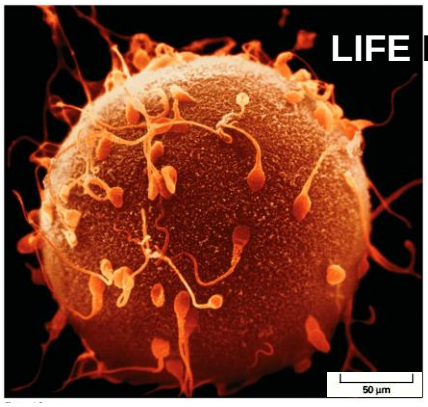
INTRODUCTION TO THE CELL

Life begins with Cells

BIOCHEMISTRY is the study of the chemistry of life

1. What are the chemical and three-dimensional structures of biological molecules?
2. How do biological molecules interact with each other?
3. How does the cell synthesize and degrade biological molecules?
4. How is energy conserved and used by the cell?
5. What are the mechanisms for organizing biological molecules and coordinating their activities?
6. How is genetic information stored, transmitted and expressed?

Biochemistry allow us to understand and appreciate the unique and mysterious condition that we call LIFE



LIFE BEGINS WITH CELLS

Single cells can grow, reproduce, process information, respond to stimuli, and carry out an amazing array of chemical reactions

LIFE

The cell is the fundamental unit of life

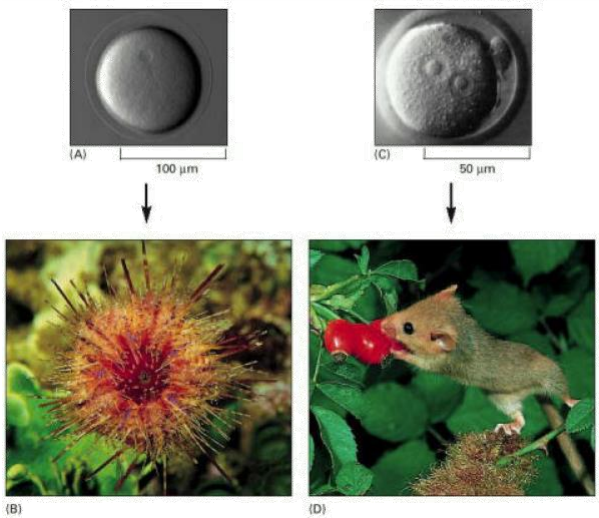
We start in this course

by introducing the diversity of cells,

their chemical components and critical functions, and

what we can learn from the various ways to study cells

The hereditary information in the egg cell determines the nature of the whole multicellular organism

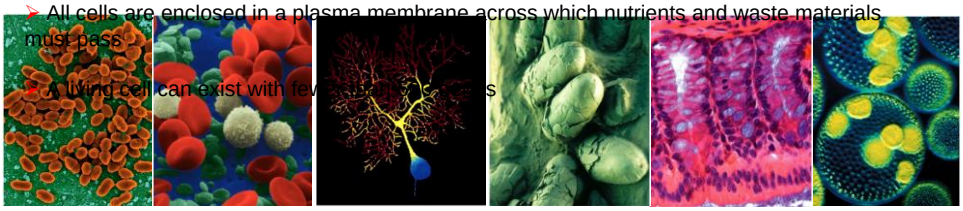


2002 by Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walter. The Molecular Biology of the Cell.

The diversity and commonality of Cells

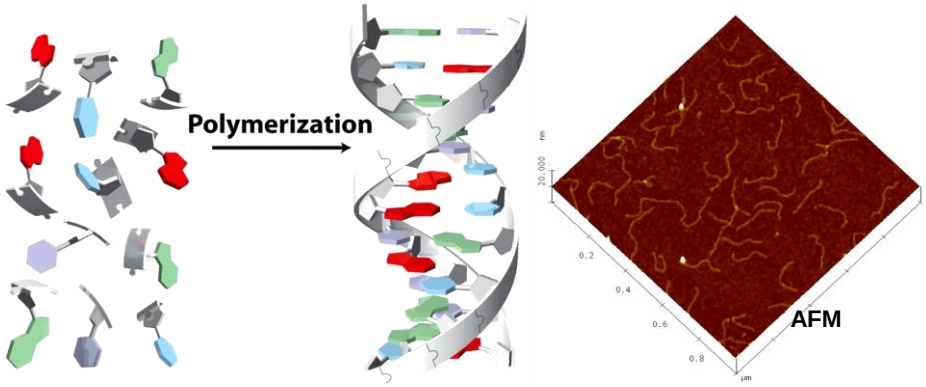
Cells come in an amazing assortment of shapes and sizes. In addition to morphology, they differ in their ability to move, internal organization, and metabolic activities.

- All cells store their hereditary information as the same linear chemical code (DNA)
- All cells replicate their hereditary information by templated polimerization
- All cells transcribe portions of their hereditary information into the same intermediary form (RNA)
- All cells use proteins as catalysts
- All cells translate RNA in to protein in the same way
- All cells function as biochemical factories dealing with the same basic molecular building blocks
- All cells are enclosed in a plasma membrane across which nutrients and waste materials must pass
- A living cell can exist with few [illegible] s



All cells store their hereditary information as the same linear chemical code (DNA)

All living cells on Earth, without any known exception, store their hereditary information in the form of double-stranded molecules of DNA, long unbranched paired polymer chains, formed always of the same four types of monomers: A, T, C, G.



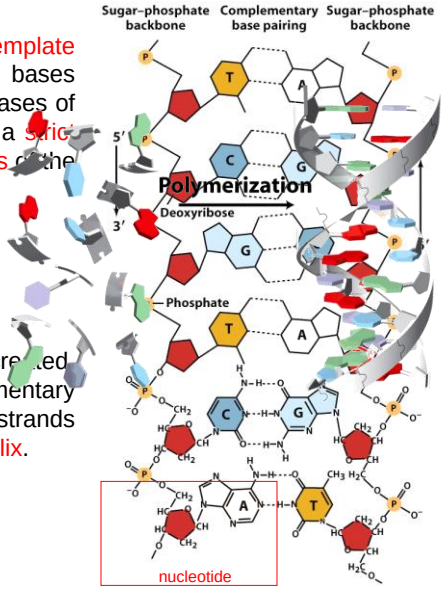
All cells replicate their hereditary information by templated polimerization

In the living cell, DNA is synthesized on a template formed by a preexisting DNA strand. The bases protruding from the existing strand bind to bases of the strand being synthesized, according to a strict rule defined by the complementary structures of the bases:

A binds to T

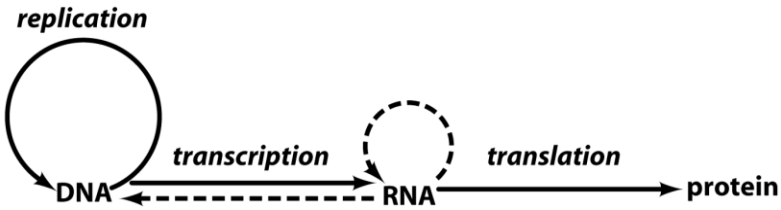
C binds to G

In this way, a double-stranded structure is created consisting of two exactly complementary sequences of As, Cs, Ts, and Gs. The two strands twist around each other, forming a double helix.

