Alberts - Essential Cell Biology

Chapter 1: Introduction to Cells

The cell has a distinct anatomy. It is enclosed by a *membrane*, in the middle lies the *nucleus*. Around the nucleus lies the *cytoplasm*, that fills the cell's interior together with the *organelles.* The entire cell is surrounded by the *extracellular matrix*, which separates one cell from another.

The external membrane of a cell is called the *plasma membrane*, while the membranes surrounding organelles are called *internal membranes*.

Cells that have a nucleus are called *eucaryotes*, cells that do not have a nucleus are *prokaryotes*. The possession of a nucleus goes hand in hand with possession of other organelles.

The nucleus is enclosed within 2 concentric membranes that form the *nuclear envelope*. The nucleus contains *DNA*, these giant molecules become visible under the microscope as chromosomes. Bacteria do not keep their DNA enclosed in a envelope.

The *mitochondria* is enclosed in 2 separate membranes (inner one is folded). Mitochondria contain their own DNA and reproduce by dividing in 2 (they are thought to derive from bacteria, because of their close resemblance). Mitochondria are generators of chemical energy, they harness energy from the oxidation of food molecules to produce the basic chemical fuel *adenosine triphosphate* (ATP).

During this process the mitochondria uses O_2 and produces CO_2. Organisms that use oxygen in that way are called *aerobic*, organisms that are unable to live in environments containing oxygen are termed *anaerobic*.

The cytoplasm contains other organelles as well, most of them are enclosed by a single membrane:

- The *endoplasmatic reticulum*, an irregular maze of spaces enclosed by a membrane, is the site at which most cell membrane components, as well as materials destined for export from cell, are made.
- The *Golgi apparatus*, stacks of flattened membrane bounded sacs, receives and often modifies chemically the molecules made in the E.R. and then directs them to the exterior of the cell or to various other locations.
- *Lysosomes* are small organelles in which cellular digestion occurs, releasing nutrients from food particles and breaking down unwanted molecules for recycling or excretion.
- *Perixosomes* are small membrane bounded vesicles that provide a contained environment for reaction where a dangerous reactive chemical (hydrogen peroxide) is generated and degraded.

Membranes also forms many different types of small *vesicles* involved in the transport of materials between one membrane bound organelle and another. The membrane bounded vesicles pinch off from the membrane of one organelle and fuse with another.

The cell's cytoplasm excluding all organelles is called the *cytosol*. It contains a host of large and small molecules. The cytosol is the site of many chemical reactions that are fundamental

to the cell's existence. The early steps in breakdown of nutrient molecules take place within the cytosol and it is in the cytosol that the cell manufactures proteins. The *ribosomes* are the tiny molecular machines that make proteins.

The system of filaments in the cells is called the *cytoskeleton*:

- *Actin filaments*, thinnest of all, present in all cells but especially in muscle cells, where they serve as part of the machinery that generates contractile forces.
- *Microtubules*, thickest filament, they have the form of minute hollow tubes, they become reorganised in to spectacular arrays in dividing cells.
- Intermediate filaments, intermediate in thickness, serves to strengthen the cell mechanically.

Essential concepts:

1. Cells are the fundamental units of life.
2. Cells of animal and plant tissue are typically 5-20 µm in diameter and can be seen using a light microscope, which also reveals some of their internal organelles.
3. The electron microscope permits the smaller organelles and even individual molecules to be seen, but specimens require elaborate preparation and cannot be viewed alive.
4. The most prominent organelle in most plant and animal cells is the nucleus. This contains the genetic information of the organism, stored in the structure of the DNA molecules. The rest of the cell's contents, excluding the nucleus, constitute the cytoplasm.
5. The cytoplasm of plant and animal cells contains a variety of other internal membrane bounded organelles with specialized chemical functions. Such organelles include mitochondria, which carry out the oxidation of food molecules, and in plant cells, chloroplasts that perform photosynthesis.
6. The remaining intracellular compartment, excluding the membrane bounded organelles, is the cytosol. This contains a concentrated mixture of large and small molecules that carry out many essential biochemical processes.
7. A system of protein filaments called the cytoskeleton extends throughout the cytosol. This controls the shape and movement of the cell and enables organelles and molecules to be transported from one location to another in the cytoplasm.
8. All present day cells are believed to have evolved from the same ancestral cell that existed more than 3000 million years ago.
9. All cells contain DNA as a store for genetic information and use it to guide the synthesis of proteins, and all cells make their DNA and their proteins from the same two small sets of building blocks.
10. Bacteria, the simplest of present-day living cells, are prokaryotes: although they contain DNA they lack a nucleus and other organelles and probably resemble most closely the ancestral cell.
11. Different species of bacteria are diverse in their chemical capabilities and inhabit an amazingly wide range of habitats. Two fundamental evolutionary subdivisions are recognized: eubacteria and archaebacteria.

