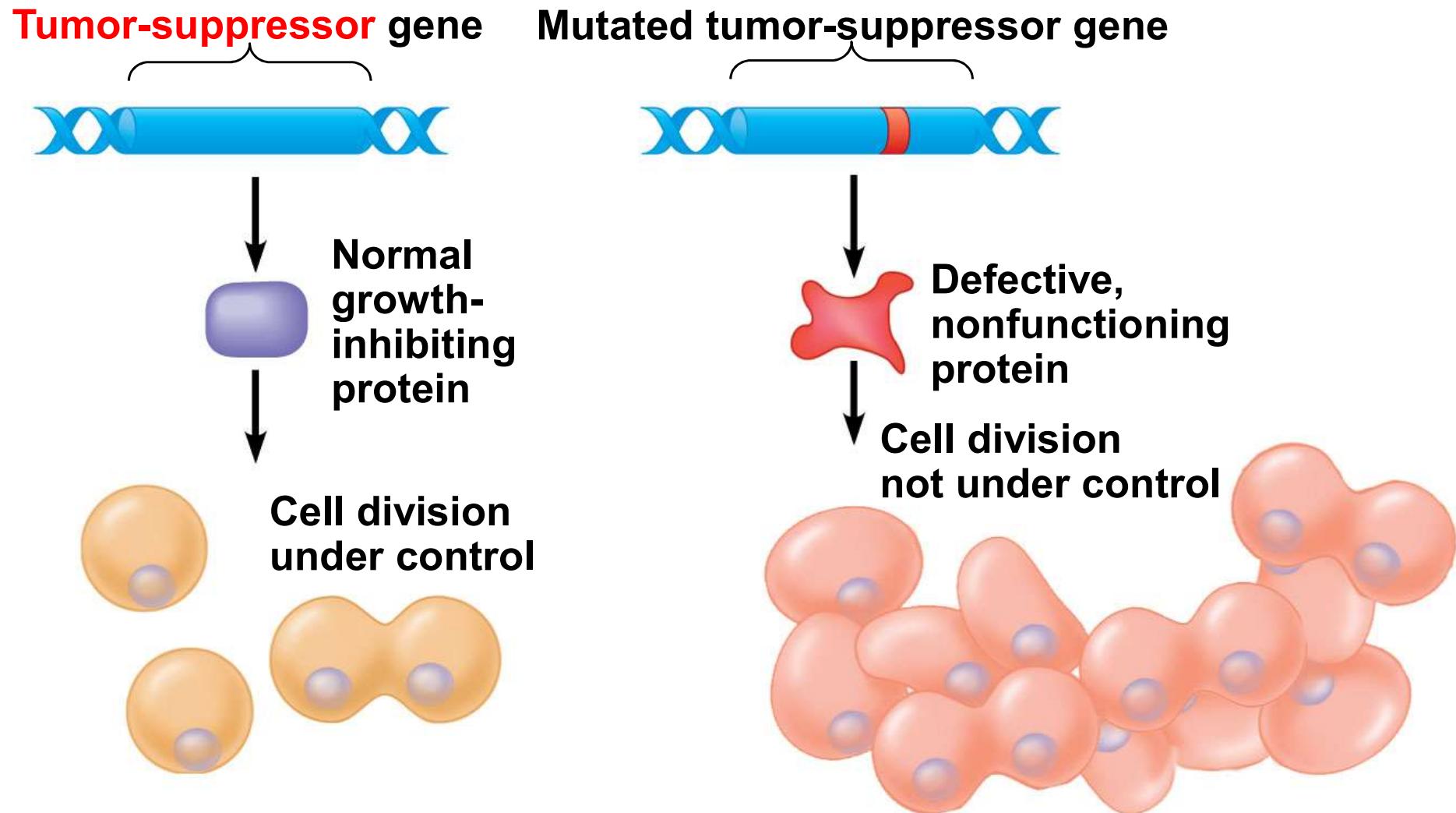
- Tumor-suppressor genes normally **inhibit cell division** or function in the **repair** of DNA damage.
- Mutations inactivate the genes and allow uncontrolled division to occur.