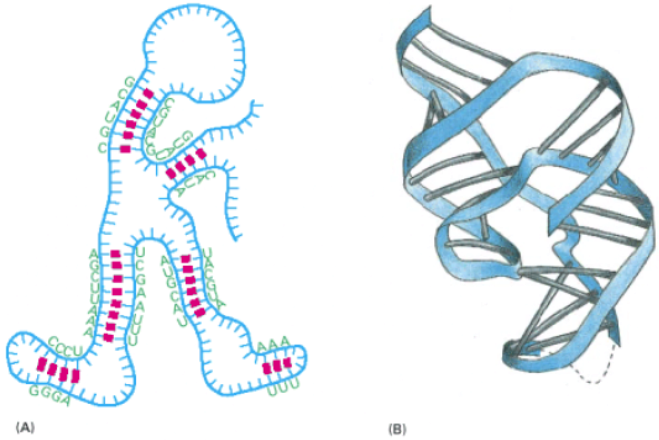


All cells transcribe portions of their hereditary information into the same intermediary form (RNA)

The genetic information is read out and put to use through a two-steps process. First, a templated polymerization called transcription, in which segments of the DNA sequence are used as templates to guide the synthesis of shorter molecules of the closely related polymer ribonucleic acid, or RNA. Later, in the more complex process of translation, many of these RNA molecules serve to direct the synthesis of polymers of a radically different chemical class: the proteins

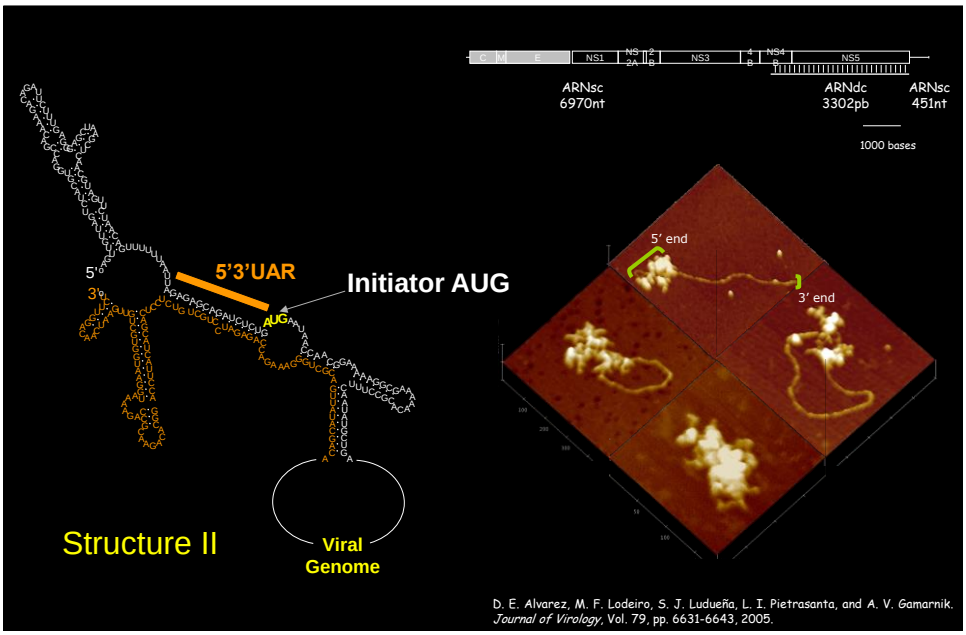


The conformation of an RNA molecule



(A) Nucleotide pairing between different regions of the same RNA polymer chain causes the molecule to adopt a distinctive shape. (B) The three-dimensional structure of an actual RNA molecule, from hepatitis delta virus, that catalyzes RNA strand cleavage. (B, based on A.R. Ferré D'Amaré, K. Zhou, and J.A. Doudna, *Nature* 395:567 574, 1998. © Macmillan Magazines Ltd.)

Visualización de las interacciones ARN-ARN en el genoma del virus del Dengue



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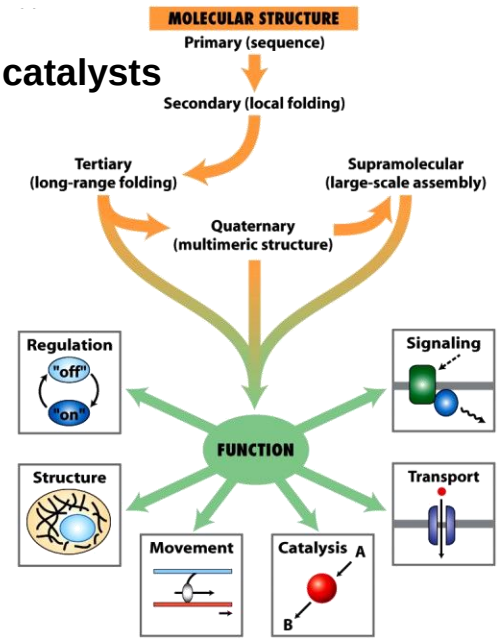
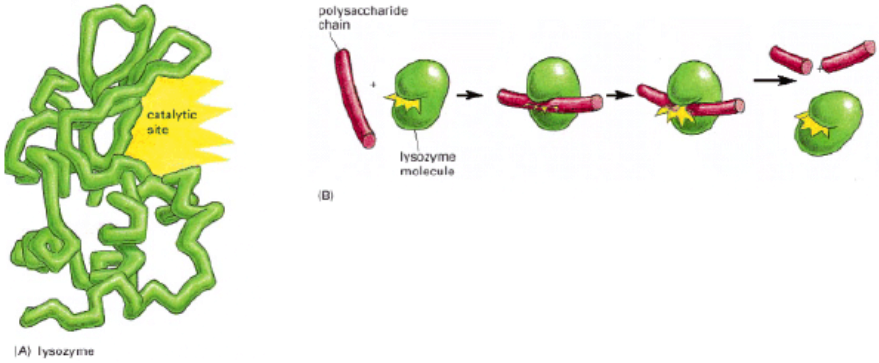
- A living cell can exist with fewer than 500 genes

All cells use proteins as catalysts

Proteins are at the center of action in biological processes. They are the principal catalysts for almost all the chemical reactions in the cell; their other functions include the selective import and export of small molecules across the plasma membrane that forms the cell's boundary. The specific function of each protein depends on its amino acid sequence, which is specified by the gene that codes for that protein.



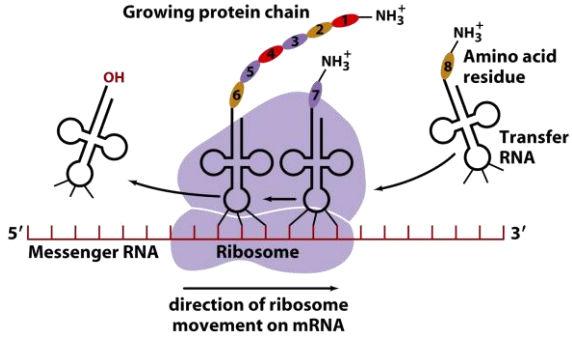
How a protein molecule acts as catalyst for a chemical reaction



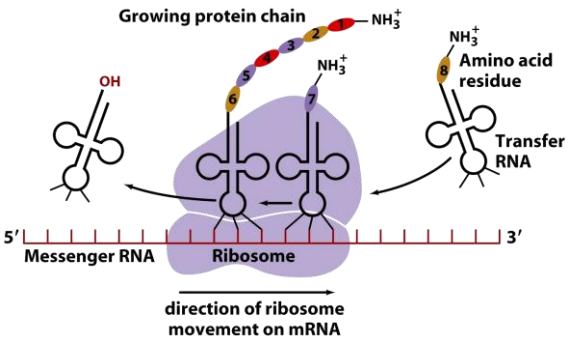
(A) In a protein molecule the polymer chain folds up to into a specific shape defined by its amino acid sequence. A groove in the surface of this particular folded molecule, the enzyme lysozyme, forms a catalytic site. (B) A polysaccharide molecule *(red)* a polymer chain of sugar monomers binds to the catalytic site of lysozyme and is broken apart, as a result of a covalent bond-breaking reaction catalyzed by the amino acids lining the groove.

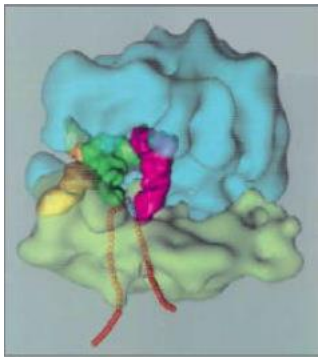
All cells translate RNA in to protein in the same way

The information in the sequence of a mRNA molecule is read out in groups of three nucleotides at a time: each codon, specifies (codes for) a single amino acid in a corresponding protein. The code is read out by a special class of small RNA molecules, the transfer RNAs (tRNAs). Each type of tRNA becomes attached at one end to a specific amino acid, and displays at its other end a specific sequence of three nucleotides—an anticodon—that enables it to recognize, through base-pairing, a particular codon or subset of codons in mRNA. This whole complex of processes is carried out by a giant multi molecular machine, the ribosome, formed of two main chains of RNA, called ribosomal RNAs (rRNAs), and more than 50 different proteins.



