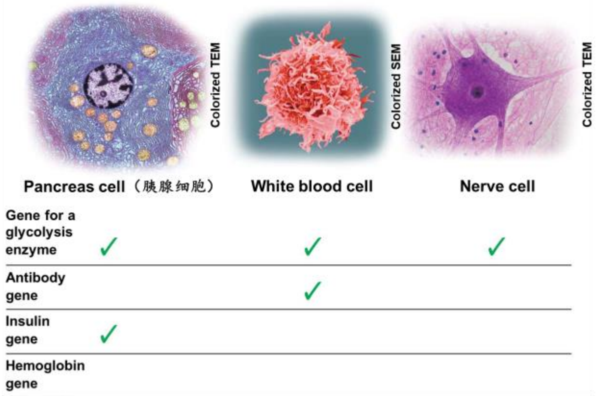
Chapter 11 How Genes Are Controlled

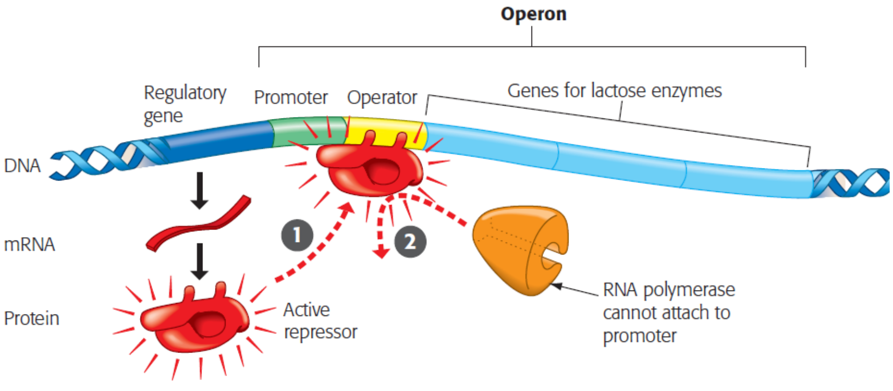
1. How and Why Genes Are Regulated

- **Gene Regulation**: mechanisms that turn on certain genes while other genes remain turned off.
- The overall process by which genetic information flows from genes to proteins is called **gene expression**.



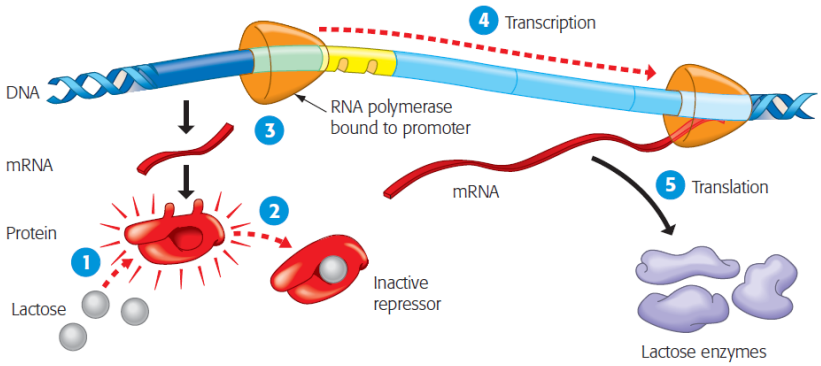
	Pancreas cell（胰腺细胞）	White blood cell	Nerve cell
Gene for a glycolysis enzyme	✓	✓	✓
Antibody gene		✓	
Insulin gene	✓		
Hemoglobin gene			

- **Gene Regulation in Bacteria**
  - a cluster of related genes and sequences that control them is called an **operon**（操纵子）
  - *lac* **operon**（乳糖操纵子）
  - **Promoter**（启动子）, is the site where the enzyme **RNA polymerase** attaches and initiates transcription.
  - **Operator**（操纵基因）acts as a switch that is turned on or off, depending on whether a specific protein is bound there.
  - ***lac* operon in “off” mode (no lactose available)**
    - a protein called a repressor () binds to the operator () and
    - physically blocks the attachment of RNA polymerase () to the promoter ().



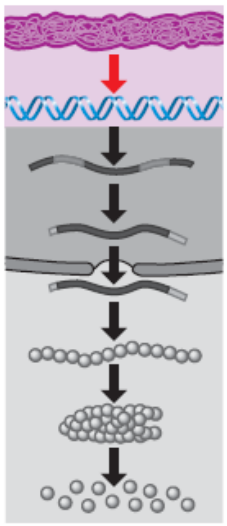
Operon turned off (lactose absent)

  - ***lac* operon in “on” mode (lactose available)**
    - The lactose () interferes with attachment of the lac repressor to the operator by binding to the repressor and
    - Changing the repressor’s shape. In its new shape (), the repressor cannot bind to the operator, and the operator switch remains on.
    - RNA polymerase is no longer blocked, so it can now bind to the promoter and from there
    - transcribe the genes for the lactose enzymes into mRNA.
    - Translation produces all three lactose enzymes (purple).



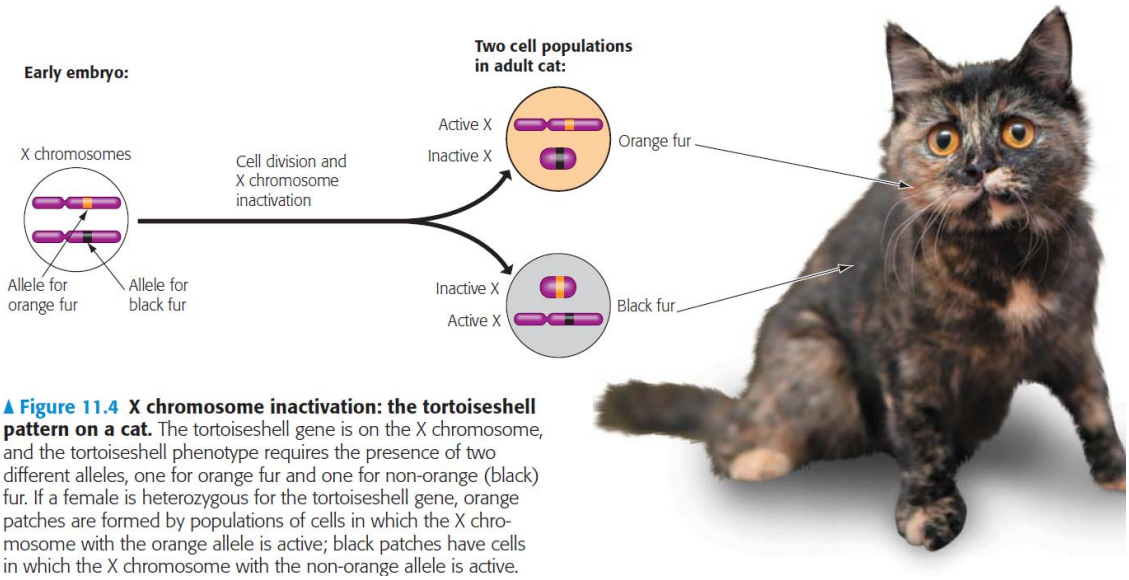
Operon turned on (lactose inactivates repressor)