Figure 11.16A



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Figure 11.16B



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## 11.16 Multiple genetic changes underlie the development of cancer

- Usually **four or more somatic mutations** are required to produce a full-fledged cancer cell.
- Colon cancer illustrates the gradual progression from somatic mutation to cancer. 結直腸癌
  1. An oncogene arises or is activated, resulting in increased cell division in apparently normal cells in the colon lining.
  2. Additional DNA mutations cause the growth of a small benign tumor (polyp) in the colon wall.
  3. Additional mutations lead to a malignant tumor with the potential to **metastasize**.

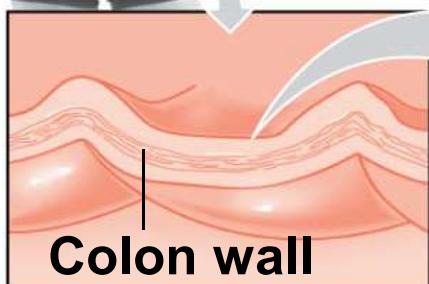
Figure 11.17A



DNA changes: An oncogene is activated A tumor-suppressor gene is inactivated A second tumor-suppressor gene is inactivated

Cellular changes: Increased cell division

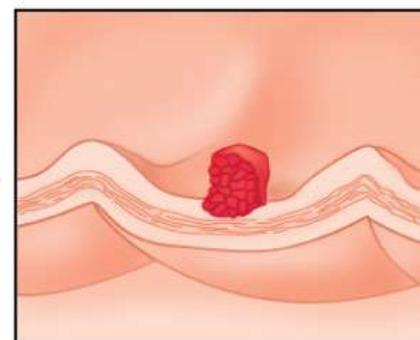
①



Colon wall

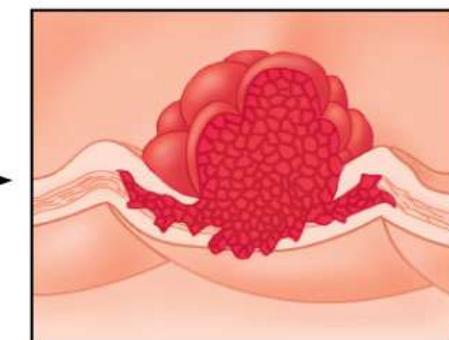
Growth of a polyp

②



Growth of a malignant tumor

③

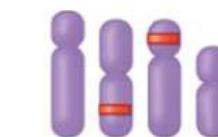


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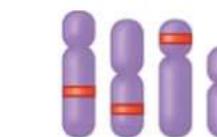
大腸鏡  
息肉



