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Molecular Biology

Department of Molecular Biology and Pharmaceutical Biotechnology (45-308)

Mgr. Marie Brázdová, Ph.D. (FAF, BFU AVČR)
Mgr. Denis Šubert (BFU AVČR)
Mgr. Daniel Renčiuk (BFU AVČR)
PharmDr. Jakub Treml, Ph.D. (FAF)

brazdovam@pharm.muni.cz,

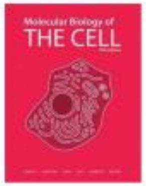
Examination requirements:

Exam has both written and oral part

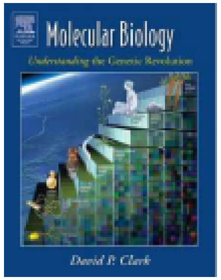
Test: min 60% to pass (E), ….90-95% (A)

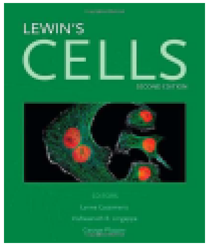
Suggested literature

- **Molecular Biology of the Cell, Fifth Edition,** Alberts, Johnson, Lewis, Raff, Roberts, Walter, Garland Science Publ. 2008



- **Molecular Biology, Understanding the Genetic Revolution,** Clark D.P., Elsevier, 2005





- **Lewin´s Cells, Second edition,** Cassimeris L., Lingappa V.R., Plopper G (eds), Jones and Barlett Publishers, 2011

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outline of the first lecture

defining molecular biology
historical context
living systems: types, properties
prokaryotic x eukaryotic cells
cell-free systems
model systems in molecular biology

What is molecular biology?

field studying relationships between physical structure, mutual interactions of biomolecules and the properties of living systems

explores relationships between two levels of living systems: between physical/chemical (structure and function of biomacromolecules) and biological (properties and functions of cells/organisms

Molecular biology x Biochemistry

biomolecular interactions, mainly information biomacromolecules, the functions and properties of living systems.

The goal of molecular biology is to explain the functions and features of living systems and the relationships in between the structure and interactions of their molecules (macromolecules).

These relationships are explained from a complex point of view integrating physical, chemical and biological methods.

Studies processes that take place in living systems at the **molecular level** and in which **genetic information** is processed

Biochemistry

Biochemistry addresses **chemical processes** in living organisms. The field of study in biochemistry is the structure and function of the basic building blocks of living matter like sugars, fats, proteins, nucleic acids and other biomolecules.

Principles of Molecular Biology are making their way into all biology fields

originally focused on heredity – maintenance and expression of genetic information and its inheritance (molecular genetics)

currently concerned with common characteristics of life at the molecular level, which are valid across the outer diversity of living creatures and the essence of processes taking place in cells and organisms

practical applications: biotechnology, paleontology, archeology, evolution, medicine, anthropology, criminalistics, determining parenthood, etc.

Importance of molecular biology

research moves **to a level that is common to all living systems**

Enables **cellular manipulations**– affect their characteristics in desired the direction (human and veterinary medicine, biotechnology, gene engineering, agriculture, etc.)

Brings in **new possibilities to study** phylogenetics, evolution, etc.

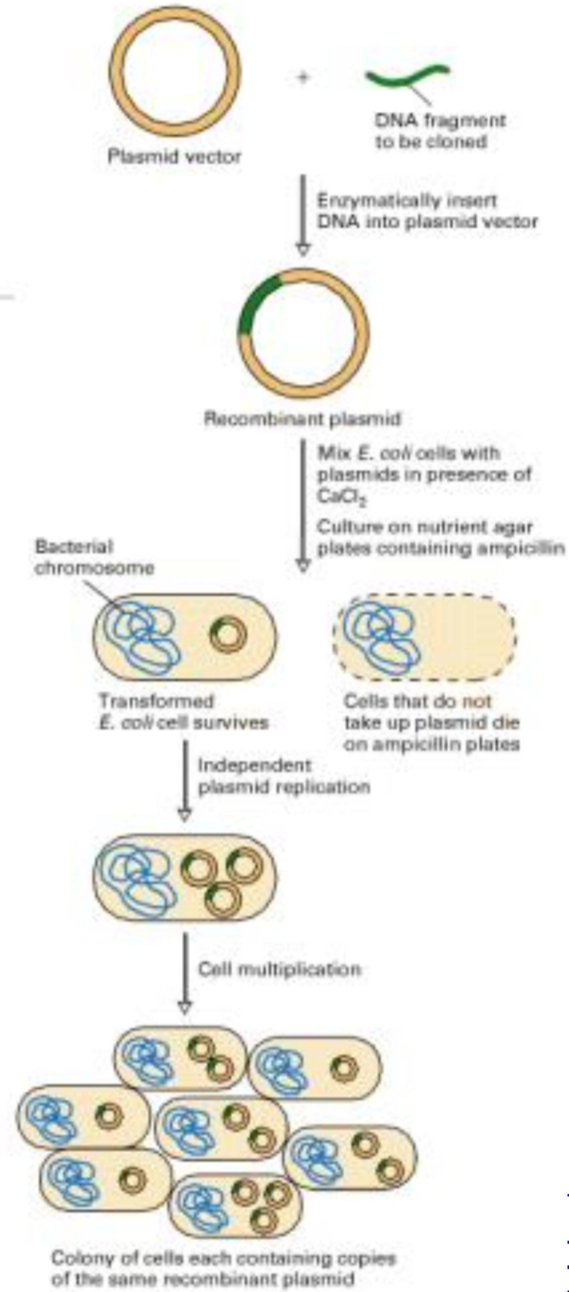
Molecular biology belongs along with information technology to the most progressive fields of present times

Historical background

Crossbreeding of plants and animals is done for thousand of years, yet genetics as a science arose only in the **80s of the 19th century**

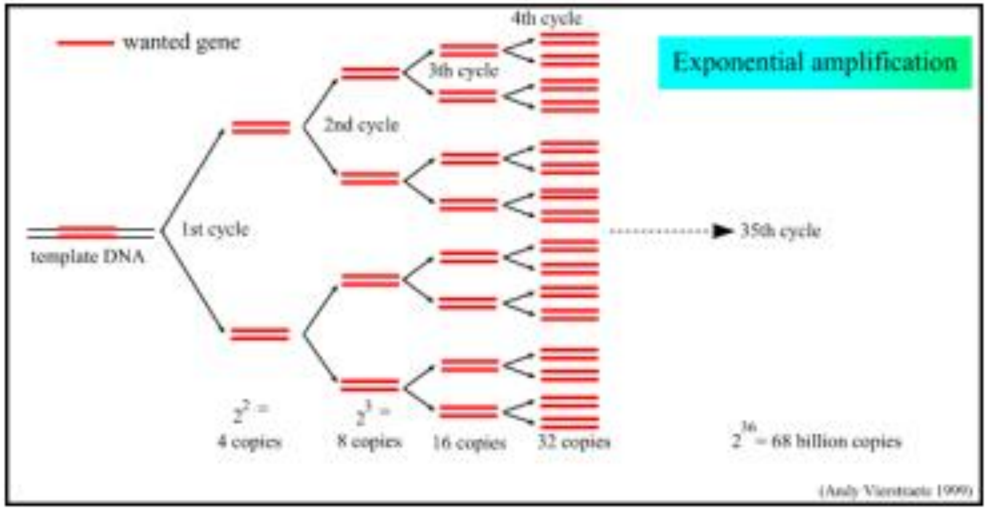
Techniques for investigating the associations between genes and observable traits are available only a few decades

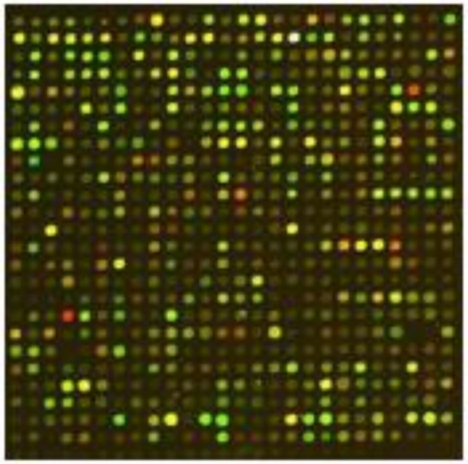
The era of **DNA cloning** and executing targeted alterations to genetic information began in 70s of the 20th century (Stanford University, UCSF, Genentech) – biotechnology used to prepare drugs



Gathering information about molecules of life dramatically speeded up in the last several years

milestones: DNA double-helix discovery, central dogma of molecular biology, restriction endonucleases, gene cloning, reverse transcription, DNA sequencing,h PCR, monoclonal antibodies, microarrays, RNA interference, stem cells, artificial nucleases, etc…





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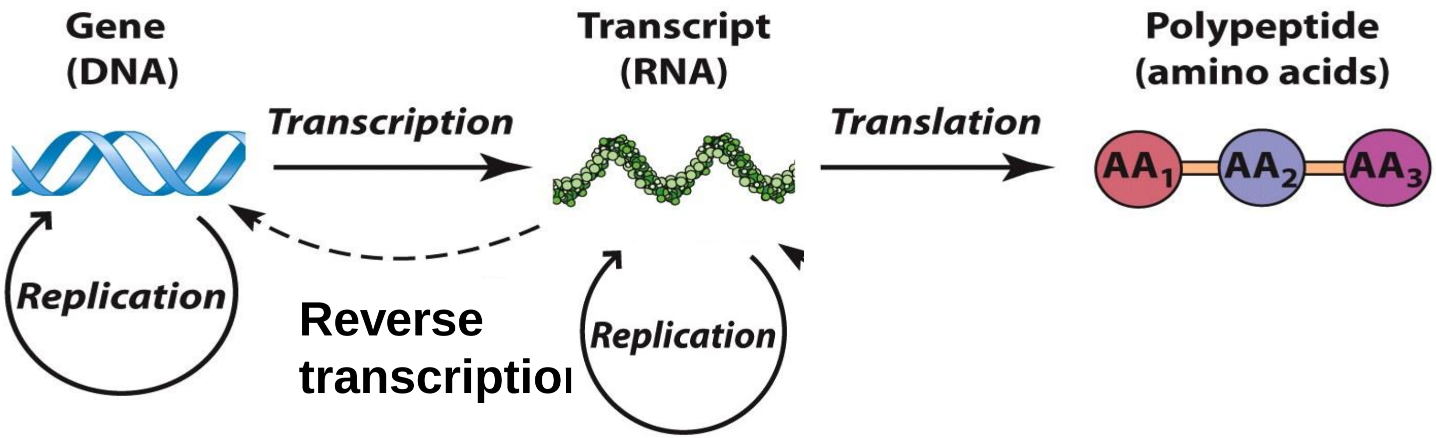
Important milestones in molecular biology