- **Gene Regulation in Eukaryotic Cells**
  - **The Regulation of DNA Packing**



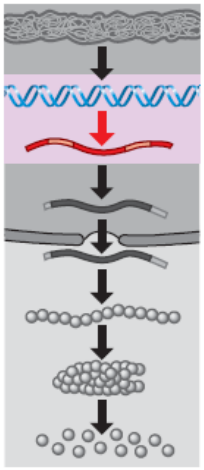
Cells may use DNA packing for long-term inactivation of genes: DNA packing tends to prevent gene expression by preventing RNA polymerase and other transcription proteins from binding to the RNA.

- X chromosome inactivation occurs in **female mammals**, takes place early in **embryonic**（胚胎的）development, and is when one of the two **X chromosomes** in each cell is inactivated at random.
- After one X chromosome is inactivated in each embryonic cell, all of that cell's descendants（后代）will have the same X chromosome turned off. If a female has different versions of a gene on each of her X chromosomes, about half of her cells will express one version, while the other half will express the alternate version.



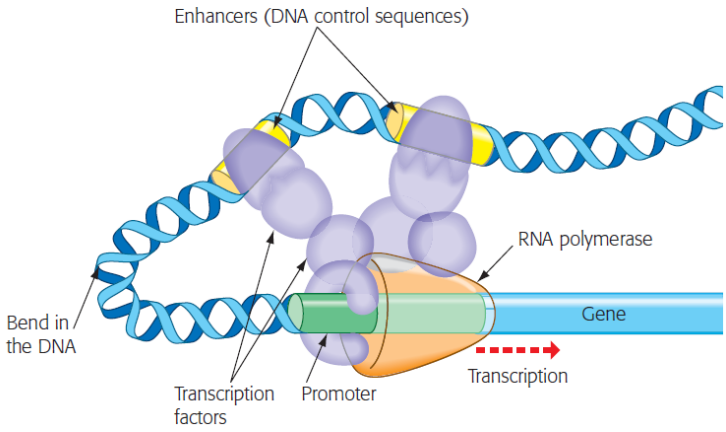
▲ **Figure 11.4 X chromosome inactivation: the tortoiseshell pattern on a cat.** The tortoiseshell gene is on the X chromosome, and the tortoiseshell phenotype requires the presence of two different alleles, one for orange fur and one for non-orange (black) fur. If a female is heterozygous for the tortoiseshell gene, orange patches are formed by populations of cells in which the X chromosome with the orange allele is active; black patches have cells in which the X chromosome with the non-orange allele is active.

■ The Initiation of Transcription

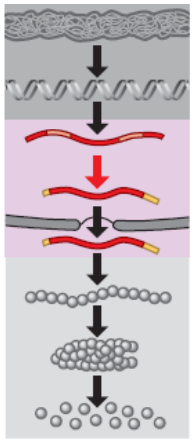


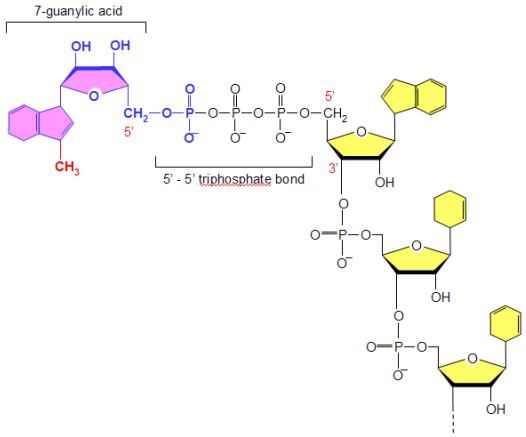
- **Transcription factors**（转录因子）, acting in concert to bind to DNA sequences called **enhancers**（增强子）and to the **promoter**.
- **Repressor proteins** which may bind to DNA sequences called **silencers**, inhibit the start of transcription
- **Activators**: proteins that turn genes on by binding to DNA
- **The "default" state** for most genes in multicellular eukaryotes seems to be off, with the exception of "housekeeping" genes for routine activities such as the digestion of glucose.

▼ Figure 11.5 A model for turning on a eukaryotic gene.
A large assembly of transcription factors (proteins shown in purple) and several control sequences in the DNA are involved in initiating the transcription of a eukaryotic gene.



■ RNA Processing and Breakdown



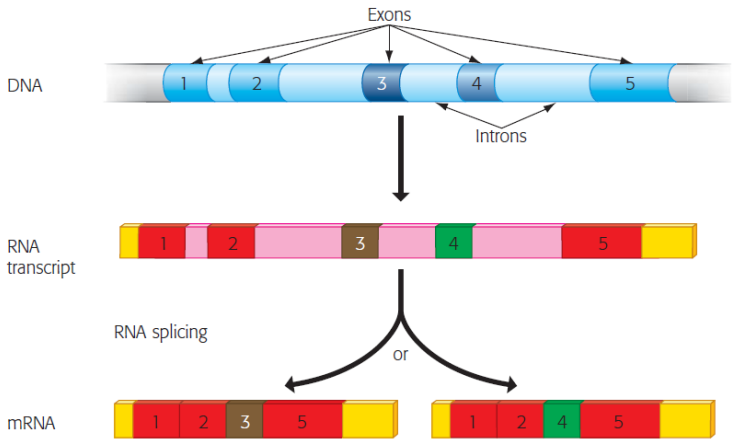


Addition of a cap

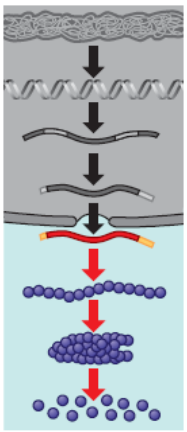
- RNA Processing: addition of a cap and tail (poly A); removal of any introns, and splicing together of the remaining exons