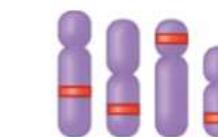
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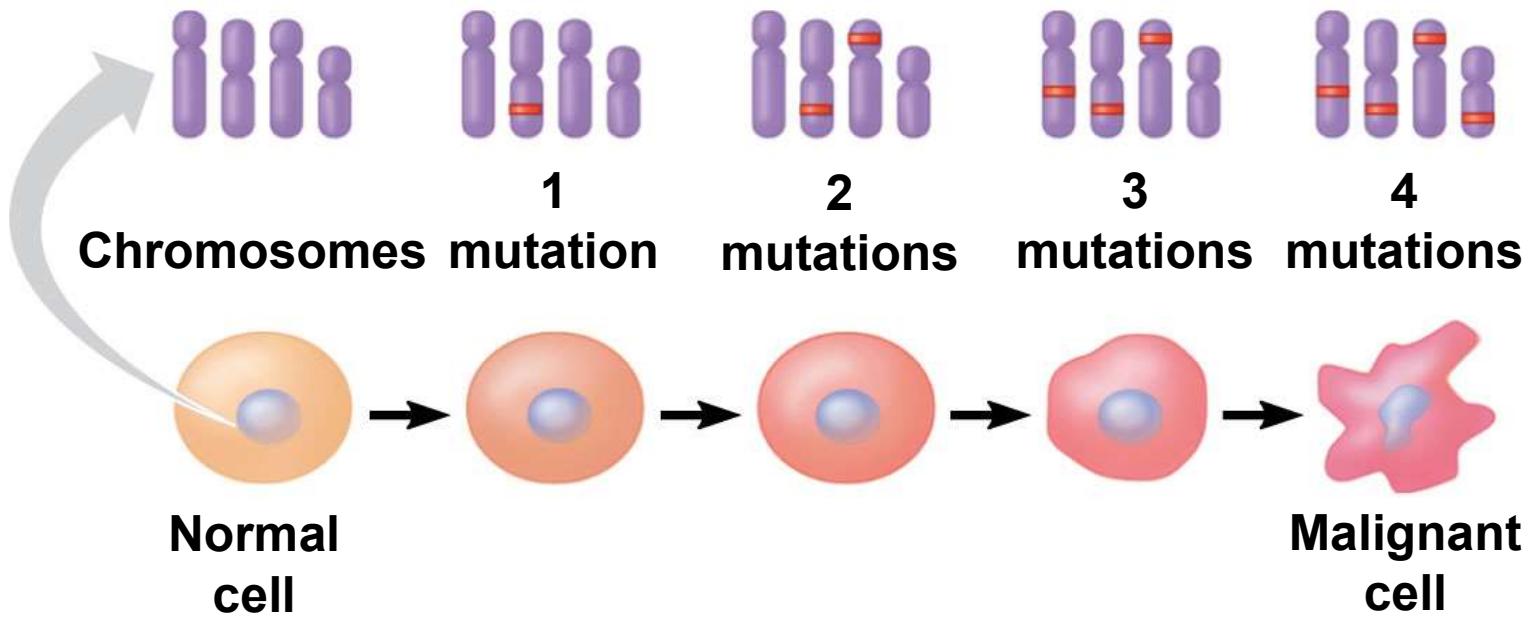
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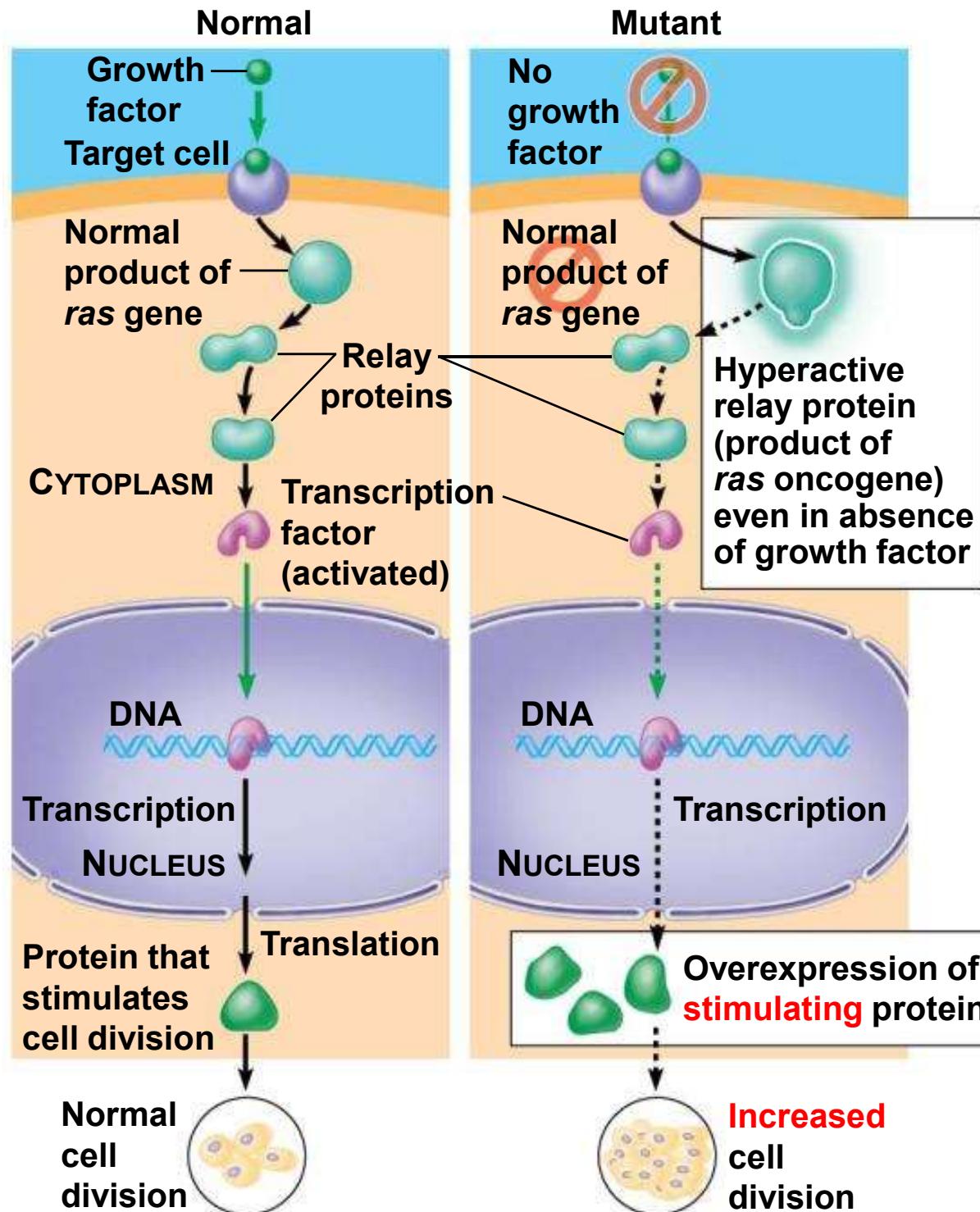
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## 11.17 Faulty proteins can interfere with normal signal transduction pathways