1944 – purified DNA used to transform bacteria
1953 – model of DNA structure (J. Watson, F. Crick, M. Wilkins)
1956 – genetic information is written in DNA as a sequence of bases
1958 – complementary DNA strands separate during replication
1958 – isolation of DNA-polymeraseI and DNA synthesis *in vitro*
1958 – postulating central dogma of molecular biology
1960 – discovering mRNA and prooving its function
1961 – mRNA used to decipher genetic code
1961 – experimental evidence to central dogma of MB
1961 – operon theory postulation – regulation of gene expression
1966 – complete deciphering of genetic code
1970 – first restriction enzyme was isolated
1970 – reverse transcriptase discovered in retroviruses
1972 – first recombinant DNA molecules prepared *in vitro*
1973 – beginnings of gene clonning – GI basis

1958 – postulating central dogma of molecular biology

The central dogma of molecular biology



- genetic information is passed by transfer of the DNA into RNA and protein (this postulate is called the central dogma of MB)
- In some viruses (e.g. HIV), RNA is used as a template for DNA synthesis by reverse transcription
- many genes encode a polypeptide, however RNA molecules in the cell play important roles

•**Structure genes** --- proteins

•Regulatory genes---RNA

•Genes for RNA – tRNA, rRNA

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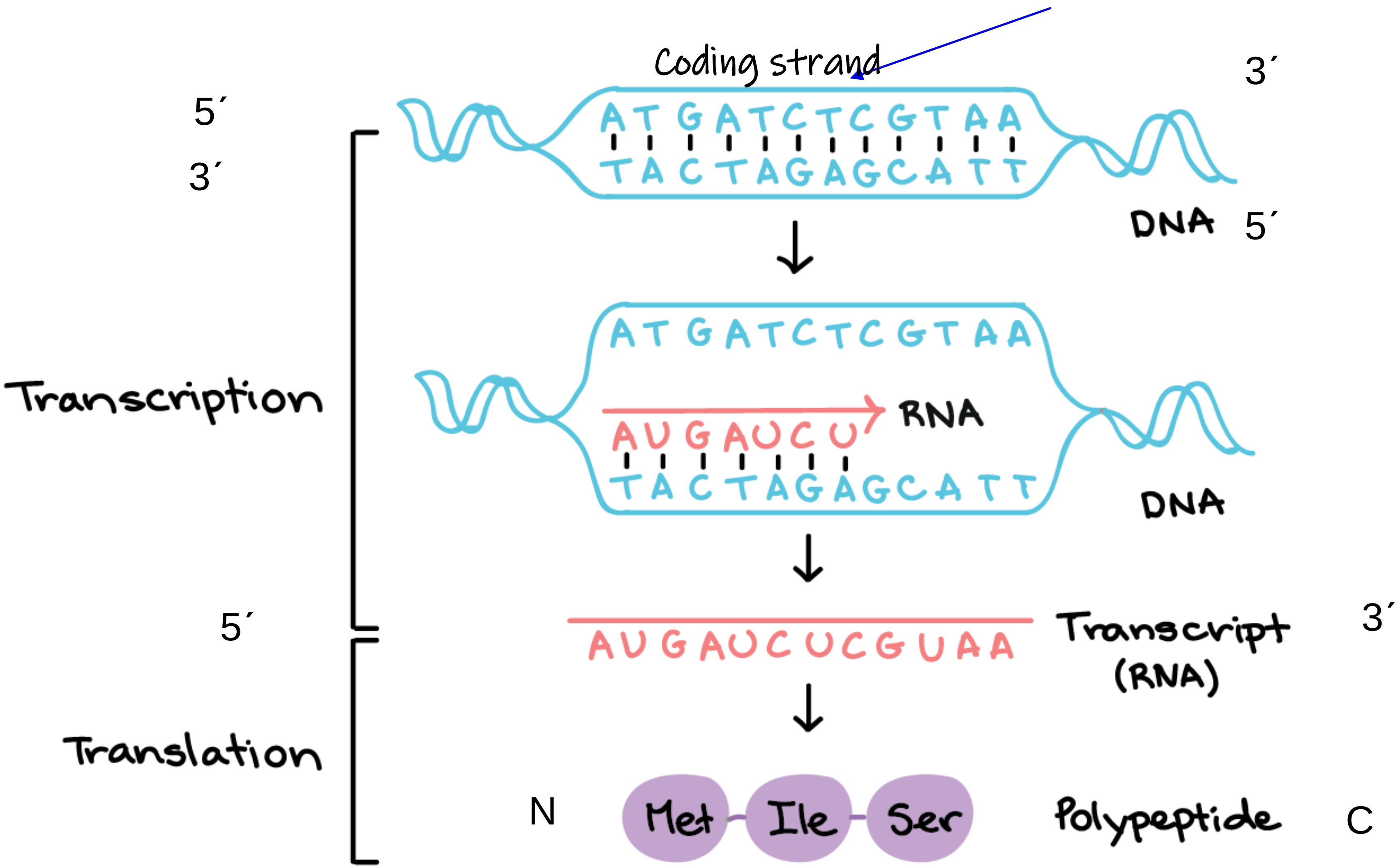

Coding strand
5´
3´
3´
5´
A T G A T C T C G T A A
T A C T A G A G C A T T
DNA
Transcription
A T G A T C T C G T A A
RNA
A U G A U C U
T A C T A G A G C A T T
DNA
5´
A U G A U C U C G U A A
Transcript (RNA)
3´
Translation
N
Met
Ile
Ser
Polypeptide
C

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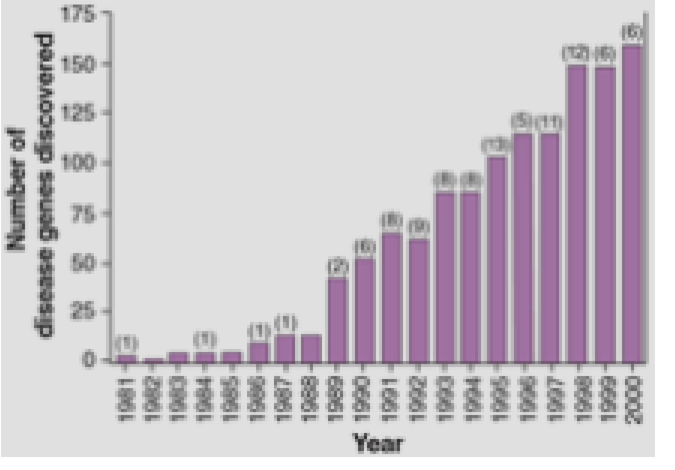
Important milestones in molecular biology

- 1975 – Asilomar conference – moratorium on work with recombinant DNA
- 1977 – first recombinant molecules to carry mammal genes
- 1977 – discovery of composed genes – exons/introns – pre-mRNA splicing
- 1977 – introducing DNA sequenation
- 1981 – discovery of RNA catalytic activity – ribosomes
- 1982 – human insulin produced commercially inside bacteria
- 1983 – bacteriophage λ - whole DNA sequence acquired

-starting projects to sequence genomes of model organisms

Genomic and postgenomic era

- analysing genome sequences
- genome x proteome
- bioinformatic approach



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Present

Since 2003 we have access to DNA nucleotide sequence that constitutes the human genome (approximately 20.000 genes, 23 chromosome pairs, $3x10^{9}$ base pairs/haploid cell)

We thus have the information necessary for the establishment and functioning of human beings

only 1,5% of the human genome consists of genes encoding the proteins, the rest consists of areas coding RNA, regulatory sequences, introns

The functions of many human genes are not sufficiently explored, even less is known about non-coding sequences

Present - challenges

- understanding of the mechanisms coordinating gene expression and their relationship to human health (all diseases have hereditary component that gets co-decided by genes)

- Curing hereditary diseases: resulting from faulty gene function carried over from parents to offspring – to understand the cause we must first understand the function of healthy genes

- Cancer treatment: also a consequence of gene dysfunctions, search for early diagnosis markers and appropriate targets for gene therapy, search for new chemotherapeutic agents

- Gene engineering and biotechnologies in agriculture: food source improvement (resistance to external adversities)

What is life?

- satisfactory definition does not exist

Generally accepted characteristics of living organisms:

- highly organised
- composed of one or more cells
- contain their own plan of arrangement, ie. the genetic program (genotype)
- acquire and use energy
- implement and control many chemical reactions
- grow and change their appearance and abilities (ie. phenotype)
- keep a relatively constant internal environment
- reproduce
- respond to changes in the environment
- They may evolve over time

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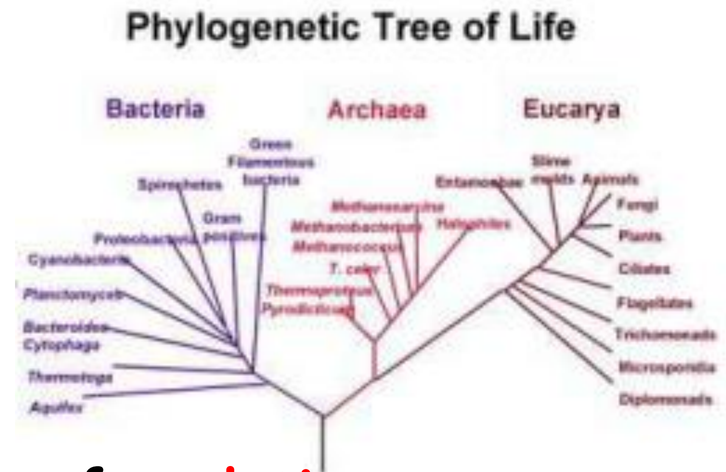
What is life?