- **Alternative RNA splicing: (mRNA is spliced into many different ways and thus will different timing for breaking down)**

Figure 11.6 Alternative RNA splicing: producing multiple mRNAs from the same gene. Two different cells can use the same DNA gene to synthesize different mRNAs and proteins. In this example, one mRNA has ended up with exon 3 (brown) and the other with exon 4 (green). These mRNAs, which are just two of many possible outcomes, can then be translated into different proteins.



- Small single-stranded RNA molecules, called **microRNAs** (miRNAs), can bind to complementary sequences on mRNA molecules in the cytoplasm and trigger **breakdown of their target mRNA or block translation**
- **The Initiation of Translation**

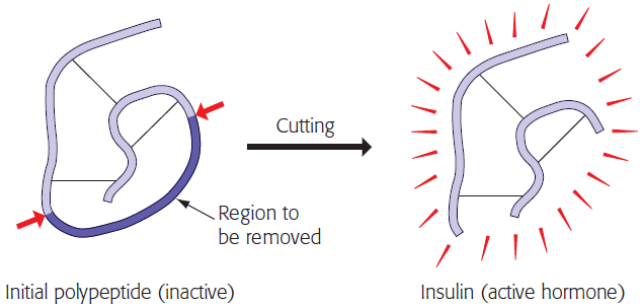


- The process of translation—in which an mRNA is used to make a protein—offers additional opportunities for control by regulatory molecules.

- **Protein Activation and Breakdown**

The cell may activate the finished protein in various ways (for instance, by cutting out portions or chemical modification). Eventually, the protein may be selectively broken down.

Figure 11.7 The formation of an active insulin molecule. Only in its final form, with a central region removed, does insulin act as a hormone.



- **Cell Signaling**
  - **Signal transduction pathway**: a series of molecular changes that converts a signal received outside a cell to a specific response inside the target cell.
  - **Cell-signaling pathway**
    - First, the signaling cell secretes the **signal molecule** ( ).
    - This molecule binds to a specific **receptor protein** ( ) embedded in the target cell's plasma membrane.
    - The binding activates a signal transduction pathway consisting of a series of **relay proteins** (green) within the target cell. Each relay molecule activates the next.
    - The last relay molecule in the series activates a **transcription factor** ( ) that
    - triggers the **transcription** of a specific gene.
    - Translation of the mRNA produces a protein that can then perform the function originally called for by the signal.

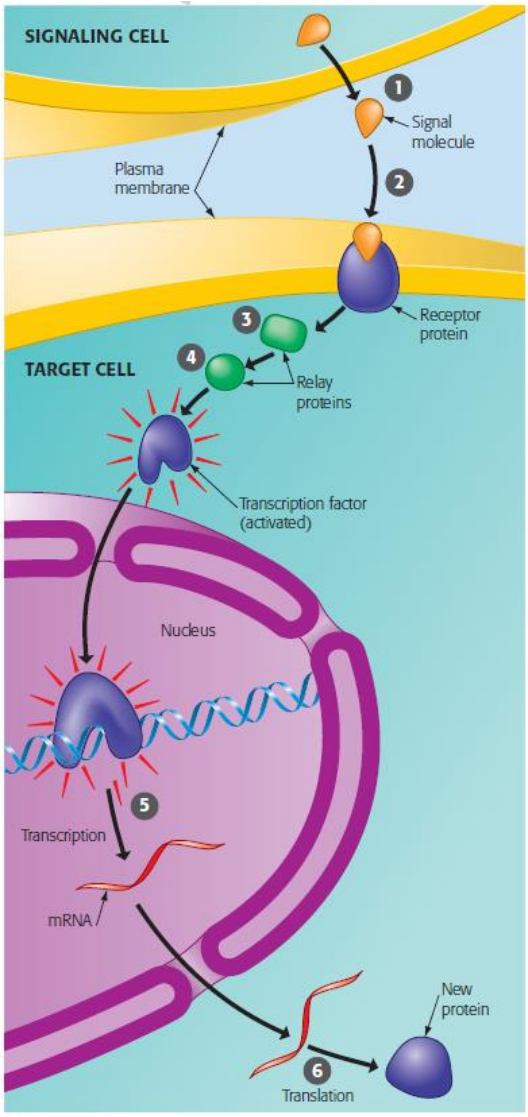
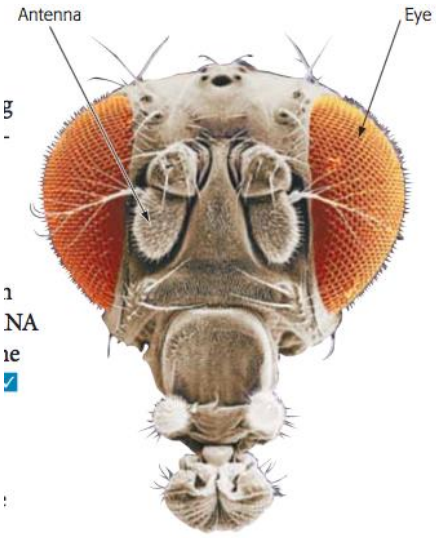
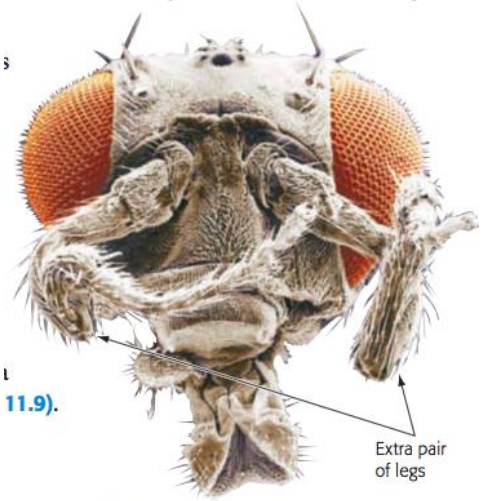


Figure 11.8 A cell-signaling pathway that turns on a gene. The coordination of cellular activities in a multicellular organism depends on cell-to-cell signaling that helps regulate genes.