A ribosome at work





(A) The diagram shows how a ribosome moves along an mRNA molecule, capturing tRNA molecules that match the codons in the mRNA and using them to join amino acids into a protein chain. The mRNA specifies the sequence of amino acids. (B) The three-dimensional structure of a bacterial ribosome *(pale green* and *blue),* moving along an mRNA molecule *(orange* beads*),* with three tRNA molecules *(yellow*, *green*, and *pink)* at different stages in their process of capture and release. The ribosome is a giant assembly of more than 50 individual protein and RNA molecules. (B, courtesy of Joachim Frank, Yanhong Li, and Rajendra Agarwal.)

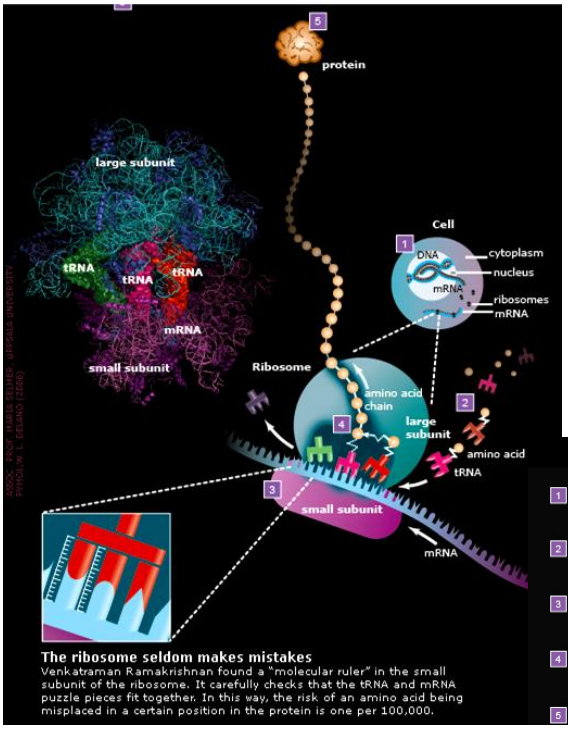
Nobelprize.org
The Official Web Site of the Nobel Prize

The Nobel Prize in Chemistry 2009 was awarded jointly to Venkatraman Ramakrishnan, Thomas A. Steitz and Ada E. Yonath *"for studies of the structure and function of the ribosome"*.

Venkatraman Ramakrishnan
US citizen. Born in 1952 in Chidambaram, Tamil Nadu, India. Senior Scientist and Group Leader at Structural Studies Division, MRC Laboratory of Molecular Biology, Cambridge, UK.

Thomas A. Steitz
US citizen. Born in 1940 in Milwaukee, WI, USA. Sterling Professor of Molecular Biophysics and Biochemistry and Howard Hughes Medical Institute Investigator, both at Yale University, CT, USA.

Ada E. Yonath
Israeli citizen. Born in 1939 in Jerusalem, Israel. Martin S. and Helen Kimmel Professor of Structural Biology and Director of Helen & Milton A. Kimmelman Center for Biomolecular Structure & Assembly, both at Weizmann Institute of Science, Rehovot, Israel.



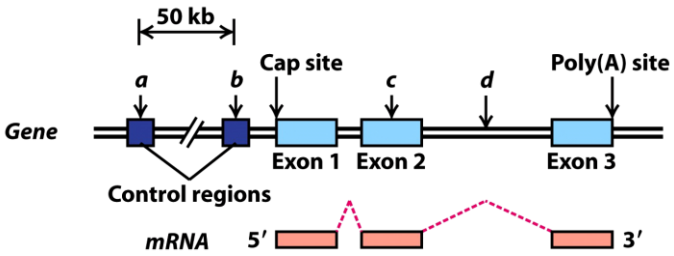
Nobelprize.org
The Official Web Site of the Nobel Prize

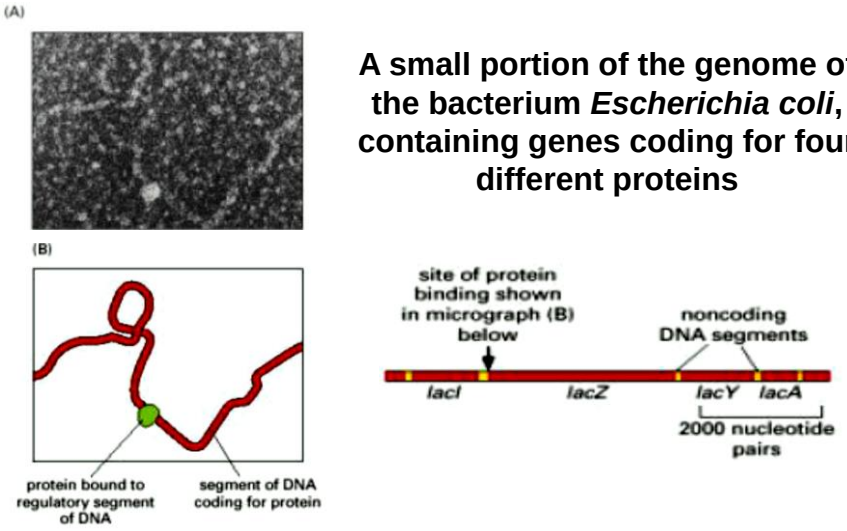
How the DNA code becomes life

structure-based drug design (SBDD)

The fragment of genetic information corresponding to one protein is one gene

A gene is defined as the segment of DNA sequence corresponding to a single protein. In all cells, the expression of individual genes is regulated. The genome of the cell dictates not only the nature of the cell's proteins, but also when and where they are to be made.



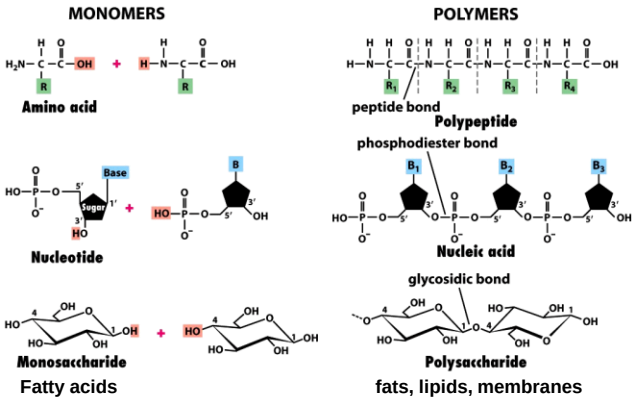


A small portion of the genome of the bacterium *Escherichia coli*, containing genes coding for four different proteins

(A) The protein-coding DNA segments *(red)* have regulatory and other noncoding DNA segments *(yellow)* between them. (B) An electron micrograph of DNA from this region, with a protein molecule (encoded by the *lac1* gene) bound to the regulatory segment; this protein controls the rate of transcription of the *lacZ*, *lacY*, and *lacA* genes. (C) A drawing of the structures shown in (B). (B, courtesy of Jack Griffith.)

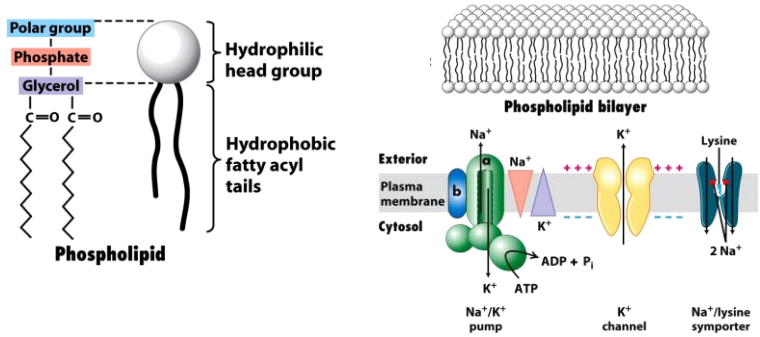
All cells function as biochemical factories dealing with the same basic molecular building blocks

All cells have to contain and manipulate a similar collection of small molecules, including simple sugars, nucleotides, and amino acids, as well as other substances that are universally required for their synthesis. All cells, for example, require ATP as a building block for the synthesis of DNA and RNA; and all cells also make and consume this molecule as a carrier of free energy and phosphate groups to drive many other chemical reactions.