- Proto-oncogenes and tumor-suppressor genes often code for proteins involved in **signal transduction** pathways leading to gene expression.
- **Two main types** of signal transduction pathways lead to the synthesis of proteins that influence cell division:
  1. One pathway produces a product that ***stimulates*** cell division.
  2. A second pathway produces a product that ***inhibits*** cell division.

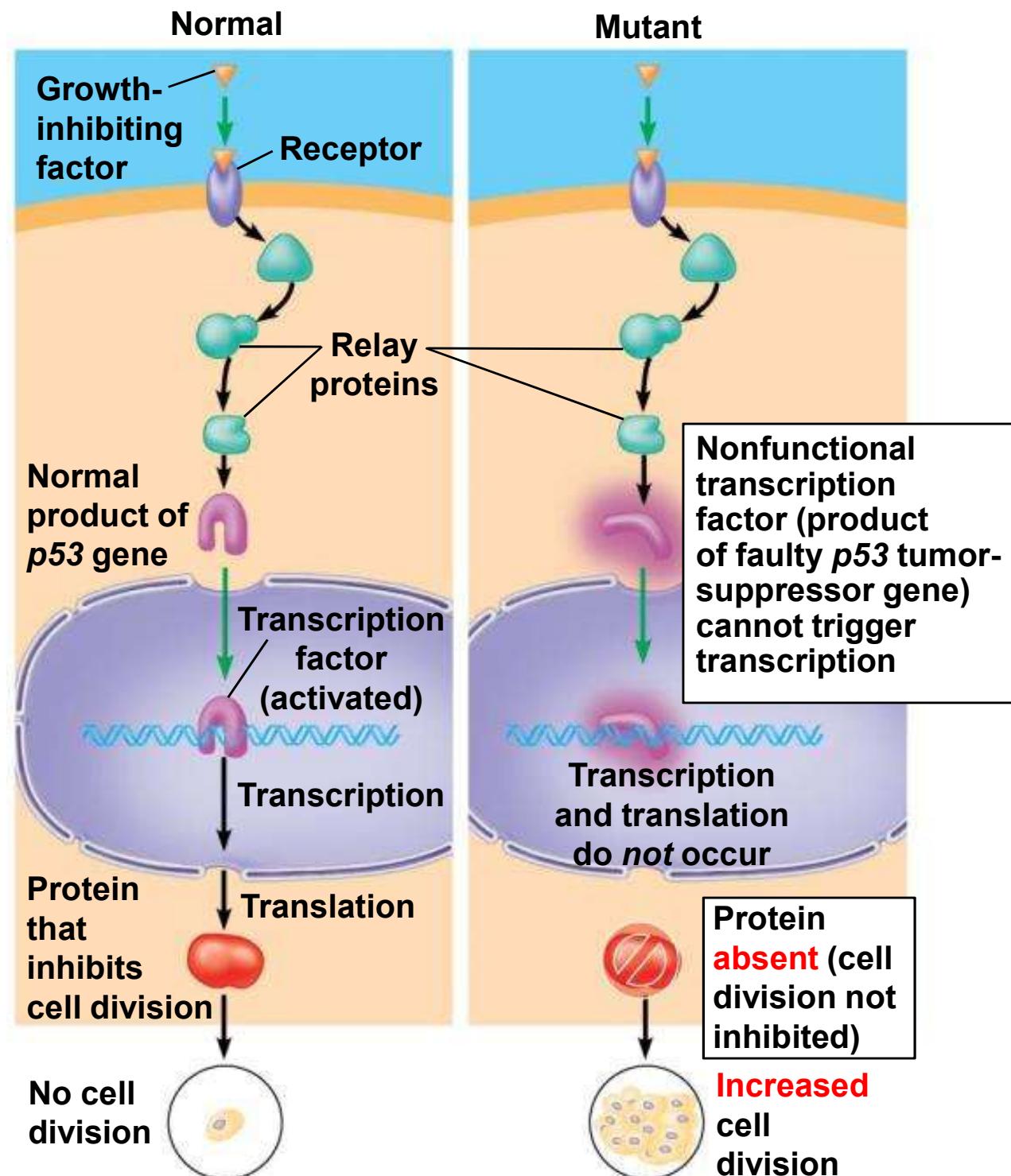
## 11.17 Faulty proteins can interfere with normal signal transduction pathways