- **Homeotic Genes**
  - Master control genes called **homeotic genes** regulate groups of other genes that determine what body parts will develop in which locations (e.g. fruit flies)
  - **Homeotic genes** arose very early in the history of life and that the genes have remained remarkably **unchanged** over eons of animal **evolution**

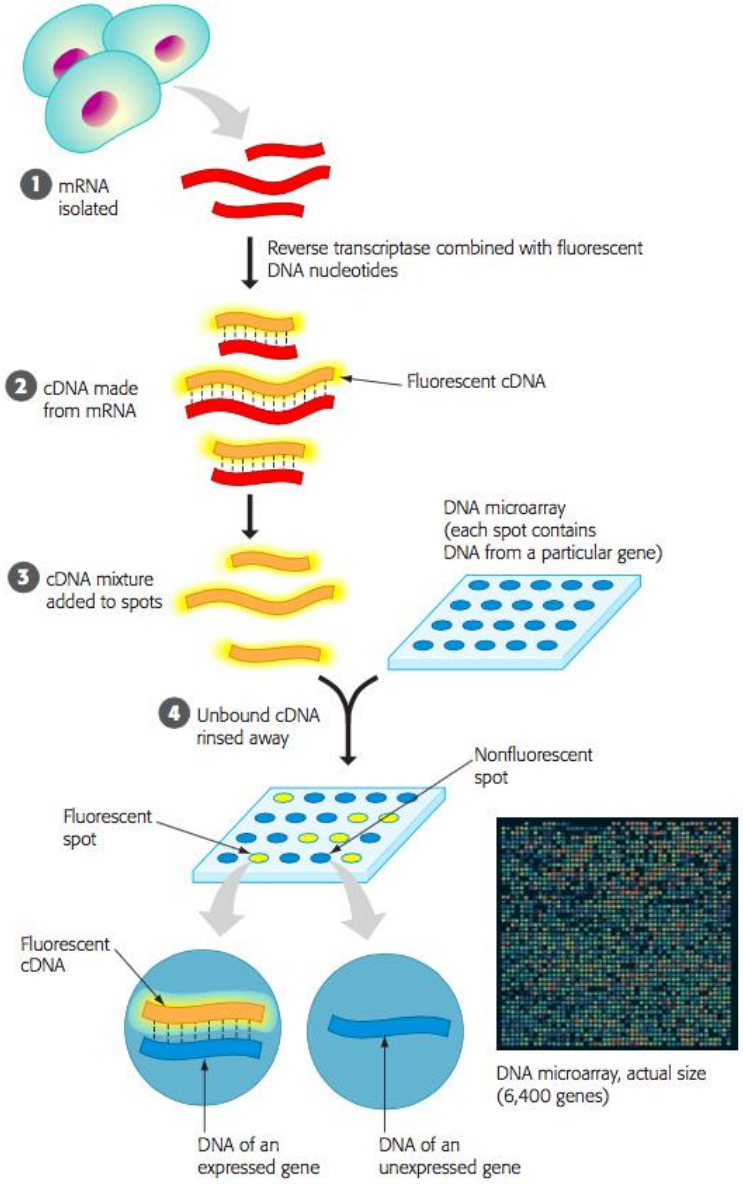


Normal head due to presence of normal homeotic gene



Head with extra legs growing due to presence of mutant homeotic gene

- **DNA Microarrays: Visualizing Gene Expression**
  - A **DNA microarray** is a slide with thousands of different kinds of single-stranded DNA fragments attached in a tightly spaced array (grid).
  - **How microarrays are used**
    - Collects all of the mRNA of cell, mixed with reverse transcriptase, a viral enzyme that
    - produces complementary DNA (cDNA) to each mRNA sequence using nucleotides that have been modified to fluoresce (glow). The fluorescent cDNA collection thus represents all of the genes being actively transcribed in the cell.
    - A small amount of the fluorescently labeled cDNA mixture is added to the DNA fragments of the microarray. The cDNA molecule binds to its complementary DNA fragments at a particular location on the grid, becoming fixed there.
    - After unbound cDNA is rinsed away, the remaining cDNA glows in the microarray.

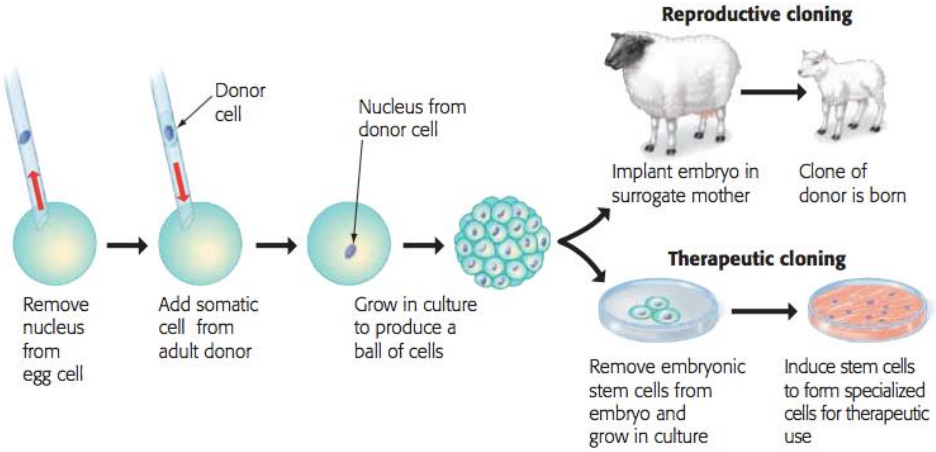


▲ **Figure 11.10 Visualizing gene expression using a DNA microarray.**

2. Cloning Plants and Animals

Gene regulation affects two important processes: **cloning** and **cancer**.