All cells are enclosed in a plasma membrane across which nutrients and waste materials must pass

The plasma membrane is formed of a set of molecules that have the simple physico-chemical property of being amphipathic such as the phospholipid (PL) molecules. This container acts as a selective barrier that enables the cell to concentrate nutrients gathered from its environment and retain the products it synthesizes for its own use, while excreting its waste products.



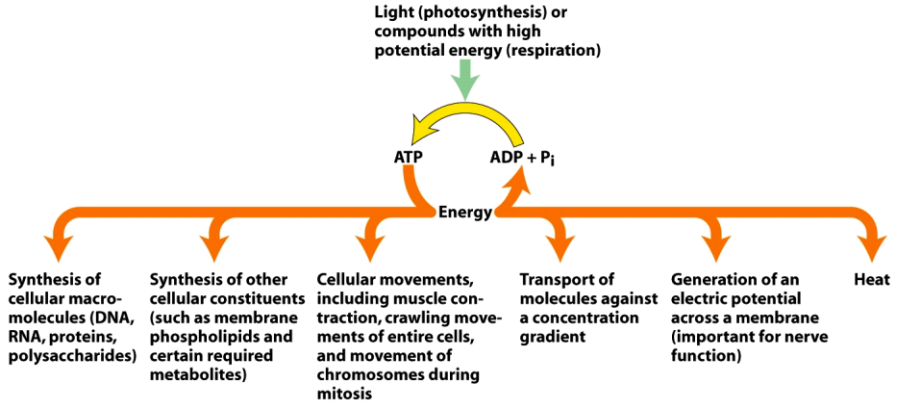


Figure 1-14
Molecular Cell Biology, Sixth Edition

A living cell can exist with fewer than 500 genes

The basic principles of biological information transfer are simple enough but how many components are needed to build a living cell? The genome project has started to provide answers to what is the minimal complexity, compatible with the living state……

The simplest cell…	*Mycoplasma genitalium*	477 genes
	Treponema pallidum	1041 genes
By comparison…	*Escherichia coli*	4289 genes
	Saccharomyces cerevisiae	~ 6300 genes
	Drosophila melanogaster	~ 14,000 genes
	Homo sapiens	30,000- 35,000 genes

Complexity grows exponentially with the number of parts in machinery

On the basis of cell structure…..

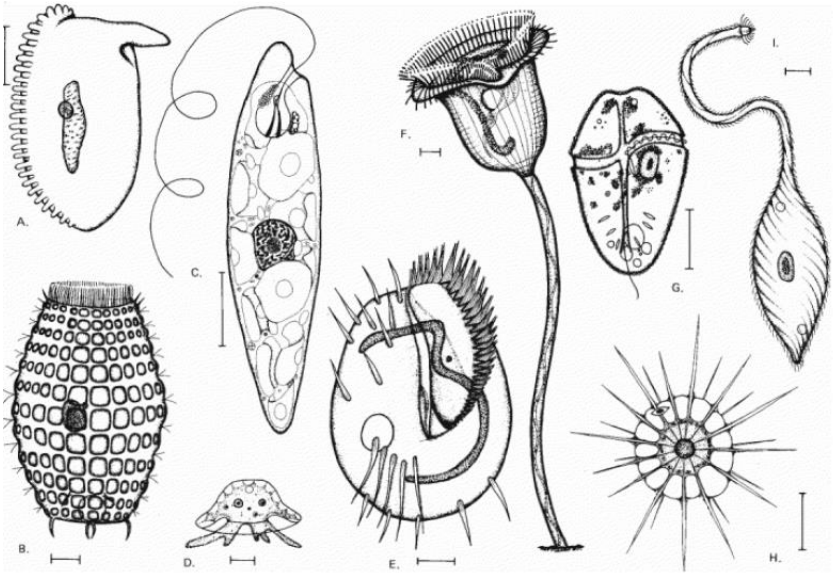
All Cells Are Prokaryotic or Eukaryotic

PROKARYOTES include

- Bacteria (EUBACTERIA)
- Archaea (ARCHAEBACTERIA)

EUKARYOTES include four kingdoms

- plants
- animals
- fungi
- protists



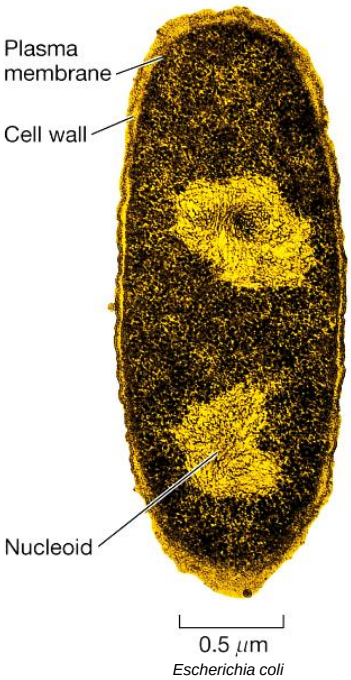
An assortment of protists: a small sample of an extremely diverse class of organisms. The drawings are done to different scales, but in each case the scale bar represents 10 mm. The organisms in (A), (B), (E), (F), and (I) are ciliates; (C) is a euglenoid; (D) is an amoeba; (G) is a dinoflagellate; (H) is a heliozoan. (From M.A. Sleigh, Biology of Protozoa. Cambridge, UK: Cambridge University Press, 1973.)

PROKARYOTES

Prokaryotic cells consist of a single closed compartment that is surrounded by the plasma membrane, lacks a defined nucleus, and has a relatively simple internal organization.

They often have a tough protective coat, called a cell wall, beneath which a plasma membrane encloses a single cytoplasmic compartment containing DNA, RNA, proteins, and the many small molecules needed for life.

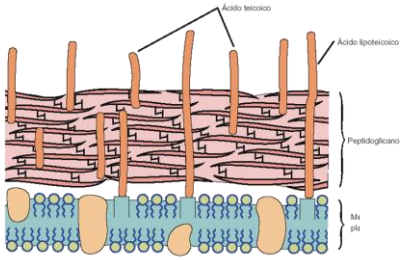
Bacteria are classified as gram-positive (thick wall) or gram-negative (thin wall covered by a complex outer membrane) according to whether or not they take up Gram stain.



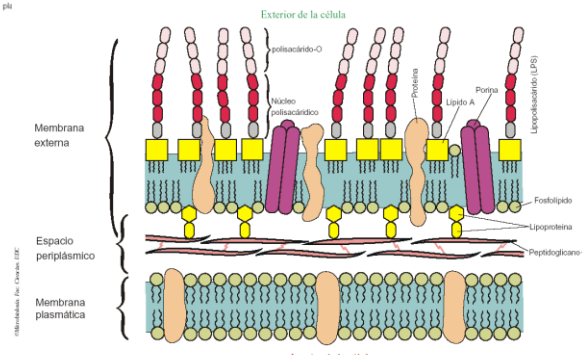
Escherichia coli

bacteriólogo danés Christian Gram (1853-1938)

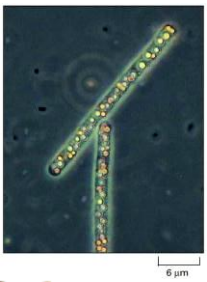
Estructura de la Pared Celular
de bacterias Gram positivas

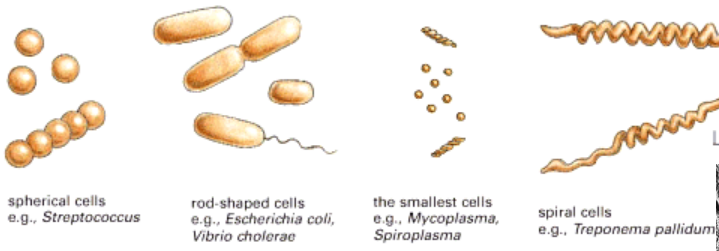


Estructura de la Pared Celular
de bacterias Gram negativas



Most prokaryotic cells are small and simple in outward appearance, and they are typically spherical or rod-shaped and measure a few micrometers in linear dimension. They live in an enormous variety of ecological niches, and they are varied in their biochemical capabilities.