1. One pathway produces a product that *stimulates* cell division.
  - In a healthy cell, the product of the *ras* proto-oncogene relays a signal when growth factor binds to a receptor.
  - But in a cancerous condition, the product of the *ras* proto-oncogene relays the signal **in the absence of a growth factor**, leading to uncontrolled growth.
  - Mutations in *ras* occur in more than 30% of human cancers.



## 11.17 Faulty proteins can interfere with normal signal transduction pathways

2. A second pathway produces a product that *inhibits* cell division.
  - The normal product of the *p53* gene is a **transcription factor** that normally activates genes for factors that inhibit cell division.
  - In the absence of functional *p53*, cell division continues because the inhibitory protein is not produced.
  - Mutations in *p53* occur in more than 50% of human cancers.



# 11.18 Lifestyle choices can reduce the risk of cancer

- After heart disease, cancer is the second-leading cause of death in most industrialized nations. But First in Taiwan!!!
- Cancer can run in **families** if an individual inherits an oncogene or a mutant allele of a tumor-suppressor gene that makes cancer one step closer.
- But most cancers cannot be associated with an inherited mutation.

華人健康網

106年國人十大死因VS十大癌症

NO	十大死因	十大癌症
1	惡性腫瘤(癌症) 203.9	氣管、支氣管與肺癌
2	心臟疾病 87.6	肝和肝內膽管癌
3	肺炎 53.0	結腸、直腸和肛門癌
4	腦血管疾病 49.9	女性乳癌
5	糖尿病 41.8	口腔癌
6	事故傷害	前列腺(攝護腺)癌
7	慢性下呼吸道疾病	胃癌
8	高血壓性疾病	胰臟癌
9	腎炎、腎病症候群及腎病變	食道癌
10	慢性肝炎及肝硬化	子宮頸及部位未明子宮癌

資料來源：衛生福利部統計處；製表：洪毓琪

數字：每10萬人口

歷年來台灣地區十大死因一覽表  
腸胃炎-->肺結核-->癌症

	民國41年	民國51年	民國61年	民國71年	民國81年	民國87-96年
1	胃腸炎	肺炎	腦血管疾病	惡性腫瘤	惡性腫瘤	惡性腫瘤
2	肺炎	中樞神經系之血管病變	惡性腫瘤	腦血管疾病	腦血管疾病	腦血管疾病
3	結核病	胃腸炎	傷害事故	意外傷害	意外事故及不良影響	心臟疾病
4	心臟疾病	心臟疾病	心臟疾病	心臟疾病	心臟疾病	事故意外
5	中樞神經系之血管病變	惡性腫瘤	結核病	高血壓性疾病	糖尿病	糖尿病
6	周產期之死因	周產期之死因	肺炎	慢性肝病及肝硬化	慢性肝病及肝硬化	慢性肝病及肝硬化
7	腎炎及腎水腫	結核病	支氣管炎、肺氣腫	支氣管炎、肺氣腫及氣喘	肺炎	肺炎
8	惡性腫瘤	意外傷害	肝硬化	結核病	腎炎、腎臟候群及腎變性病	腎炎、腎臟候群及腎變性病
9	支氣管炎	自殺	高血壓性疾病	肺炎	高血壓性疾病	高血壓性疾病
10	瘧疾	腎炎及腎水腫	腎炎及腎水腫	自殺	支氣管炎、肺氣腫及氣喘	自殺

## 11.18 Lifestyle choices can reduce the risk of cancer

- **Carcinogens** are **cancer-causing agents** that alter DNA.
- Most **mutagens** (substances that **promote mutations**) are carcinogens.
- Two of the most potent carcinogens (mutagens) are
  - X-rays and ultraviolet (UV) radiation in sunlight.
- The one substance known to cause more cases and types of cancer than any other single agent is tobacco.
  - More people die of lung cancer than any other form of cancer.
  - Although most tobacco-related cancers come from smoking, passive inhalation of second-hand smoke is also a risk.
  - Tobacco use, sometimes in combination with alcohol consumption, causes cancers in addition to lung cancer.