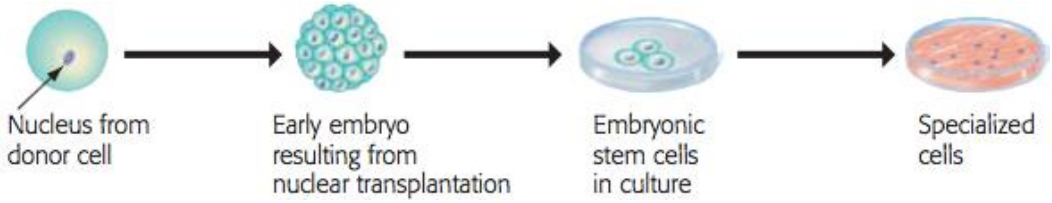
- **The Genetic Potential of Cells**
  - Most differentiated cells retain a complete set of genes, so an orchid plant, for example, can be made to grow from a single orchid cell.
  - **Regeneration**, the regrowth of lost body parts
- **Reproductive Cloning of Animals**
  - **Nuclear transplantation** is a procedure whereby a donor cell nucleus is inserted into an egg from which the nucleus has been removed. Embryonic, umbilical cord (脐带), and adult stem cells all show promise for therapeutic uses.
  - Implant the new embryo into uterus（子宫）of a **surrogate mother**（代孕母亲）



▲ **Figure 11.12 Cloning by nuclear transplantation.** In nuclear transplantation, a nucleus from an adult body cell is injected into a nucleus-free egg cell. The resulting embryo may then be used to produce a new organism (reproductive cloning, shown in the upper branch) or to provide stem cells (therapeutic cloning, lower branch).

- **Therapeutic Cloning and Stem Cells**

  - The purpose of **therapeutic cloning** is to produce embryonic stem cells for medical uses.
  - In mammals, **embryonic stem cells** (ES cells) （胚胎干细胞）are obtained by removing cells from an early embryo and growing them in laboratory culture.

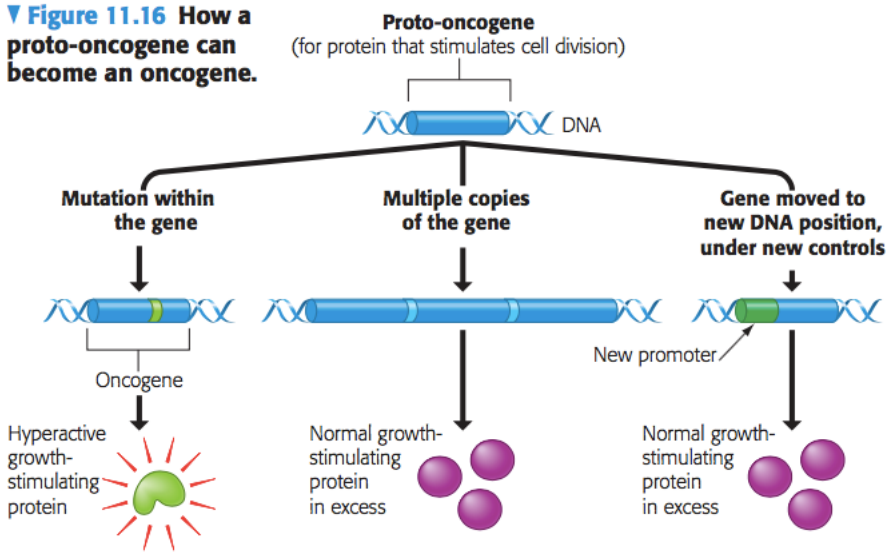


3. The Genetic Basis of Cancer

- **Genes That Cause Cancer**

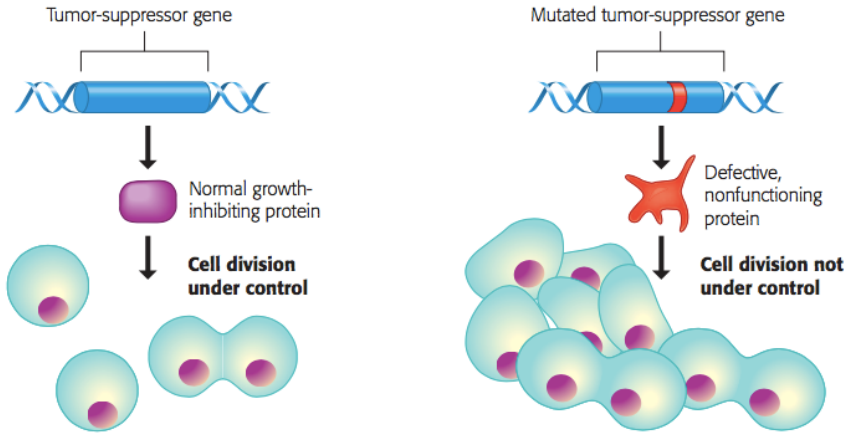
  - A gene that causes cancer is called an **oncogene**（致癌基因）.
  - A normal gene with the potential to become an oncogene is called a **proto-oncogene**（原癌基因）.
  - A cell can acquire an oncogene from a **virus** or the **mutation** of one of its own proto-oncogenes.
  - **Growth factors**: proteins that stimulate cell division, or for other proteins that affect the cell cycle

▼ **Figure 11.16 How a proto-oncogene can become an oncogene.**



- **Tumor-suppressor genes**: Changes in genes whose products inhibit cell division are also involved in cancer.

Figure 11.17 Tumor-suppressor genes.



(a) Normal cell growth. A tumor-suppressor gene normally codes for a protein that inhibits cell growth and division. Such genes help prevent cancerous tumors from arising or spreading.

(b) Uncontrolled cell growth (cancer). When a mutation in a tumor-suppressor gene makes its protein defective, cells that are usually under the control of the normal protein may divide excessively, forming a tumor.

- **The Progression of a Cancer**

  - convert proto-oncogenes（原癌基因） to oncogenes（致癌基因） and
  - knock out tumor-suppressor genes（肿瘤抑制基因）.
  - Cancer results from a series of genetic changes in a cell lineage

- **Cancer Risk and Prevention**

Reducing exposure to carcinogens (which induce cancer-causing mutations) and making other healthful lifestyle choices can help reduce cancer risk.

Chapter 12. DNA Technology

Genetic Engineering

Genetically modified (GM) organisms: Organisms that have acquired one or more genes by artificial means.