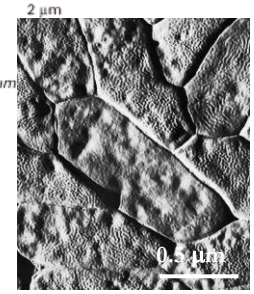
spherical cells
e.g., *Streptococcus*

rod-shaped cells
e.g., *Escherichia coli*, *Vibrio cholerae*

the smallest cells
e.g., *Mycoplasma*, *Spiroplasma*

spiral cells
e.g., *Treponema pallidum*

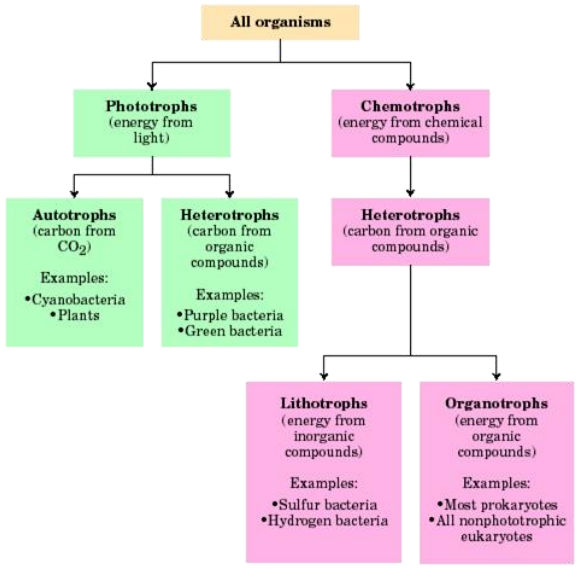
AFM



Escherichia coli

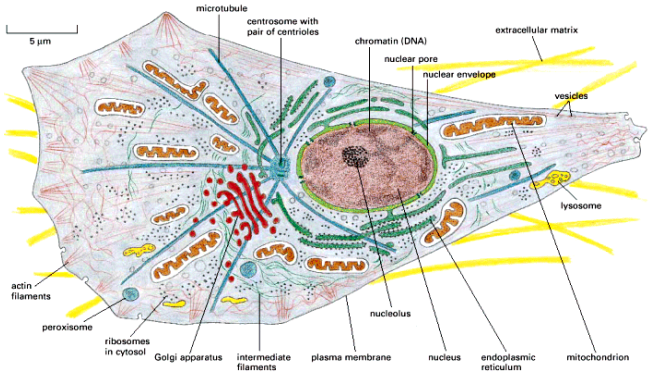
Prokaryotic cells are structurally simple but biochemically diverse!!!

Organisms can be classified according to their source of energy or oxidizable chemical compounds and their source of carbon for the synthesis of cellular material



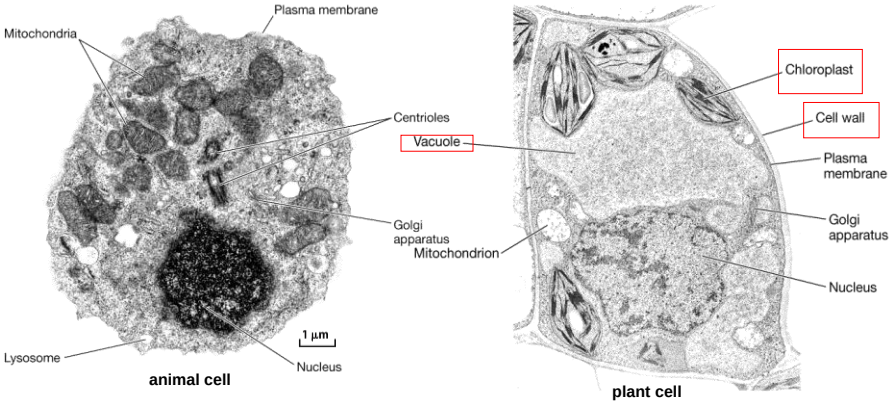
EUKARYOTES

Eukaryotes keep their DNA in a distinct intracellular compartment called the nucleus. The DNA is separated from the cytoplasm by the nuclear envelope, which consists of a double layer of membrane. The cells have an extensive internal membranes that enclose other compartments called organelles. They have, in addition, a cytoskeleton for movement, elaborate intracellular compartments for digestion and secretion, the capacity to engulf other cells, and a metabolism that depends on the oxidation of organic molecules by mitochondria. These properties *suggests* that eukaryotes originates as predator of other cells.

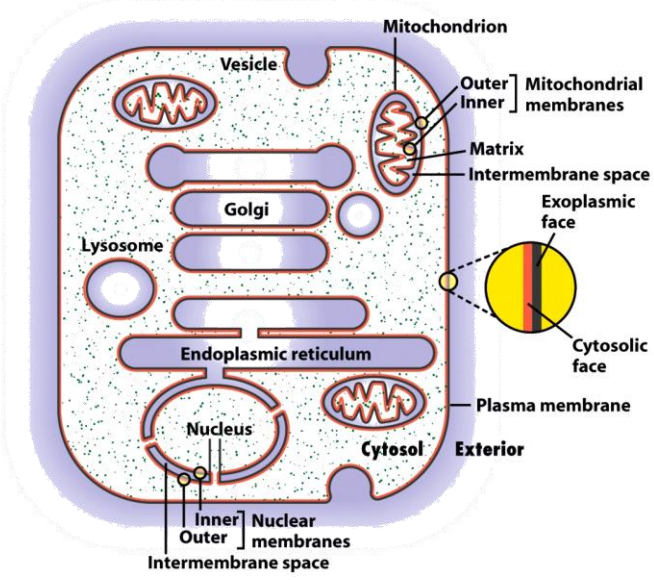


The major features of eukaryotic cells

Eukaryotic cells are typically, 10 times bigger in linear dimension, and 1000 times larger in volume than prokaryotic cells.



The faces of cellular membranes



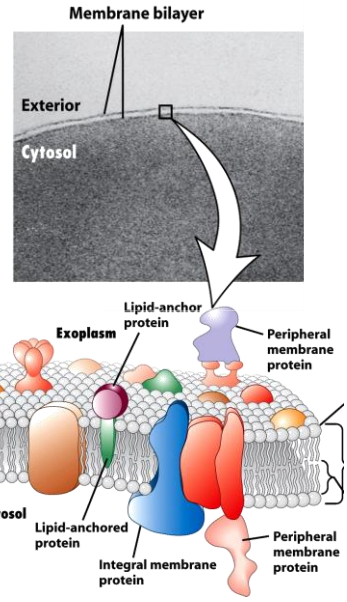
PLASMA MEMBRANE

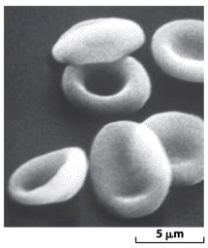
The outer boundary of the cell is the plasma membrane, a single two-dimensional lipid sheet with hydrophilic faces and a hydrophobic core, which is impermeable to water-soluble molecules and ions. Eukaryotic PMs are studded with a multitude of proteins that allow