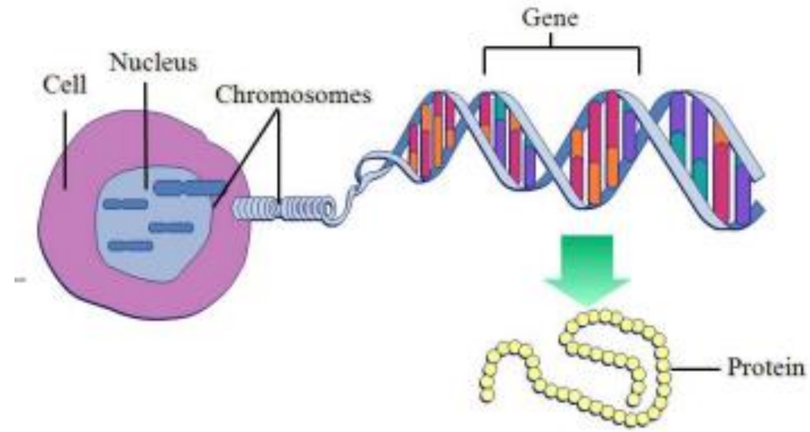
- a key feature is the ability to reproduce. That is replicating the genetic information (genome), and the structure that is its bearer and protector (cell).
- growth and reproduction requires information and energy
- energy is one of the products of metabolism
- Metabolism is a set of processes, by which are nutrient molecules transmitted and converted so that the cells are provided with energy and new building materials



Living organisms evolve

- life on earth is changing by a process of **evolution**
- organisms which are identical or very similar to parental organisms arise by reproduction
- but genetic information in progeny/offspring generations gradually accumulates changes
- accumulation of changes is related to the properties of molecules of nucleic acids and external environment
- a essential feature of life is that it **presents a dynamic balance between its precise duplication and tolerance to changes**

Terminology



- **Genetic information:** biological information written in nucleic acid (DNA or RNA) oligonucleotide sequence

- **gene**: unit of genetic information determining protein/RNA structure (physically: nucleic acid segment)

- **DNA**: serves long term genetic information storage

- **RNA**: is involved in mechanism by which genetic information is put into practical use

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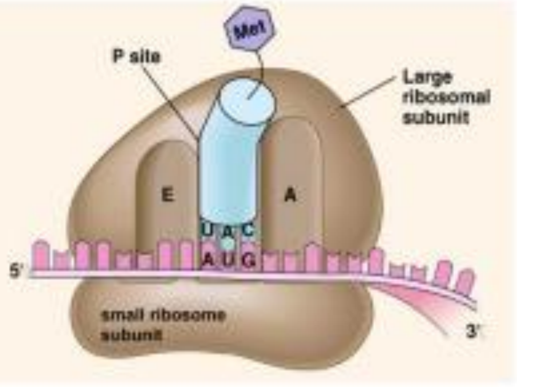
Terminology



❑**genome:** the sum of all the genetic material of an organism, cell or organelle, which copy is transmited to offspring (genes; non-coding sequences are included as well)

❑**genotype:** genetic constitution of an organism represented by a set of alleles of its genome (relative to individuals of that specie)

phenotype: the sum of characteristics, genotype manifestation in the environment

metabolism: a set of processes for energy and building the substances necessary for the biosynthesis of cellular components; term growth, reproduction and realization of genetic information

❑**ribosomes:** key components in cell apparatus, create cellular proteins according to gene instructions

Living organisms are made up by cells

- variability of the manifestations of life versus the unity of their foundations
- cellular structure based on similar ingredients occurs at all life forms
- Schleiden and Schwann in 30s of the 19th century: cells are the building blocks of life

Theodore Schwann (1810-1882)

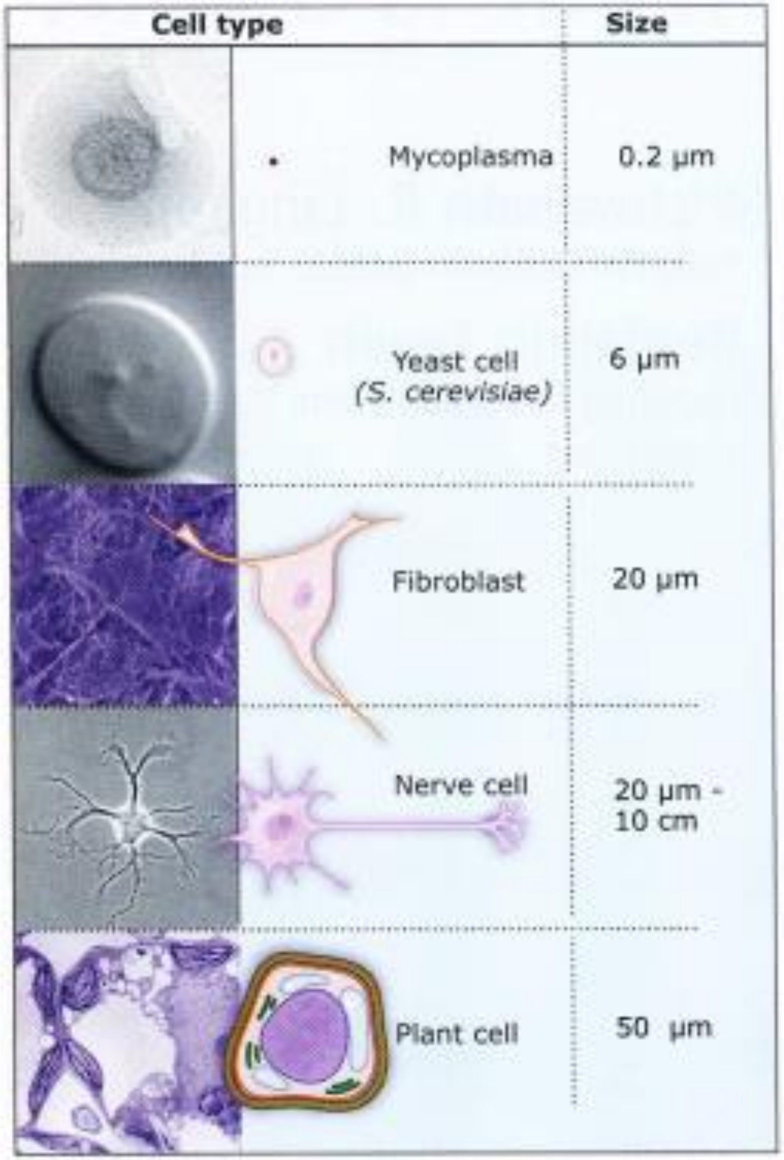
1. All living organisms are composed of one or more cells.
2. The cell is the basic unit of structure and organization in organisms.
3. Cells arise from pre-existing cells.

Matthias Jakob Schleiden (1804-1881)

Cells can differ substantially from each other…

variability in size and shape…

can live freely or be tied to a matrix or other cells



…still they have much in common

Are separated from the outer world by plasma membrane (with characteristic phospholipid structure)

Plasma membrane systems control import into the cell and export from the cell

Cellular structures are build up from food molecules processed by cells own systems using energy

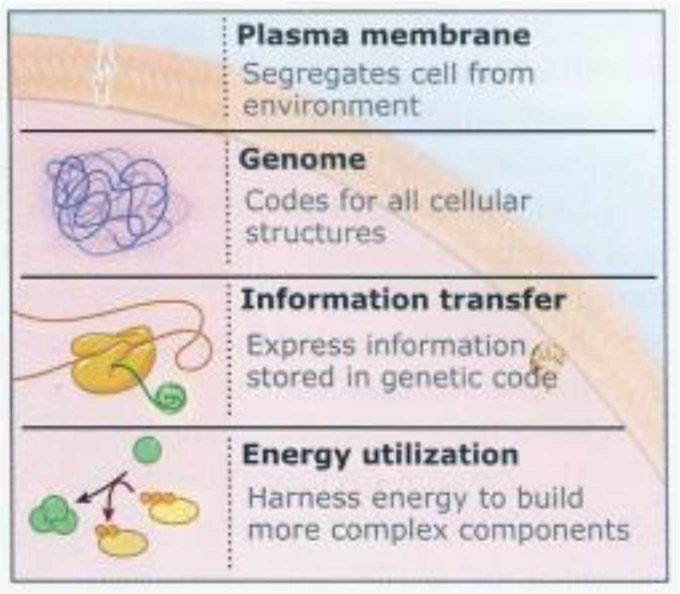
Contain genetic material carrying information needed to create/restock all cell components

Dispose of system for gene expression through which genetic information is conveyed into practical use

Particular proteins or RNAs (defined by genes) can form structures of higher order

Minimal requirements for the existence of a living cell

Plasma membrane (to separate cell from outer environment)
Ability to build up cellular structures from simple molecules via utilizing external energy sources
Presence of genetic information defining cell characteristics
Presence of system to express genetic information



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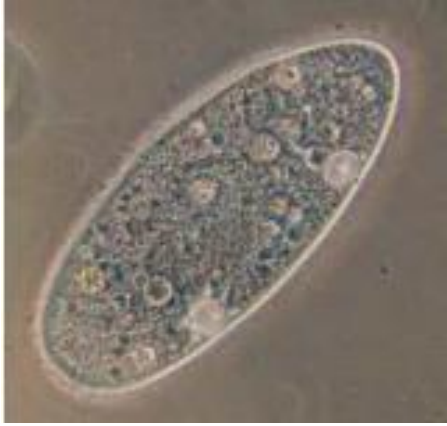
Unicellular organisms



- the simplest organisms
- they live as separate units
- reproduce
- successfully adapt to extreme conditions (high / low temperature, aerobic / anaerobic, etc.).
- often live inside other organisms

Multicellular organisms

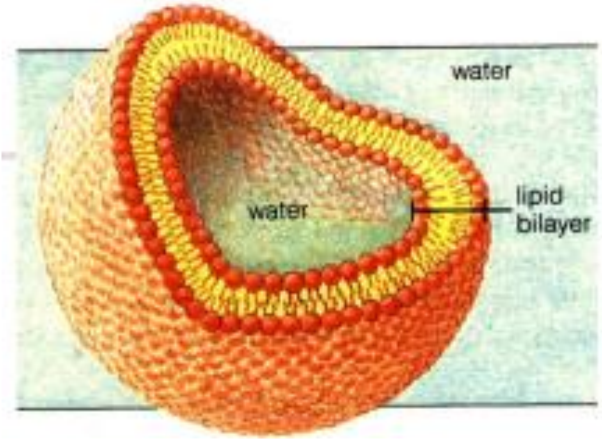
- cells specialize in certain functions - differentiate, that is - changing gene expression in different cells of the same organism, leads to their phenotypic diversification

- some cells maintain the undifferentiated state (stem cells)

- significant structural and functional specialization of cells, leads to division of labor inside the body (often accompanied by a loss of ability growth and division)

- cells communicate with each other to ensure proper function of the whole organism

Plasma membrane - function



- ensures cell autonomy (cellular components exist in a limited space)
- ensures that the aqueous medium within the cell differs from the outer medium
- contains protein complexes that control import and export of molecules through the membrane
- transmits signals between the external and internal cell environment

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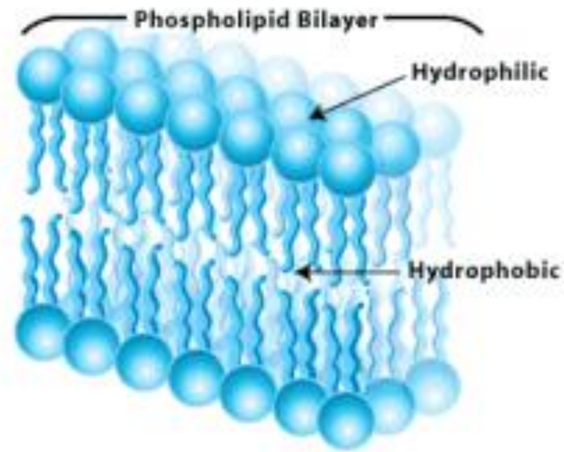
Plasma membrane - structure

- two-layer unit composed of phospholipids and proteins

Phospholipids

- Contain a **water soluble head**, which includes phosphate, exposed towards inner and outer membrane surface; and a **hydrophobic part** (a pair of fatty acid chains), which form membrane body