Transgenic organism: The recombinant organism that the newly acquired gene is from another organism, typically of another species.

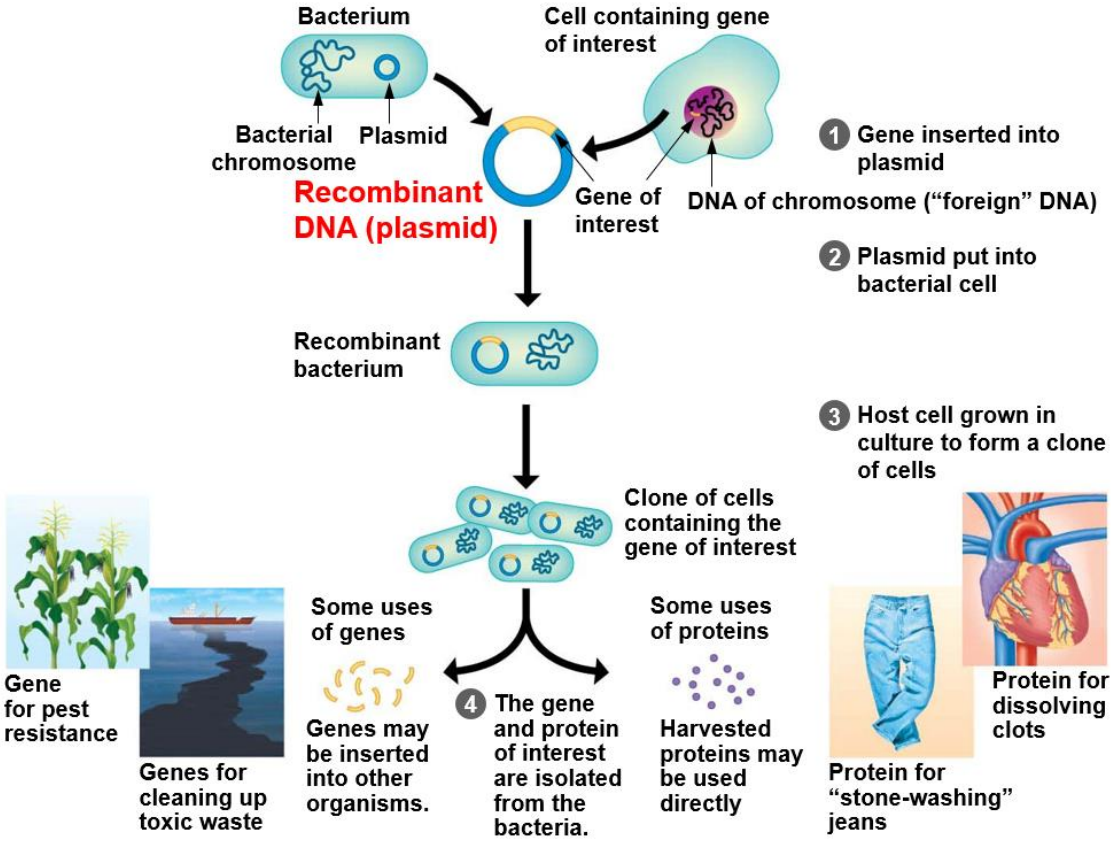
Recombinant DNA: A single DNA molecule formed by combining pieces of DNA from two different sources—often from different species.

■ Recombinant DNA Techniques

Plasmids (质粒): Small, circular DNA molecules that duplicate separately from the larger bacterial chromosome.

Gene cloning: The production of multiple identical copies of a gene-carrying piece of DNA.

- **How to clone a gene:**



✧ **Raw materials: Vector** (gene carrier)—bacterial plasmids;
The gene of interest from another organism

✧ The DNA from the two resources is joined together, resulting in recombinant DNA plasmids;

✧ The recombinant plasmids are then mixed with bacteria. Under the right conditions, the bacteria take up the recombinant plasmids;

✧ Each bacterium, carrying its recombinant plasmid, is allowed to reproduce via cell division to form a clone, a group of identical cells descended from a single original cell. As the bacteria multiply, the foreign gene carried by the recombinant plasmid is also copied.

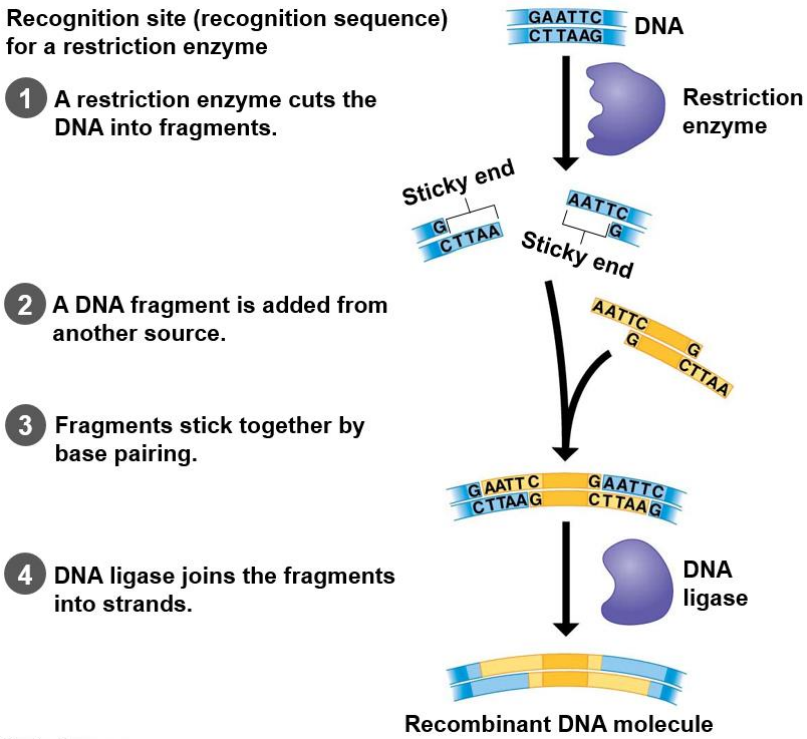
✧ The transgenic bacteria with the gene of interest can then be grown in large tanks, producing the protein in marketable quantities.