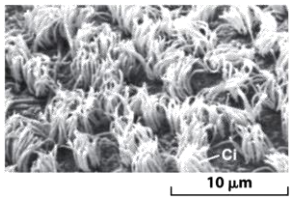
selective import and export of small molecules and ions,

recognize chemical signals

adhere to other cells and to ECM



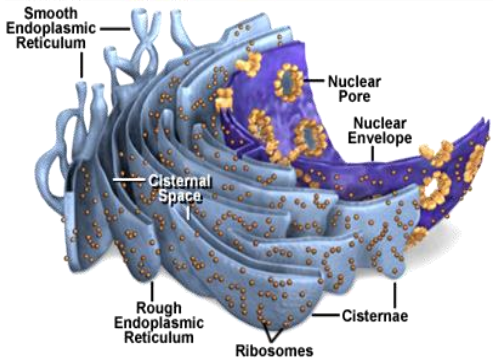


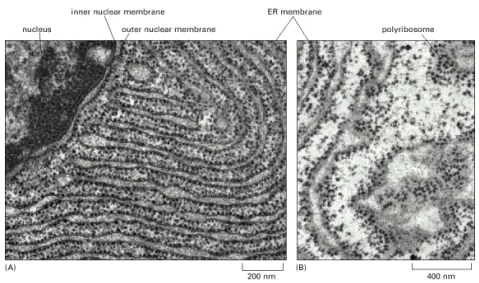


ENDOPLASMIC RETICULUM

The ER membrane is in structural continuity with the outer membrane of the nuclear envelope and it specializes in the synthesis and transport of *lipids, membrane proteins* and *secreted proteins.*

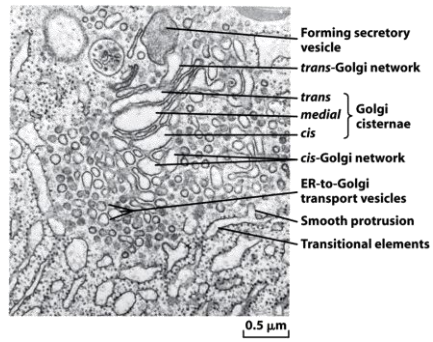
Flattened sheets, sacs, and tubes of membrane extended throughout the cytoplasm of eukaryotic cells, enclosing a large intracellular space.





GOLGI APPARATUS

A system of stacked, membrane-bounded, flattened sacs involved in modifying, sorting, and packaging macromolecules for secretion or for delivery to other organelles.



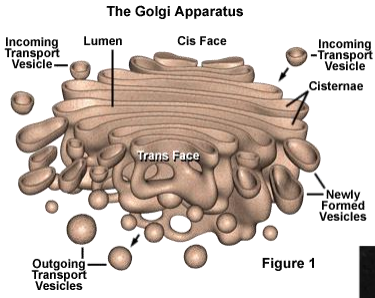
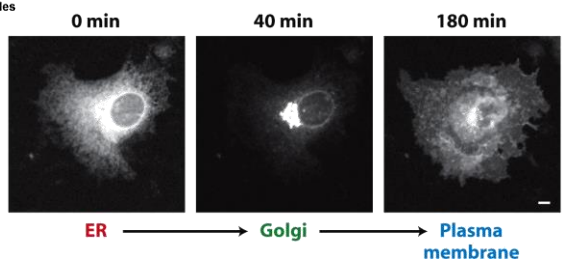


Figure 1

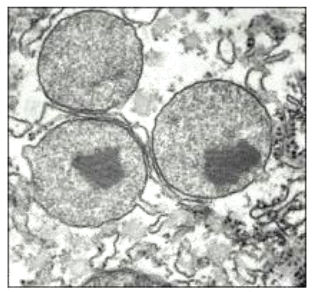


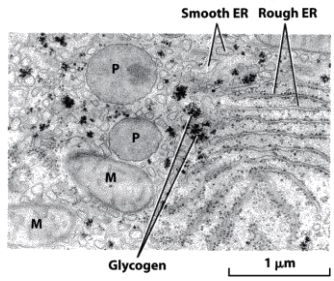
LYSOSOMES AND PEROXISOMES

Lysosomes are acidic organelles that contain a battery of degradative enzymes. They vary in size and shape, and several hundred may be present in a typical animal cell.

Several human diseases are caused by defects in specific lysosomal enzymes because their substrates accumulate inside the organelle. For example, Tay-Sachs disease, an autosomal recessive deficiency in hexosaminidase A.

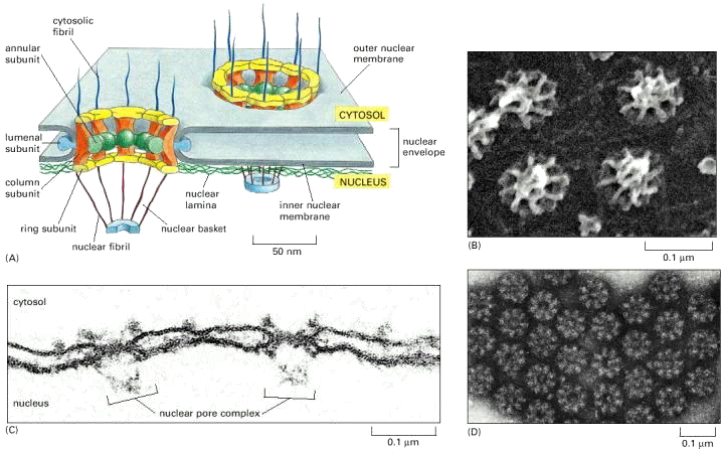
Peroxisomes are small, membrane-enclosed organelles that degrade fatty acids and toxic compounds. All animal cells (no erythrocyte) and many plant cells contain peroxisomes.





NUCLEUS

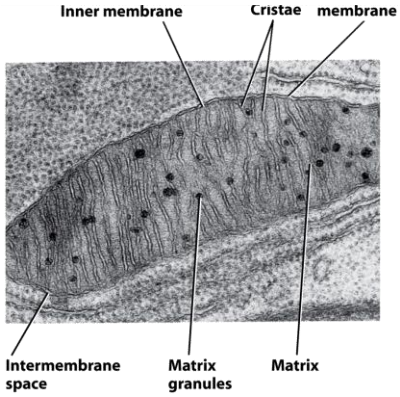
The nucleus, the largest organelle in animal cells, contains the DNA genome, RNA synthetic apparatus, and a fibrous matrix. It is surrounded by two membranes, nuclear envelope, each containing many different types of proteins. The nuclear envelope of all eukaryotes is perforated by large, ring-like complexes known as nuclear pore complexes, through which material moves between the nucleus and the cytosol.

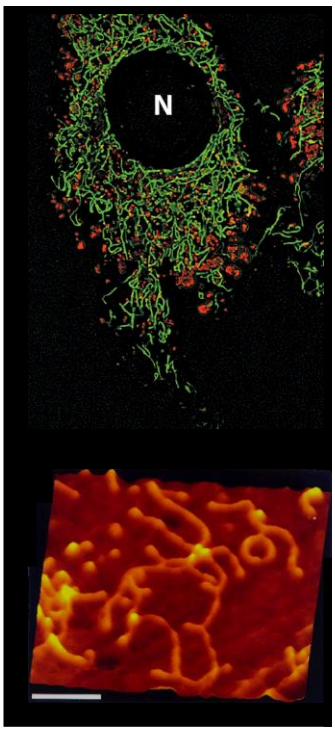


MITOCHONDRIA

Mitochondria are dynamic organelles with two structurally and functionally distinct membranes. Enzymes in the inner membrane and central matrix space carry out the terminal stages of sugar and lipid oxidation coupled to ATP synthesis.

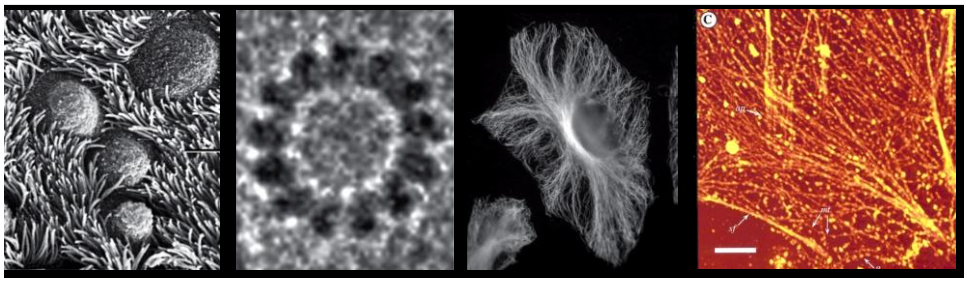
Mitochondria have their own genome in form of a circular DNA molecule, their own ribosomes and their own tRNAs.