Molecules that carry both hydrophobic and hydrophilic area called **amphipathic**

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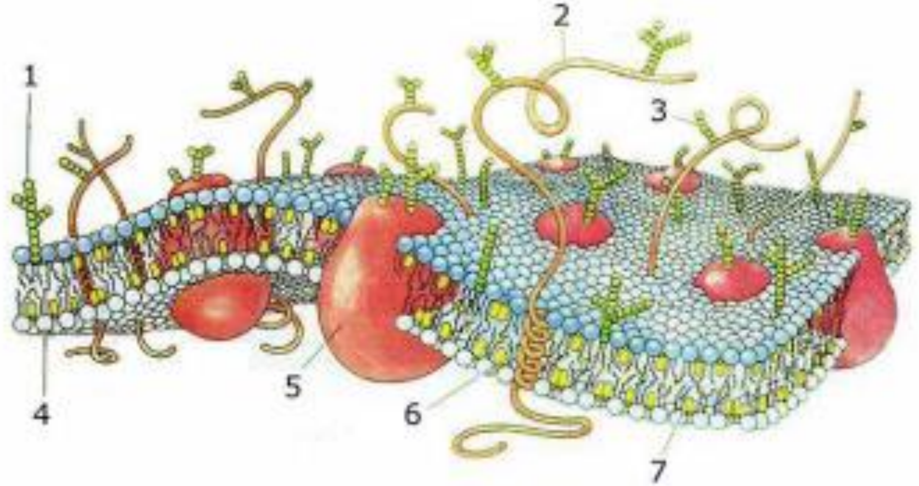
Plasma membrane - structure

• aquatic environment inside and outside the cells results in aggregation of hydrophobic lipid strings (forming the inner environment of the membrane), hydrophilic (charged phosphate) heads form the outer surfaces of the membrane

• lipid bilayer membrane allows for merging membranes and creates suitable environment for binding proteins



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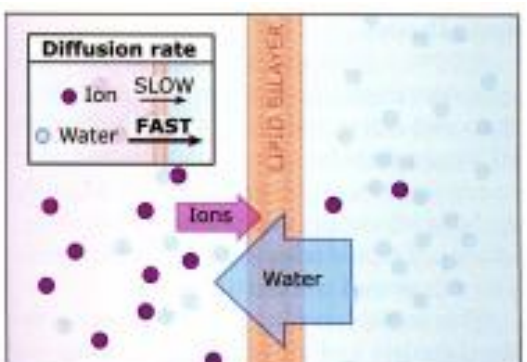
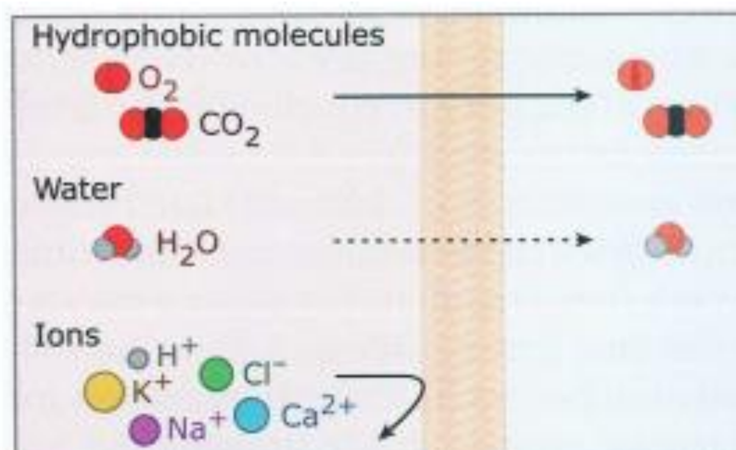
Plasma membrane - permeability

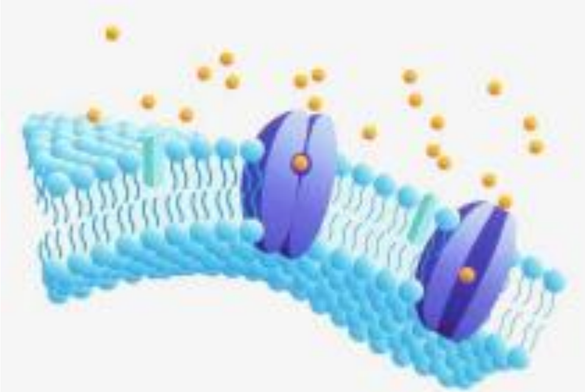
- membrane is not freely permeable to ions, small charged (hydrophilic) molecules and large molecules
- water molecules and hydrophobic molecules can pass through the membrane
- different ion concentrations on both sides of the membrane may create osmotic pressure (the movement of water molecules through the membrane towards the environment with a higher concentration of ions)
- risk of cell damage



When the ion concentrations on either side of a membrane differ, water moves across to equalize the concentration of solutes on both sides.



Cells manage their content



- intracellular pH and ion content are subjected to tight regulation
- specialised membrane transporters help to achieve required balance
- metabolism substrates (energy sources) must also pass through plasma membrane, as well as basic components of cellular structures
- unwanted metabolic products or ions must be exported through the membrane
- both directions have a high transport selectivity
- the ability of cells to maintain stable internal environment is called homeostasis

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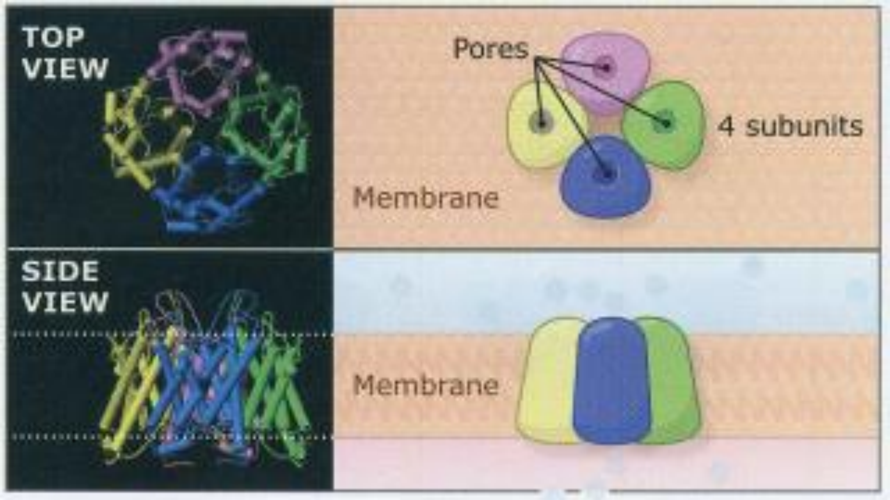
Protein channels control ion passage through plasma membrane

- create a channel in lipid bilayer
- the outer surface of protein channel is in contact with membrane lipids
- inner surface is surrounded by aqueous medium
- ions and hydrophilic molecules pass through the channel without getting into contact with membrane lipids



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Ion channels and protein carriers

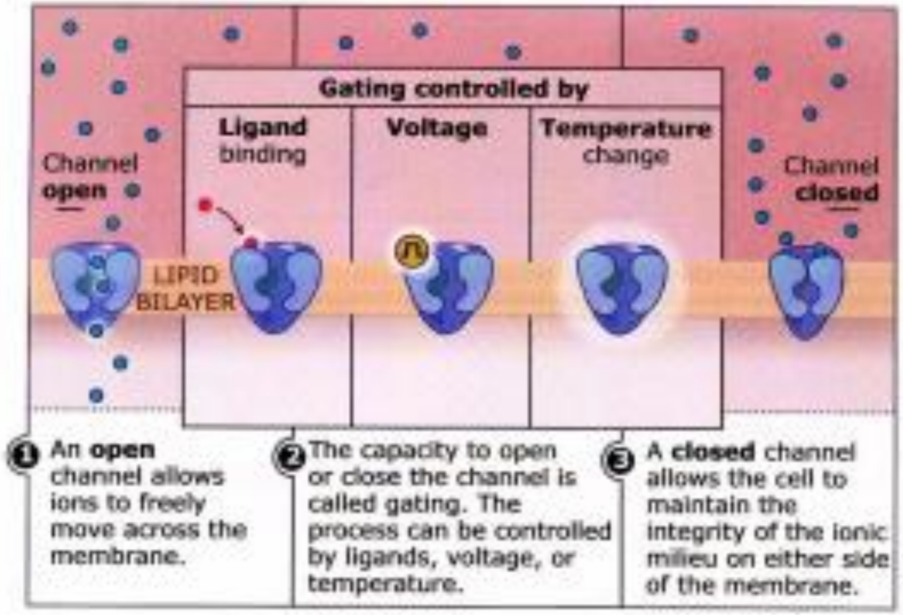
- Two mechanisms to transfer ions across membrane: according to gradient direction or against the gradient
- Ion channels are used to transport ions (without energy requirements) from places with higher ion concentration to places with lower ion concentration (in gradient direction)
- Protein carriers transport ions against electrochemical gradient, which requires energy

Controlling ion channels

Cannot be open all the time (ion concentrations would be equalized)

Open up by undertaking a conformational shift

conformational shift can be induced by various stimuli (signal molecule, electric voltage, temperature)



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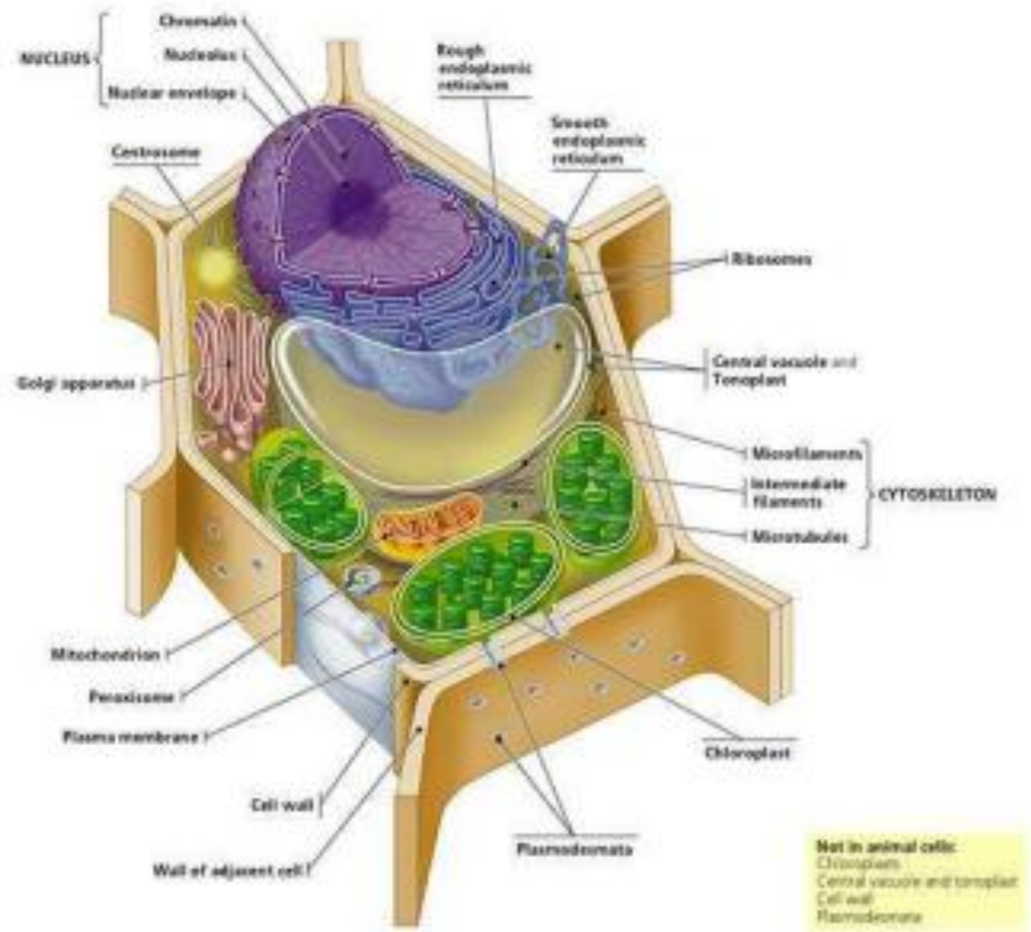
Cell membrane is not a firm/hard structure