- **Cutting and pasting DNA:**

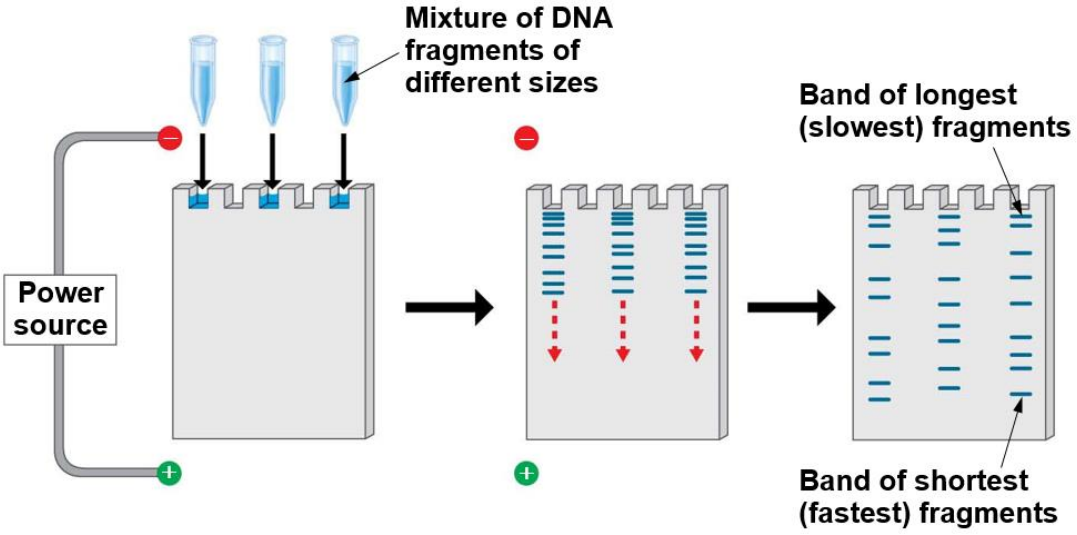
  Restriction enzymes: Bacterial enzymes, the tools used for making recombinant DNA. Each restriction enzymes recognizes a particular short DNA sequence.

  Restriction site: The DNA sequence recognized by a particular restriction enzyme.

  DNA ligase: The "pasting" enzyme, connects the DNA pieces into continuous strands by forming bonds between adjacent nucleotides.

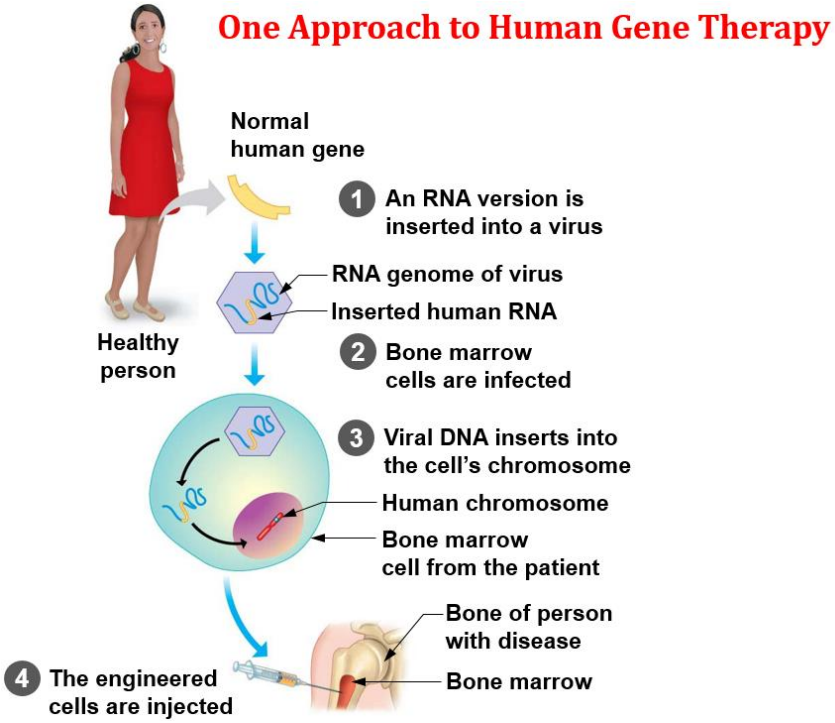


- **Gel electrophoresis:** A method for sorting macromolecules—usually proteins or nucleic acids—primarily by their electrical charge and size. So it can use to separate and visualize DNA fragments of different lengths.
  - ✧ Phosphate (PO_4^-) groups of nucleotides give DNA fragments a negative charge, the fragments move through the gel toward the positive pole.
  - ✧ **Staining (染色):** (1) by exposure onto photographic film if the DNA is radioactively labeled. (2) by measuring fluorescence if the DNA is labeled with a fluorescent dye.



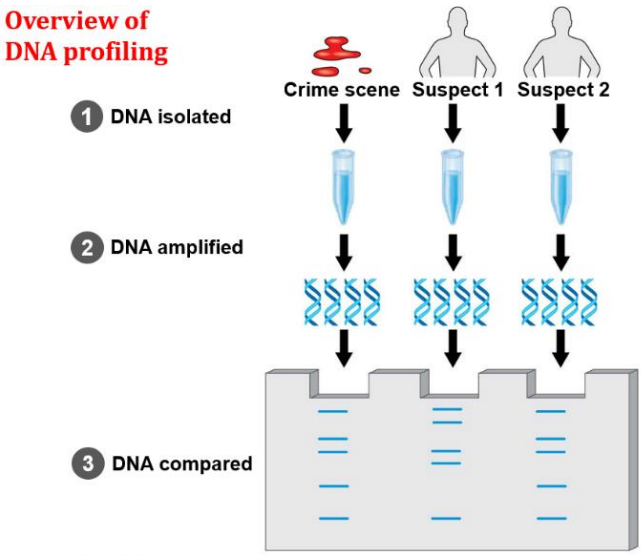
- **Pharmaceutical applications:**
  - **Humulin (胰岛素)：** Functions as a hormone and helps regulate the level of glucose in the blood. If the body fails to produce enough insulin, the result is type1 diabates.
  - **Human growth hormone (HGH)**: Abnormally low levels of this hormone during childhood and adolescence can cause dwarfism.
  - **Tissue plasminogen activator (tPA 组织纤溶酶原激活剂)**: A natural human protein that helps dissolve blood clots.
  - **Erythropoietin (EPO 红细胞生成素):** A hormone that stimulates production of red blood cells.
  - **Lysozyme (溶菌酶):** This enzyme has antibacterial properties.