CYTOSKELETON

The cytoskeleton extents throughout the cell and is attached to the plasma membrane and internal organelles, so providing a framework for cellular organization. Three types of filaments make up the animal-cell cytoskeleton: microfilaments, microtubules and intermediate filaments. This network of filaments **controls** the *shape and movement of the cell* and enables organelles and molecules to be transported from one location to another in the cytoplasm.



The work of cells

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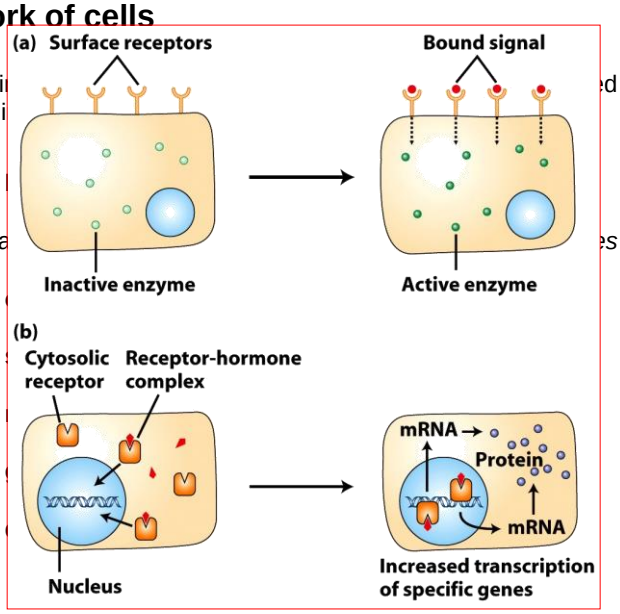
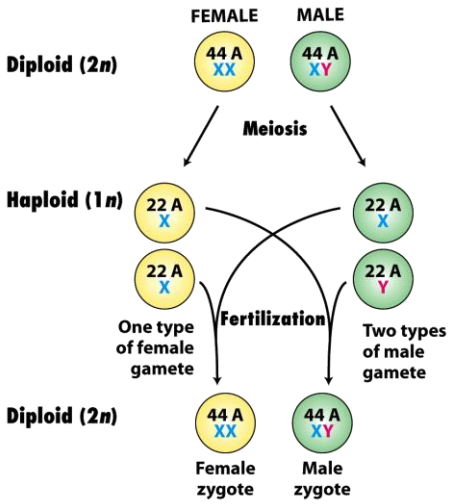
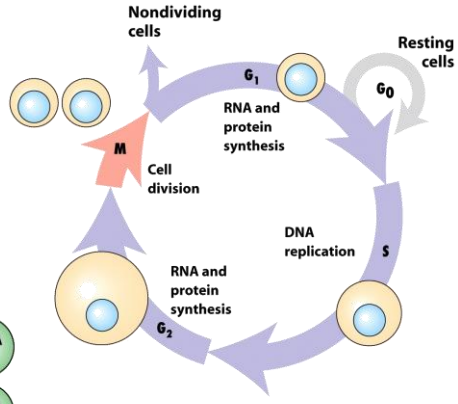


➢Cells grow and divide





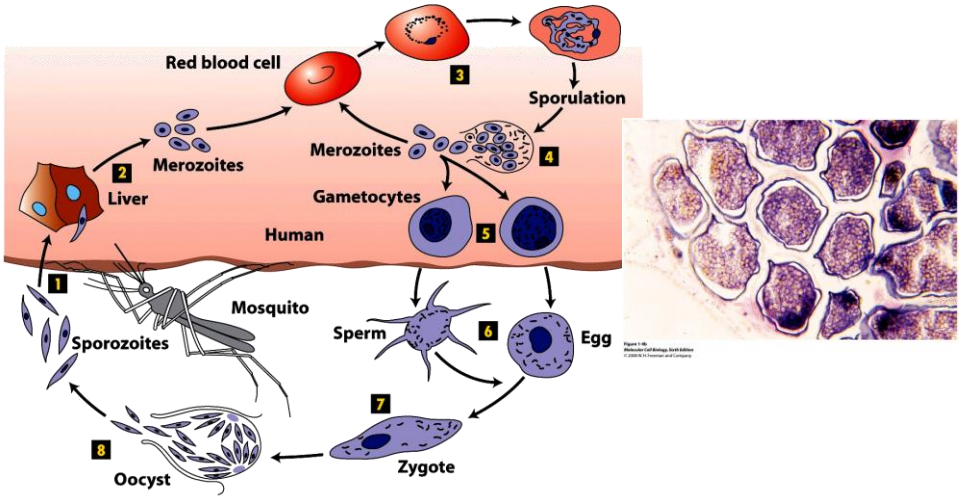
Dad made you a boy or girl

We develop from a single cell

The first few cell divisions of a fertilized egg set the stage for all subsequent development. A developing mouse embryo is shown at (a) the two-cell, (b) four-cell, and (c) eight-cell stages. The embryo is surrounded by supporting membranes. The corresponding steps in human development occur during the first few days after fertilization. [Claude Edelmann/ Photo Researchers, Inc.]

Stem cells offer medical opportunities

Unicellular Organisms Help and Hurt Us



Plasmodium organisms, the parasites that cause malaria, are single-celled protozoans with a remarkable life cycle.

Molecular Data Reveal Three Evolutionary Domains of Organisms

Traditional taxonomic schemes (**taxonomy** is the science of biological classification), which are based on gross morphology, have proved inadequate to describe the actual relationships between organisms as revealed by their evolutionary history (**phylogeny**).

Carl Woese's Three Domain System (1988)

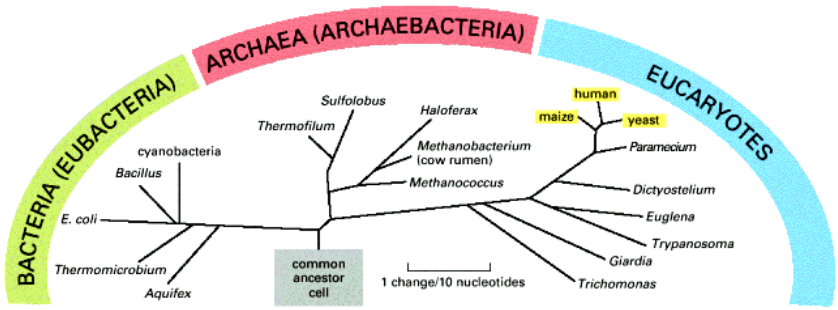
In the late 1970s, Carl Woese, at the University of Illinois, began phylogenetic analysis of all forms of cellular life based on comparison of nucleotide sequences of the small subunit ribosomal RNA (ssrRNA) that is contained in all organisms. Woese considered other conserved molecules in cells including certain proteins, and conserved genes (DNA), but settled for the ssrRNA for a number of reasons.

1. rRNA is found in all cells.
2. rRNA is present in thousands of copies and is easy to isolate from cells
3. rRNA can be analyzed to determine the exact sequence of nucleotide bases in its makeup.
4. The sequence of bases in RNA is a complementary COPY of the sequence of bases in the gene (DNA) that encodes for RNA.
5. Base sequences in different rRNA molecules can be compared by computer analyses and statistical methods to reveal precise similarities and differences in cellular genomes.

ORGANISMAL EVOLUTION

The diversity of genomes and the tree of life

The complete DNA sequence of an organism defines the species with almost perfect precision and in exhaustive detail. The number of differences between the DNA sequences of two organisms can be used to provide a direct, objective, quantitative indication of the evolutionary distance between them.



The three major divisions of the living world. The tree is based on comparisons of the nucleotide sequence of a ribosomal RNA subunit in the different species. The lengths of the lines represent the numbers of evolutionary changes that have occurred in this molecule in each lineage.

Some genes evolve rapidly, others are highly conserved

All organisms from simple bacteria to complex mammals *probably* evolved from a common, single-celled progenitor. Some parts of the genome change more easily than others in the course of evolution. Through more than 3.5 billion years the highly conserved genes remain in all living species. These genes allow us to trace family relationships between organisms. The tree of life is based on comparisons of the nucleotide sequence of the smaller ribosomal RNA subunit in the different species.