# 11.18 Lifestyle choices can reduce the risk of cancer

- Healthy lifestyles that reduce the risks of cancer include
  - avoiding carcinogens, including the sun and tobacco products,
  - exercising adequately,
  - regular medical checks for common types of cancer, and
  - a healthy high-fiber, low-fat diet including plenty of fruits and vegetables.

研究：大多數癌症的發生是因為「運氣不好」？

[http://www.bbc.com/zhongwen/trad/science/2015/01/150102\\_cancer\\_bad\\_luck](http://www.bbc.com/zhongwen/trad/science/2015/01/150102_cancer_bad_luck)

根據研究人員的分析，三分之二癌症的發生是由基因突變引起的，而不是因為生活方式。但一些比較常見的癌症。例如肺癌等確實還是主要受到生活方式的影響。

TABLE 11.18 | CANCER IN THE UNITED STATES

Cancer	Risk Factors	New Cases 2013 (est.)
Prostate	African heritage; possibly dietary fat	239,000
Breast	Estrogen	235,000
Lung	Tobacco smoke	228,000
Colon, rectum	High dietary fat; tobacco smoke; alcohol	143,000
Lymphomas	Viruses (for some types)	79,000
Melanoma of the skin	Ultraviolet light	77,000
Urinary bladder	Tobacco smoke	73,000
Kidney	Tobacco smoke	65,000
Uterus	Estrogen	62,000
Leukemias	X-rays; benzene; virus (for one type)	49,000
Pancreas	Tobacco smoke; obesity	45,000
Oral cavity	Tobacco in various forms; alcohol	41,000
Liver	Alcohol; hepatitis viruses	31,000
Brain and nerve	Trauma; X-rays	23,000
Ovary	Obesity; many ovulation cycles	22,000
Stomach	Table salt; tobacco smoke	22,000
Cervix	Sexually transmitted viruses; tobacco smoke	12,000
Total, including all other types		1,660,000

# 106年兩性十大癌症死因

氣管、支氣管和肺癌 第1名 氣管、支氣管和肺癌

肝和肝內膽管癌 第2名 肝和肝內膽管癌

結腸、直腸和肛門癌 第3名 結腸、直腸和肛門癌

女性乳癌 第4名 口腔癌

胰臟癌 第5名 食道癌

胃癌 第6名 胃癌

子宮頸及部位未明示子宮癌 第7名 前列腺（攝護腺）癌

卵巢癌 第8名 胰臟癌

非何杰金氏淋巴瘤 第9名 非何杰金氏淋巴瘤

白血病 第10名 膀胱癌

更多資訊請上 健談 havemary.com

## You should now be able to

1. Describe and compare the regulatory mechanisms of the *lac* operon, *trp* operon, and operons using activators.
2. Explain how selective gene expression yields a variety of cell types in multicellular eukaryotes.
3. Explain how DNA is packaged into chromosomes.
4. Explain how a cat's tortoiseshell coat pattern is formed and why this pattern is only seen in female cats.
5. Explain how eukaryotic gene expression is controlled.
6. Describe the process and significance of alternative DNA splicing.
7. Describe the significance of miRNA molecules.
8. Explain how mRNA breakdown, initiation of translation, protein activation, and protein breakdown regulate gene expression.
9. Describe the roles of homeotic genes in development.

10. Explain how DNA microarrays can be used to study gene activity and treat disease.
11. Explain how a signal transduction pathway triggers a specific response inside a target cell.
12. Compare the cell-signaling systems of yeast and animal cells.
13. Explain how nuclear transplantation can be used to clone animals.
14. Describe some of the practical applications of reproductive cloning and the process and goals of therapeutic cloning.
15. Explain how viruses, proto-oncogenes, and tumor-suppressor genes can each contribute to cancer.
16. Explain why the development of most cancers is a slow and gradual process.
17. Explain how mutations in ras or p53 proteins can lead to cancer.
18. Describe factors that can increase or decrease the risks of developing cancer.