- **Human gene therapy:** To treat disease by introducing new genes into an afflicted person.

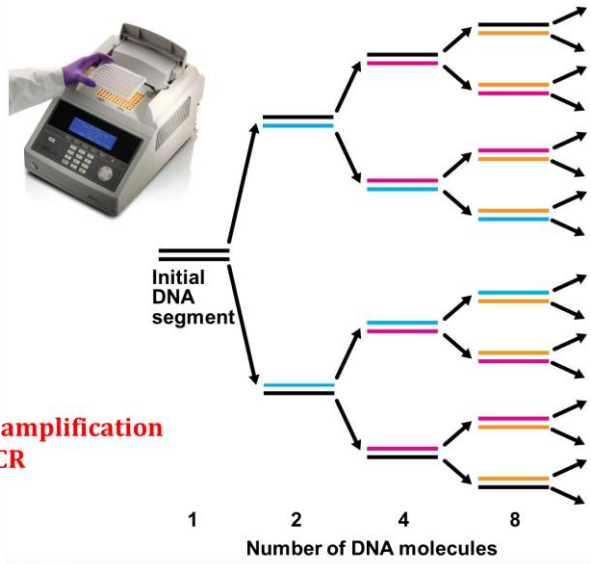


DNA Profiling and Forensic Science

- **DNA profiling:** The analysis of DNA samples to determine whether they come from the same individual.



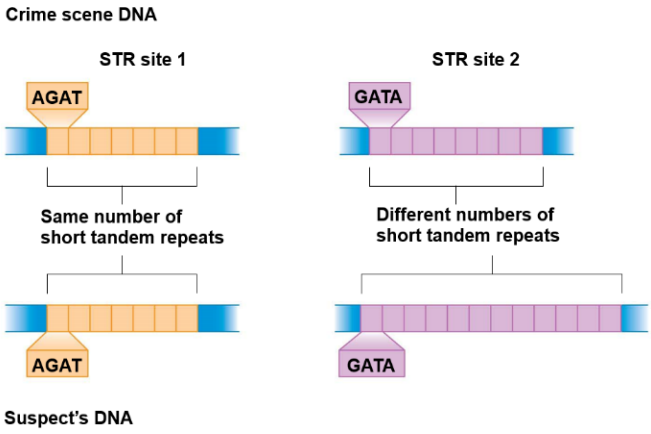
- **The polymerase chain reaction (PCR):** A technique by which a specific segment of DNA can be amplified: targeted and copied quickly and precisely.
  In principle, PCR is simple.
  - ✧ A DNA sample is mixed with nucleotides, the DNA replication enzyme DNA polymerase, and a few other ingredients.
  - ✧ The solution is then exposed to cycles of heating (to separate the DNA strands) and cooling (to allow double-stranded DNA to re-form).
  - ✧ During these cycles, specific regions of each molecule of DNA are replicated, doubling the amount of that DNA.
  - ✧ The result of this chain reaction is an exponentially growing population of identical DNA molecules.



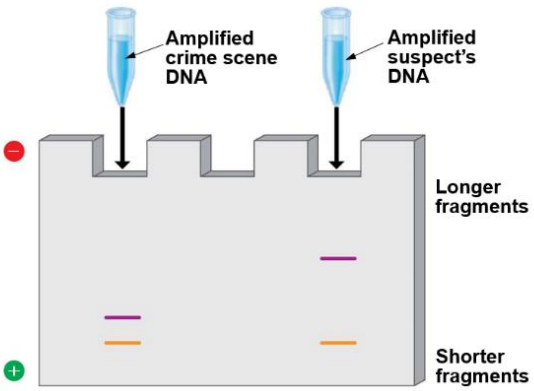
DNA amplification by PCR

- **Short tandem repeat (STR) analysis (短串联重复位点检测):** A method of DNA profiling that compares the lengths of STR sequences at specific sites in the genome.
  - ✧ **Repetitive DNA:** the sequences makes up much of the DNA that lies between genes in humans, consists of nucleotides sequences that are present in multiple copies in the genome.
  - ✧ **Short tandem repeat:** A series of repeats in the genome that the short sequences repeated many times randomly (one after another).

Short tandem repeat (STR) sites



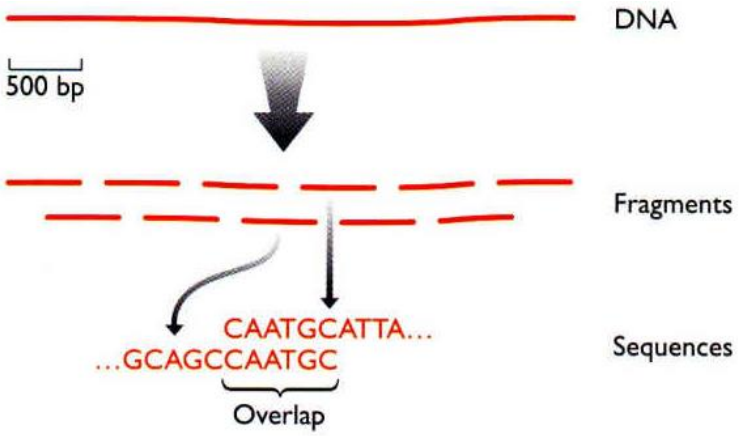
Visualizing STR fragment patterns



Bioinformatics

The application of computational methods to the storage and analysis of biological data.

- **DNA sequencing:** Exploiting the principle of complementary base pairing to determine the complete nucleotide sequence of a DNA molecule.
- **Genomics (基因组学):** The study of complete sets of genes.
- **Whole-genome shotgun method (全基因组鸟枪法):**



- ✧ Chop the entire genome into fragments using restriction enzymes.
- ✧ All the fragments are cloned and sequenced.
- ✧ Computers running specialized mapping software reassemble the millions of overlapping short sequences into a single continuous sequence for every chromosome—an entire genome.