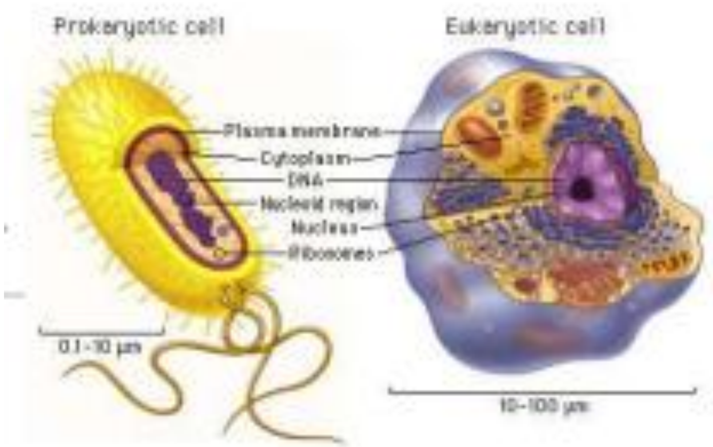
But a weak, flexible and fragile one

Mechanic support is often provided by cell wall, placed outside cell membrane, common in bacterial and plant cells

Animal cells are supported by cytoskeleton components



Two types of living cells

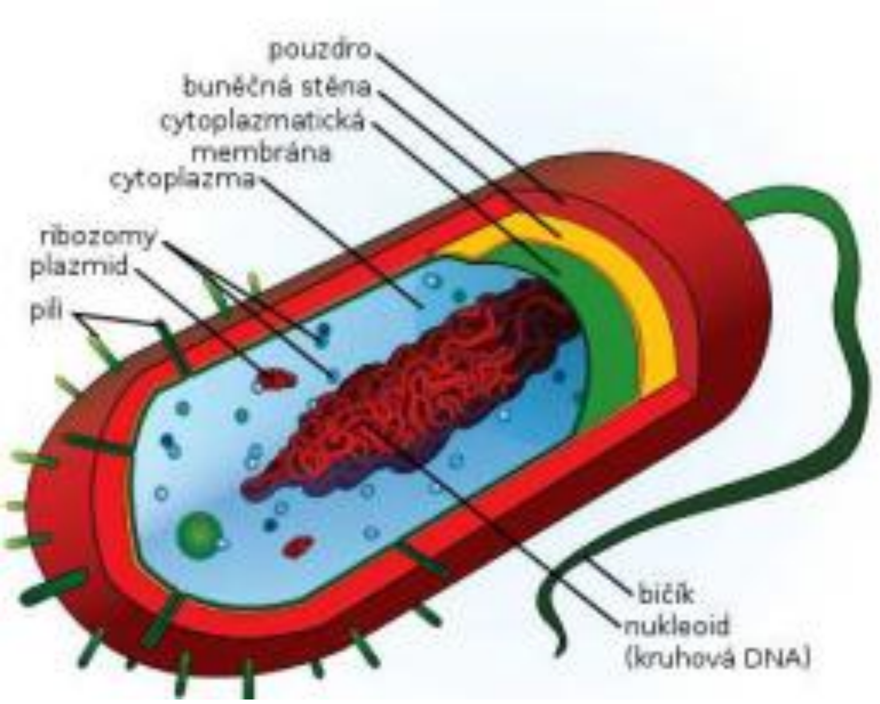


Classification by internal division, compartmentalization (compartment = membrane enclosed space)

prokaryotic cell: simpler, consists of only one compartment with the genetic material, apparatus, and products of gene expression

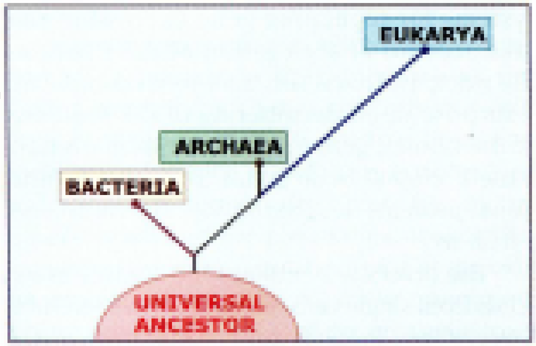
eukaryotic cell: complex, comprising at least two compartments, one of which contains the genetic material

Prokaryotes



- Unicellular organisms
- cells are surrounded by a membrane
- membrane surrounded by a cell wall providing protection
- DNA located in the cytoplasm
- it includes all chemical and structural components necessary for life
- all the genetic information present on one chromosome

Two types of prokaryotes: bacteria and archaea



phylogenetic relationship of these groups was determined relatively recently modern methods (particularly DNA sequencing): archaea are a separate group of prokaryotes

archaea have the appearance and structure similar to bacteria: Small single-celled organisms without internal membranes

they live in extreme conditions (high temperatures, acidity, salt content)

archaea often use unusual metabolic pathways, show chemical differences in the construction of cell walls, have an apparatus for **gene expression, which is more like in eukaryotes than bacteria**

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The genetic material of prokaryote

the simplest **genome** are present in bacteria that live freely
but within other organisms (**Mycoplasma**)
Host provides compounds which bacteria need, but cannot create
their genome contains only about 500 genes that encode a basic structural cellular components
genome of bacteria comprises at least **1500 genes** that encode the structural elements in addition to enzymes and also more advanced system for gene expression regulation

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classification of bacteria

2 groups that diverged about 2 billion years ago:
Gram-negative (e.g. E. coli) and
Gram-positive (e.g. B. subtitlis)
depending on how they react with Gram stain
sensitivity given by dye interaction with the cell wall

Hans Joachim Gram
(1853-1938)

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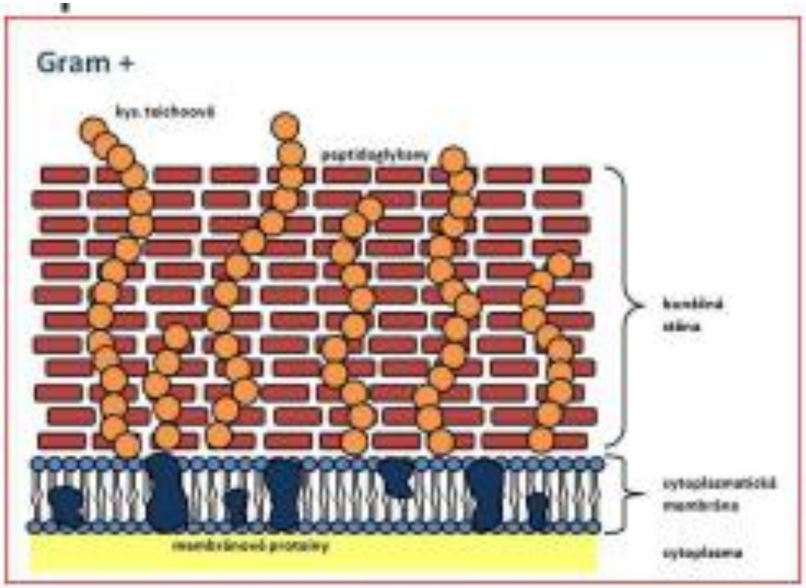
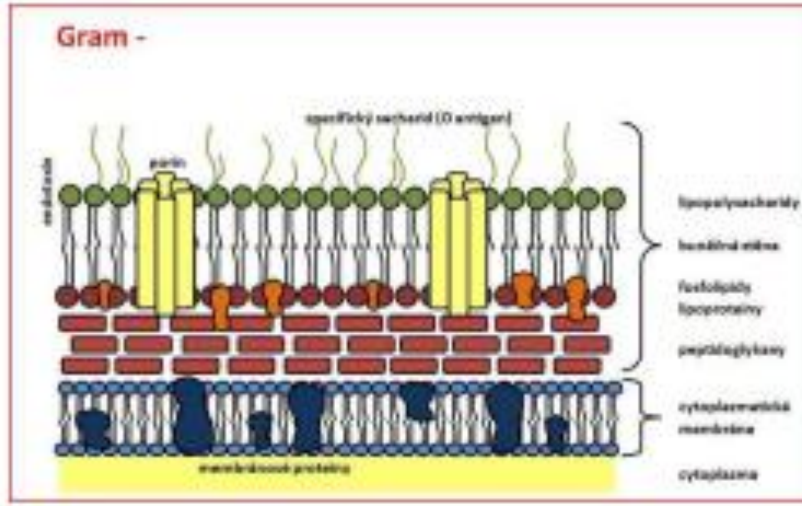
Gram staining





G+ bacteria have plasma membrane surrounded by a cell wall formed by proteoglycans and polysaccharides (blue / violet color)
Gram-negative bacteria have the outside wall surrounded by lipopolysaccharide layer (red / pink color)

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Bacteria - a model for research of basic cellular processes

advantages:

unicellular microorganisms, uniformity of response to external stimuli

low number of genes

haploid state (only one copy of each gene)

possibility of culturing under strictly controlled conditions (defined precisely by medium with the content of salts and carbon source)

high growth rate, doubling time is only 20 minutes

the possibility of storage in cold boxes (-70 °C) for 20 or more years

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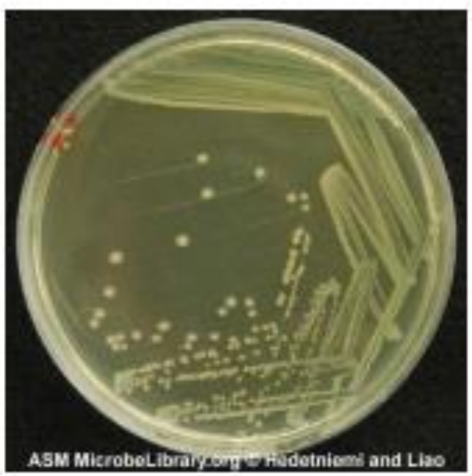
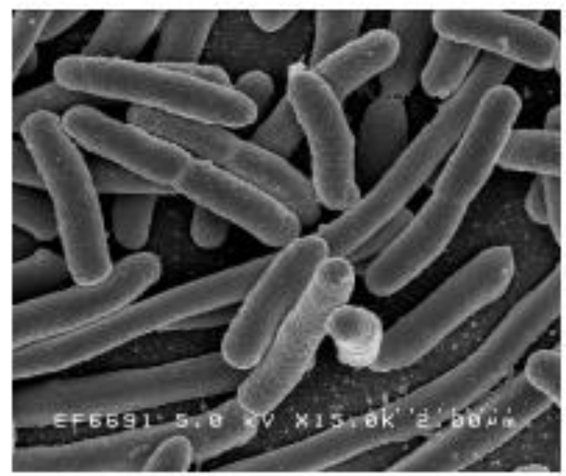
Model bacterium - *Escherichia coli*

rod-shaped bacteria (size 1 x 2.5 micron)
the natural environment of the intestine (colon- because "coli")
belongs among Gram-negative bacteria





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Where can we find bacteria in nature?