The origins of complexity

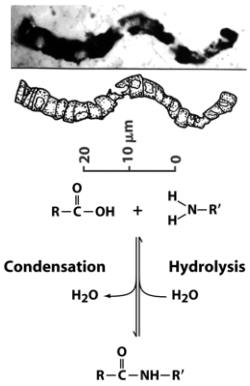
Among the significant evolutionary developments that produced the present-day cells is the emergence of mechanism for sexual reproduction (adaptability). A related development was the appearance of multiple chromosomes. At some point in the evolutionary history, single eukaryotic cells *acting in a mutually beneficial manner* gave rise to multicellular organisms.

Addition clues to the origin of eukaryotic cellular complexity lie in the mitochondria and chloroplasts. Both types of organelles resemble bacteria in size and shape, and both contain their own genetic material and protein synthetic machinery. Lynn Margulis hypothesized that *mitochondria and chloroplasts* ***evolved*** *from free-living aerobic bacteria that formed* ***symbiotic relationships*** *with primordial eukaryotes.*

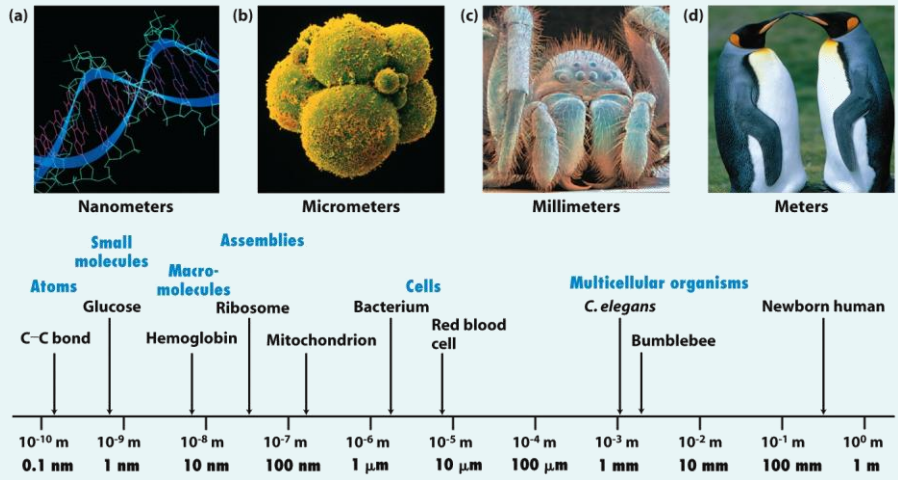
How do organisms evolve?

A model for the origin of life proposes that organisms ultimately arose from simple organic molecules that polymerized to form more complex molecules capable of replicating themselves. **Natural selection** that guided prebiotic evolution continues to direct the evolution of organisms.

Chapter 1 Opener Fundamentals of Biochemistry, 2/e



INVESTIGATING CELLS AN THEIR PARTS



SUMMARY

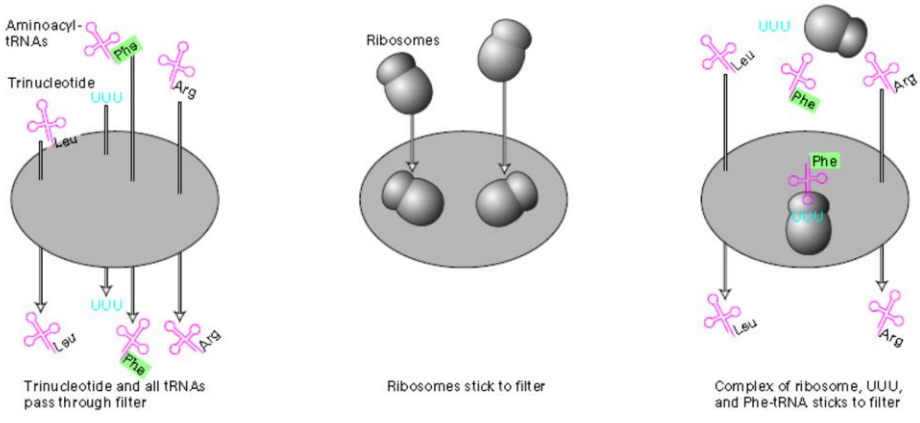
- Cells are the fundamental units of life
- All cells are either prokaryotic or eukaryotic. Eukaryotic cells contain a variety of membrane-bounded organelles
- All cells store their hereditary information as the same linear chemical code (DNA)
- All cells replicate their hereditary information by templated polimerization
- All cells transcribe portions of their hereditary information into the same intermediary form (RNA)
- All cells use proteins as catalysts
- All cells translate RNA in to protein in the same way
- All cells function as biochemical factories dialing with the same basic molecular building blocks
- All cells are enclosed in a plasma membrane across which nutrients and waste materials must pass
- A living cell can exist with fewer than 500 genes
- Phylogenetic evidence groups organisms into three domains: archaea, bacteria, and eukarya.
- All present-day cells are believed to have evolved from the same ancestral cell that existed more than 3000 million years ago.

CLASSIC EXPERIMENT

CRACKING THE GENETIC CODE
M. W. Nirenberg and P. Leder, 1964, *Science* **145:**1399

By the early 1960s molecular biologists had adopted the so-called “central dogma,” which states that DNA directs synthesis of RNA (transcription), which then directs assembly of proteins (translation). However, researchers still did not completely understand how the “code” embodied in DNA and subsequently in RNA directs protein synthesis. To elucidate this process, Marshall Nirenberg embarked upon a series of studies that would lead to the solution of the genetic code.

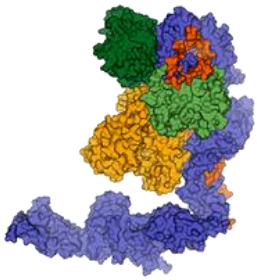
Nirenberg was awarded the Nobel Prize in Physiology or Medicine in 1968.



Assay developed by Marshall Nirenberg and his collaborators for deciphering the genetic code. They prepared 20 *E. coli* extracts containing all the aminoacyl-tRNAs (**tRNAs** with amino acid attached). In each extract sample, a different amino acid was **radioactively labeled** (**green**); the other 19 amino acids were present on tRNAs but remained unlabeled. Aminoacyl-tRNAs and trinucleotides passed through a nylon filter without binding (*left panel*); **ribosomes**, however, **bind to the filter** (*center panel*). Each of the 64 possible trinucleotides was tested separately for its ability to attract a specific tRNA by adding it with ribosomes to different extract samples. Each sample was then filtered. If the added trinucleotide causes the radiolabeled aminoacyl-tRNA to bind to the ribosome, then radioactivity is detected on the filter; otherwise, the label passes through the filter (*right panel*). By synthesizing and testing all possible trinucleotides, the researchers were able to match all 20 amino acids with one or more codons (e.g., phenyalanine with UUU, as shown here). [From H. Lodish et al., 1995, *Molecular Cell Biology,* 3rd ed. W. H. Freeman and Company. See M. W. Nirenberg and P. Leder, 1964, *Science* **145:**1399]

Feeding RNAs to a molecular shredder August 16, 2013

Max Planck scientists unravel the structure of a regulatory protein complex in RNA disposal



The ski complex plays an important role in the quality management of the cell.

Much in the same way as we use shredders to destroy documents that are no longer useful or that contain potentially damaging information, **cells use molecular machines to degrade unwanted or defective macromolecules.** Scientists of the Max Planck Institute of Biochemistry in Martinsried near Munich, Germany, have now decoded the structure of a protein complex (Ski complex) which plays an essential role in the process of degrading ribonucleic acids (RNAs). RNAs are ubiquitous and abundant molecules with multiple functions in the cell, such as allowing the translation of the genomic information into proteins. “The Ski complex we investigated feeds RNA molecules to the degradation machinery,” says Felix Halbach, scientist at the MPI of Biochemistry.

Halbach, F., Reichelt, P., Rode, M. and Conti, E.: **The yeast Ski complex: Crystal structure and substrate channeling to the RNA exosome.** *Cell*, August 15, 2013. DOI: 10.1016/j.cell.2013.07.017