Almost everywhere (60 km high in the atmosphere, 11 km below sea level, in both fresh and salt water or sewage, soil, plant roots or in bodies of animals)

the number of bacteria on earth is huge (amounts of bacterial carbon on Earth corresponds to the amount of carbon in plants)

the bacteria is likely to constitute more than half of live mass of Earth

Prokaryotes are very adaptable

their lifestyle is varied and can adapt to extreme conditions (pH, presence of oxygen, temperature, etc.).

Classification according to the ability to grow at different temperatures:

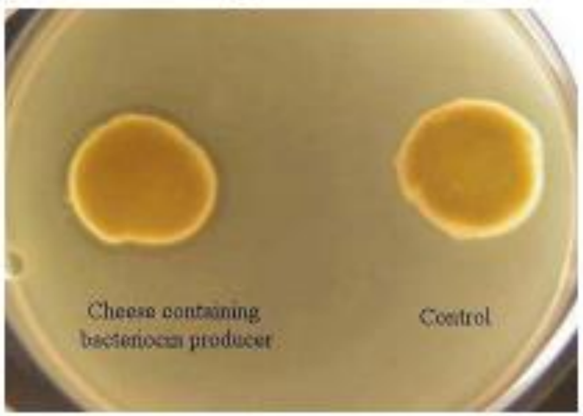
mesophilic: grow best between 25 and 40 of °C (this includes the human pathogens)

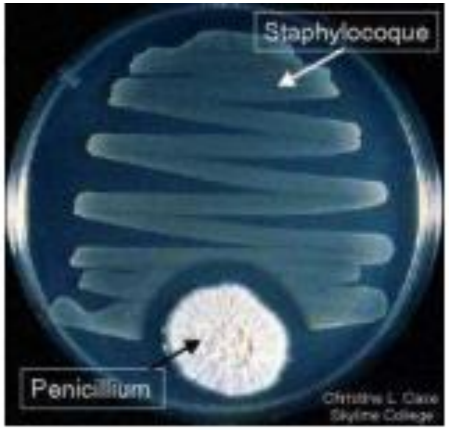
psychrophilic: grow best between 15 and 20 °C (but there are also those that live at 0 °C) - a favorite environment - cold water and land

thermophilic: grow best between 50 and 60 °C (some tolerate even 110 °C)

Bacteria are sensitive to natural substances

Various bacteria in the same environment compete for resources excretion of toxic proteins, e.g. bacteriocins - kill related bacteria, but no strains - producers (utilization of bacteriocin plasmids as vectors)





Creation of antibiotics (clinical use)

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Some bacteria are harmful, others are useful

a small portion of pathogenic bacteria: the originator of infectious diseases (cholera, tuberculosis, anthrax, syphilis, gonorrhea, whooping cough, diphtheria, etc.), what contributes to the eradication: sanitation, clean water, soap, flush toilets, as well as vaccinations and antibiotics

Most bacteria have a positive meaning: it contributes to the balance of ecosystem (decomposition of dead bodies of plants and animals)

destruction of waste products of human activity and pollution

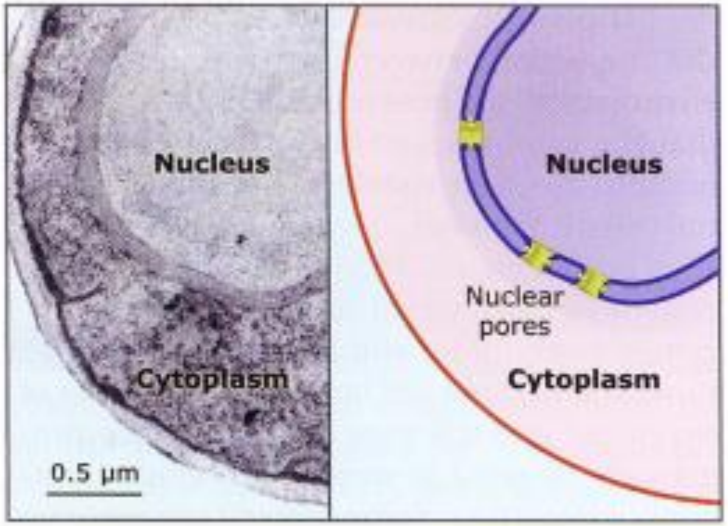
higher life forms could not survive without bacteria

Eukaryotic cell contains several compartments

increasing the complexity of the cell - the division of labor at the cellular level, interior space is divided into two main sections sealed by membrane: cytoplasm and nucleus

macromolecules are transported into and from the nucleus via the nuclear pores (protein channels)

pores are fully permeable to smaller molecules, i.e. the aqueous environment of the nucleus does not differ from the cytoplasm

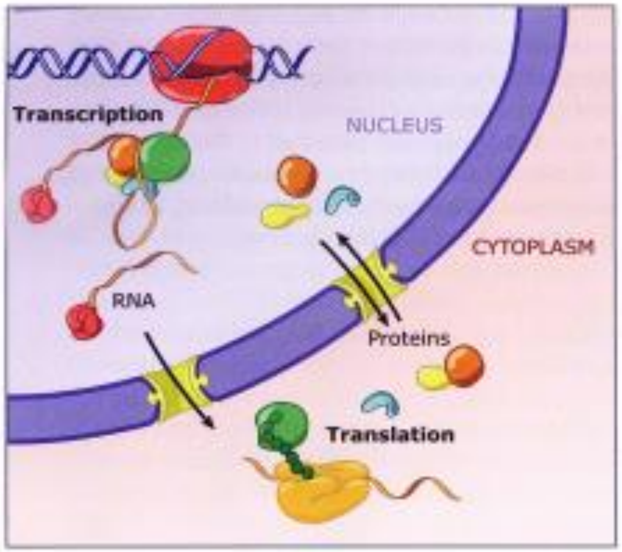


Genetic material is located in the nucleus

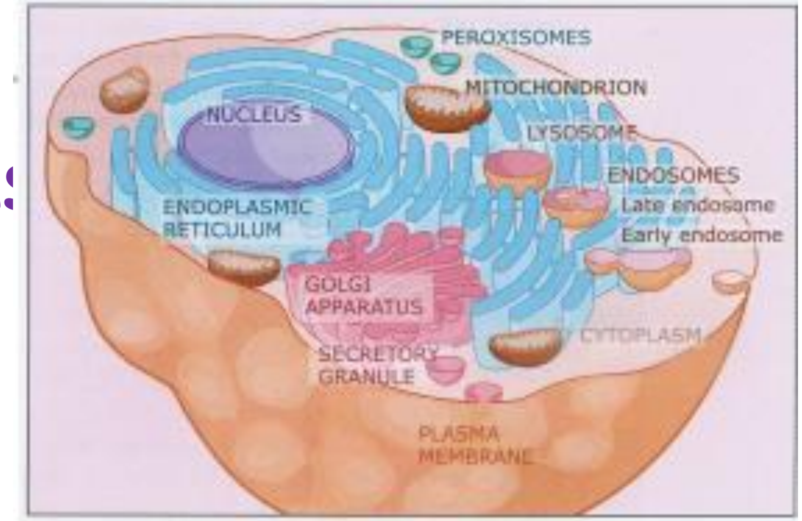
unlike prokaryotes eukaryotes genome must ensure specification of new structural elements, define the location of proteins into the correct sections, use a more complex mechanism of gene regulation

Genetic complexity of eukaryotes:

the simplest single-celled organisms eukaryotes carry about 5,000 genes, human about 20000 genes encoding proteins



Eukaryotic cell contains organelles



surrounded by membranes with
the same structural features as the plasma membrane

cytoplasmic = organelles + cytosol
cytosol is an aqueous environment of the cytoplasm, where proteins are synthesized, which remain either in the cytosol or are transported to any organelle or outside of the cell
organelle membranes are permeable, so the inner organelles environment differs from the cytosol (the exception is nucleus with its pores)

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Eukaryotic cell contains additonal organelles

endoplasmic reticulum - protein folding, assembling oligomers , (ribosomes-translation)
Golgi apparatus - secretion of proteins and other material outside the cell
lysosomes - containing digestive enzymes – decay of molecules
mitochondria - size, shape, containing circular DNA, resemble bacteria - a specialist in energy recovery - respiration
chloroplasts - specialized for photosynthesis, contain chlorophyll and other molecules necessary for capturing light, containing circular DNA like mitochondria

The diversity of eukaryotes

Unlike two genetically distinctive branches of prokaryotes, all eukaryotic organisms are genetically related

originate from a common ancestor

unicellular eukaryotes: yeast, protozoa

multicellular eukaryotes: plants, fungi and animals

Two main cell types of eukaryotes

somatic cells and gametes

in most multicellular organisms, cells are specialized into tissues and organs

Gametes are part of the reproductive system and participate in the formation of the next generation

somatic cells form the body, creating good conditions for the functioning of the gametes, do not participate in reproduction

Model organisms

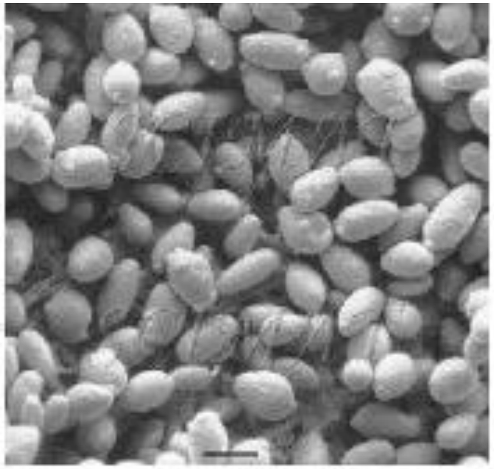
For practical reasons they are preferred in research

It assumes that the gained knowledge will apply in the other organisms, at least for those related to model organisms
it is not always true for human medicine or agriculture that we should examine directly target organisms

Yeast - model unicellular eukaryotes

unicellular eukaryote - similar benefits as bacteria
genome was sequenced first (in eukaryotes) - in 1996
belong among fungi - similar to animals and plants
alternation of diploid and haploid phase, you can work with haploid cultures, which facilitates genetic analysis
haploid genome contains only about 6,000 genes

Yeast



only few genes (about 5%) contain introns
They grow in a chemically defined medium, forming colonies on agar plates
the generation time of approximately 90 minutes
the ability to easily preserve in frozen state
specific multiplication by budding
model is suitable for studying the function of genes and cell cycle

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Nematodes

Caenorhabditis elegans
non-pathogenic soil nematodes
genome has a 7x higher DNA content than yeast
higher content of introns and non-coding sequences
1 mm body composed of 959 cells
evolution of each one from the original zygote is described
model for studying development, apoptosis, aging
RNA interference was first described in this model

C. elegans

S. Brenner
(nar. 1927)

Flies

T.H. Morgan
(1866-1645)

***Drosophila melanogaster*:**
life cycle of two weeks
14 000 *genes*
research on cell differentiation, development of an organism, cell signaling and behavior

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Zebrafish - a model for the study of evolution of vertebrates

Zebrafish/Danio rerio: small freshwater fish (2,5 cm)

fertilized egg develops outside the womb - can be monitored by microscopy

Development from egg to adult organism takes 3 months, thanks to the transparency we can follow the development of internal organs

Easy microinjection of foreign DNA into the egg

Molecular genetics of development

25 chromosomes, 75% homology with the human genome

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Mouse

model organism for humans
lives 1-3 years, reaching sexual maturity after 4 weeks
contains a 20 chromosome pairs
less than 1% of mouse genes does not have a human homolog
used to study gene function

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Human

for ethical reasons we can not experiment with people
it is possible to cultivate human or animal cells in culture
immortal cell lines (e.g. HeLa cells) are formed by tumor cells
HeLa cells are tumor cells derived from cervical cancer of Henrietta Lacks in 1951
cell line is a suitable model for molecular biology studies

Arabidopsis – model for plants

molecular biology of plant has historically been somewhat lagging behind other organisms

often they have many genes (rice: 40 000 to 50 000 genes)

reason: they can not protect themselves by movement, thus accumulate genes for protection and adaptation

the challenge now: genetic improvement of crops

Arabidopsis thaliana: structural simplicity, small genome, five pairs of chromosomes and about 25,000 genes

maturing plants to produce seeds takes 6 to 10 weeks

can be cultivated in the haploid state - advantage for genetic analysis

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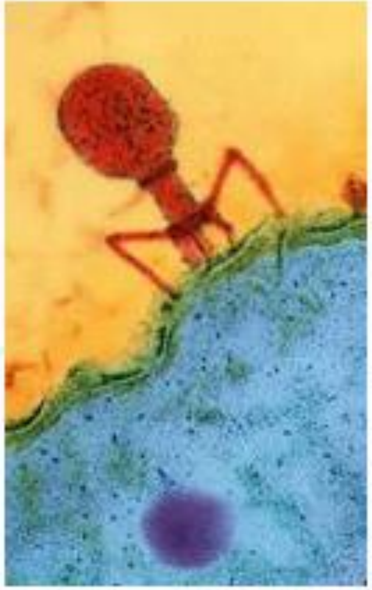
Virus



does not have the cell structure

contain their own genes wrapped in a protein coat,
but it can not express them
lacks apparatus which ensures the cells energy
cellular parasite, replication and expression of viral genes is carried out by infected cell
viral genetic information is stored in the DNA or RNA
he is able to cause disease
applies in genetic engineering

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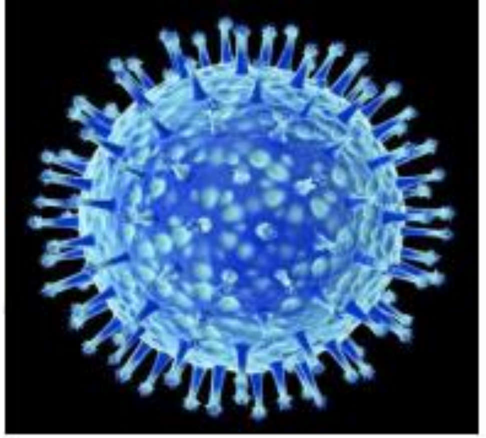
Bacterial virus = bacteriophage

infects a bacterial cell that is caused to produce new bacteriophages, eventually bursts, releasing a new generation of bacteriophages

each of the new virions can infect additional bacteria

within a few hours phage epidemic can destroy bacteria cultures of the number exceeding several human population

Human viruses



infects human cells, originator of common diseases (measles, mumps, chickenpox, colds and flu) and serious diseases (polio, Ebola, AIDS)

Infection of less dangerous virus may provide resistance against much more dangerous virus

viral infection can not be cured; necessary prevention – immunization

can transfer genes from one organism to another host (importance for evolution and genetic engineering)

Antibiotics have no sense in fighting viral infections, can only help with parallel bacterial infection

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Other genetic elements

are widespread in the biosphere

various functions: they can cause serious illness or existence is almost unnoticeable

They carry genetic information, but do not have tools for the life functions, do not exist outside the host cell

Viruses are one of the most advanced

viroids and plasmids: autonomous nucleic acid molecules that do not have protein shell

viroids are RNA molecules that infect plants and force them to produce new viroids released into the environment

Other genetic elements

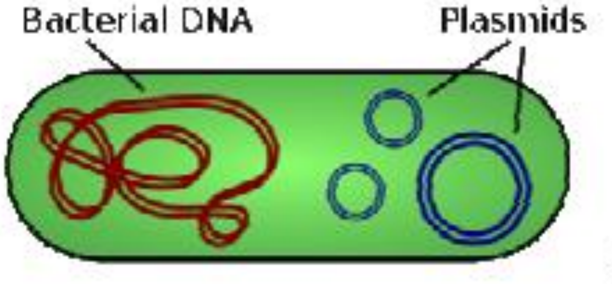
plasmids

DNA molecules that are stably maintained within the host cell

They may pass from one cell to another only if between them there is contact

do not kill the host cell

widely used in genetic engineering



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Other genetic elements

transposable elements (transposons)

DNA molecules that do not replicate as separate units

for its replication they require incorporation into other DNA molecules that have self replication ability

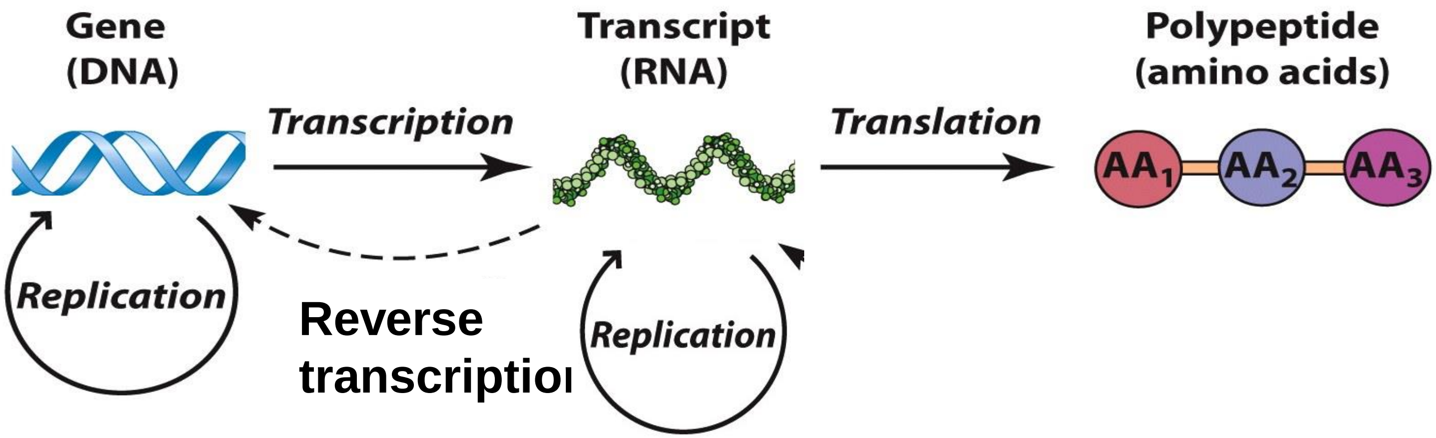
have the ability to jump from one host DNA to another

Other genetic elements

prions

infectious protein molecules
they contain no nucleic acid
infect cells of the nervous system of animals and cause serious illness (eg. mad cow disease)
represent incorrectly folded version of the normal protein of the nerve cells
if they penetrate into the cell they cause incorrect folding of the corresponding normal protein which kills the cell

The central dogma of molecular biology



- genetic information is passed by transfer of the DNA into RNA and protein (this postulate is called the central dogma of MB)
- In some viruses (e.g. HIV), RNA is used as a template for DNA synthesis by reverse transcription
- many genes encode a polypeptide, however RNA molecules in the cell play important roles

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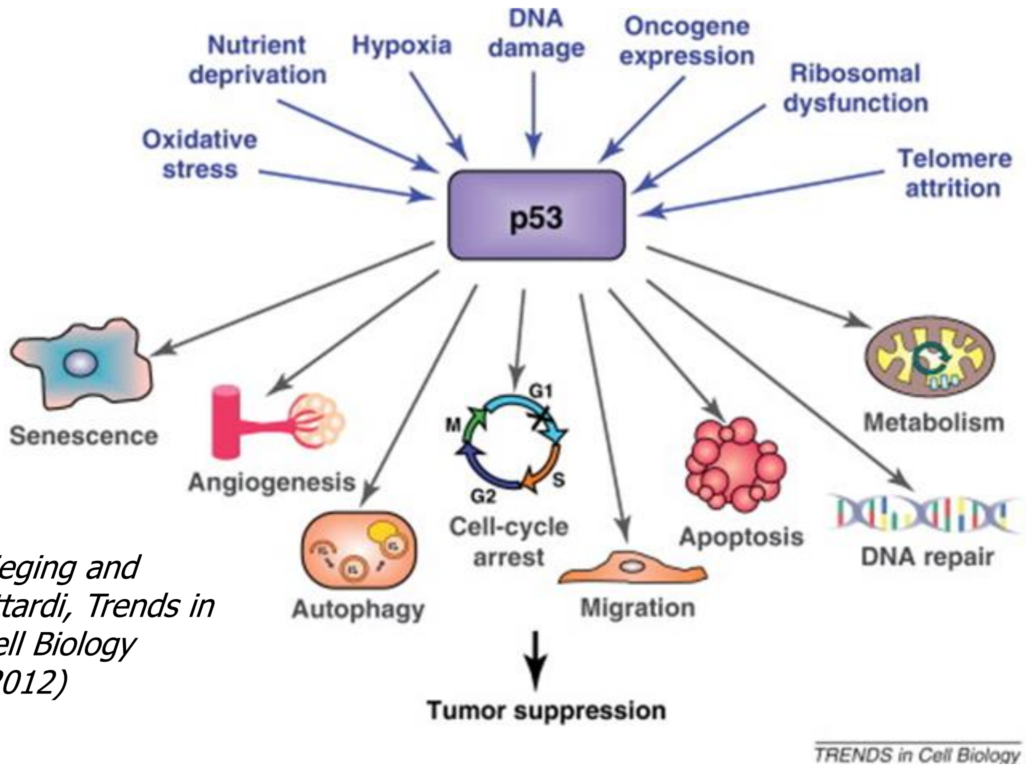
p53 tumor suppressor and p53 binding to human genome



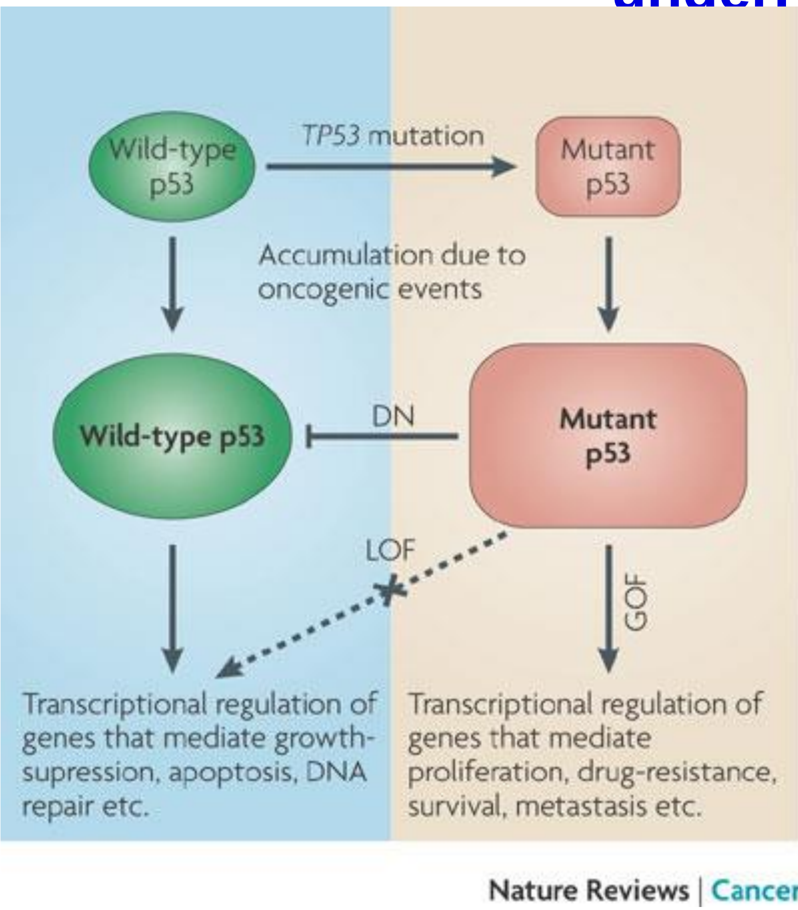
Bieging and Attardi, Trends in Cell Biology (2012)

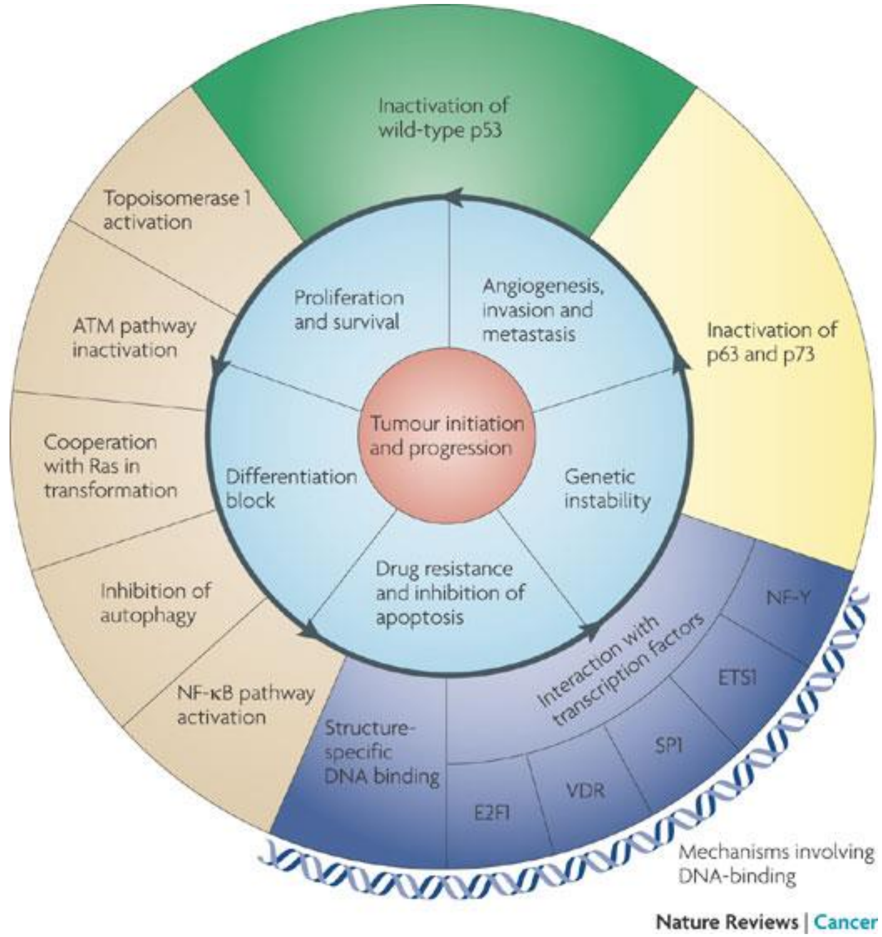
- maintaining genomic stability
- transcription-dependent tumor suppres

- in response to various inputs, the p53 protein becomes stabilized
- upon stabilization of p53, various transcriptional outputs determined by:
- the strength of the p53 RE
- posttranslational modification status of p53
- specific p53 binding partners
- the epigenetic landscape of target gene promoter
- conformation of DNA, non-B DNA structures

How does p53 select its targets?

Selected oncogenic properties of mutant p53 and their underlying





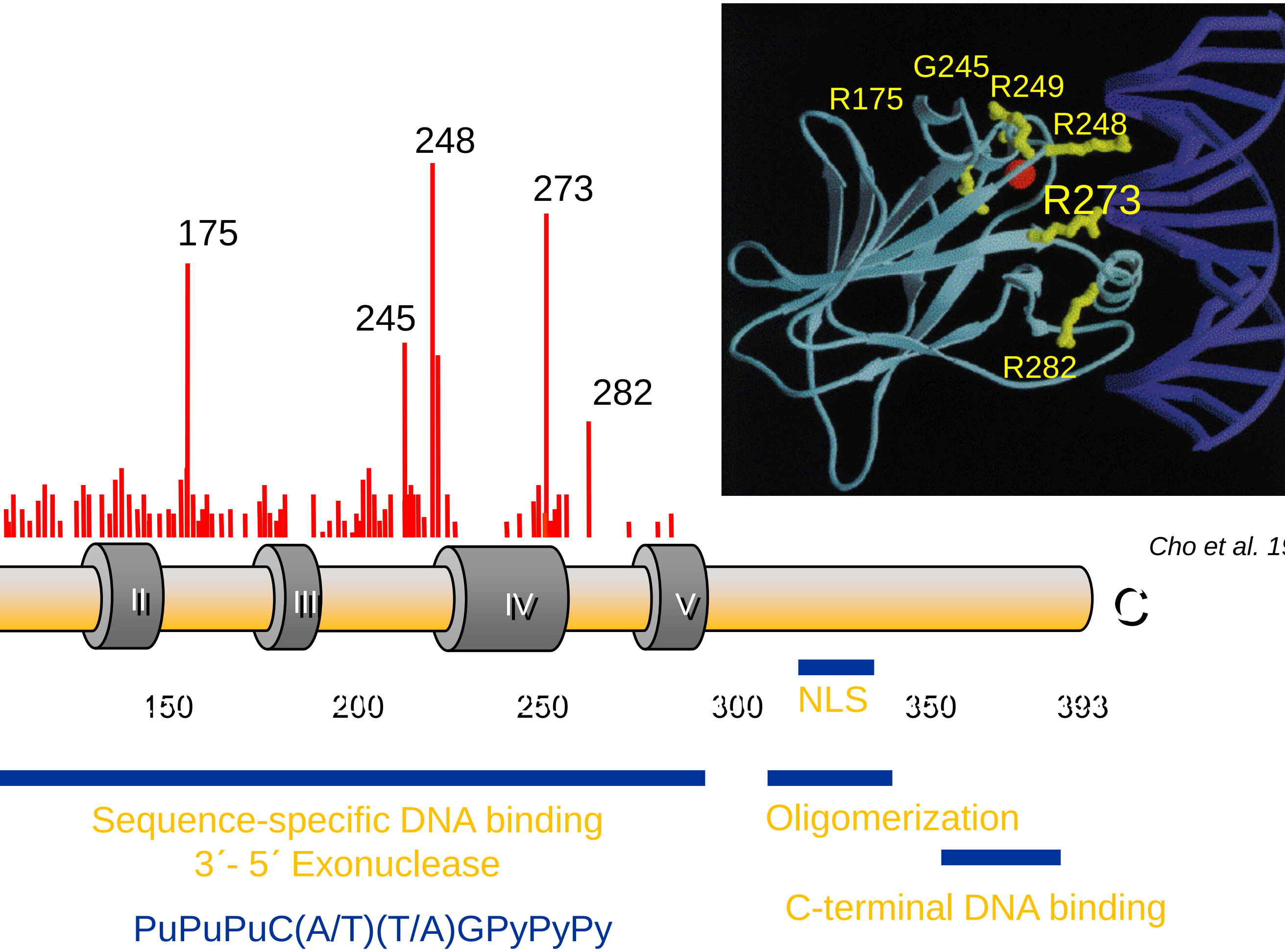
Ran Brosh & Varda Rotter
Nature Reviews Cancer 9, 701-713 (2009)

Structure/sequence motifs in DNA

MAR/SAR elements in DNA (mutp53CD, C-terminus)
(Muller et al., 1996; Deppert et al., 2000)

Mutation of TP53

A point mutation in *TP53* leads to loss of p53 tumor suppressive function



Cho et al. 1994

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