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Chapter 2 Chemical components of cells

Chemistry of life is based on carbon compounds → organic chemistry

Chemical bonds
Atom: is the smallest particle that still retains its distinctive chemical propeties. The centre is a massive posetively charged nucleus, surrounded by a negatively charged cloud of electrons. They stay in orbit by electrostatic attraction. The nucleus containes positively charged protons and non-charged neutrons. The cloud of electrons has the exact opposite charge of the protons. Neutrons contribute to the structural stability of the nucleus.

Isotopes have a different neutron-count, but an equal proton-count. They are chemically identical.

The number of protons and neutrons determines the atom weight. The electrons are too light.

One Dalton = equal to the mass of a hydrogen atom.

Avogadro's number = $6{,}2 \times 10^{-23}$ gram
(mol x Na = gram)

Atoms are able to react because of their incomplete outer electron shells.

Ionic bond = when electrons are donated by one atom to another
Covalent bond = when two atoms share a pair of electrons

Valence = number of atoms that an atom must acquire or loose in order to attain a filled outer shell.
When an electron jumps from Na to Cl, both atoms become electricically charged ions.

Positive ions = cations
Negative ions = anions

Na^+ and Cl^- are bonded by an ionic bond. The structure is called a salt. It is a noncovalent bond.

A molecule is a cluster of atoms held by covalent bonds. Electrons are shared.

Bond strength is measured by the amount of energy that must be supplied to break the bond.

The making and breaking of covalent bonds are violent events. In living cells catalysts called enzymes control them.
Non-covalent bonds are weaker.

Covalent bond between multiple atoms is characterized by specific bond lengths, angles and energies.

A double bond is shorter and stronger than a single bond.

Two atoms attract the shared electrons each to different degrees.
F O Cl N Br I S C H
The F attracts the electrons strong, as the H does not.
A polar structure is one with positive charge concentrated toward one end and negative charge concentrated to the other end.

Polar covalent bonds allow molecules to interact through electrical forces.

A cell exists of 70% water.

In a water molecule the two H atoms are linked to the O by covalent bonds. This is a polar bond, because the electron distribution is unequal. The water molecules can form hydrogen bonds (waterbruggen). They help maintain structural stability. They also help large molecules to fold up in unique ways.

If a substance can form a hydrogen bond with water it will dissolve easily in water (hydrophilic).
Other substances do not form hydrogen bonds and will not dissolve in water (hydrophobic).

ACIDS AND BASES
The H atom in the molecule has almost given his electron away entirely. It almost exists as a naked positively charged hydrogen nucleus. In other words a proton (H^+). It can react with another negative charge to form e.g. a H_3O^+. The reverse reaction also takes place, so you have to imagine an equilibrium state.

An acid releases its proton, a base accepts the proton. The H^+ concentration is expressed in the pH scale.
A base of the water molecule is called a hydroxyl

Neutral when the pH is 7, acid when it is lower and base when it is higher.

Molecules in cells
A cell is build by carbon compounds, it can form large molecules. It can form 4 covalent bonds. The carbon compounds in the cell are called organic molecules.

Cells contain 4 families of small organic molecules: the sugars, the fatty acids, the amino acids and the nucleotides.

The sugars are monosaccharides with the formula $(CH_2O)_n$.
Sets of molecules with the same chemical formula but a different structure are called optical isomers.
Linking monosaccharides together can become polysaccharides. Links are formed by condensation reactions (a molecule of water is expelled). Hydrolysis is the opposite.
Glucose has a central role for the energy supply of a cell. Breaking the glucose frees energy. This glucose is called glycogen.
Sugars do not only function as the storage and production of energy, but also as polysaccharides. They can also form lipids, used in cell membranes.

A fatty acid molecule has a hydrocarbon chain, that is hydrophobic, and a carboxyl (COO^-) group, which is hydrophilic. The hydrocarbon chain is saturated (verzadigd). They are also an energy reserve and are stored in the cytoplasm of the cells.
Fatty acids and their derivates are lipids. They are insoluble in water. The most important function of fatty acids is the construction of cell membranes. They are formed by phospholipids.
The glycerol is joined by two fatty chains and one phosphate group. Because of the water hating chains, but the water loving phosphate group the molecule is called amphipathic.

The amino acids all posses a carboxyl group and an amino group linked by a single carbon atom. When they link together they form proteins. The links are called peptide bonds. The NH_2 is linked to the COOH. There are 20 very important proteins, the body can't do without. All proteins except 1 have optical isomers.
Proteins have many different functions, such as catalysing processes, build structural components, and produce movement.

The nucleotides are the subunits of DNA and RNA. It is made of nitrogen and a sugar and a phosphate. The sugar can be ribose (RNA) or desoxyribose (DNA).
The nitrogens are the bases for historical reasons. They are devided into Guanine, Cytosine, Adenine, Thymine, Uracil and Purine. Each nucleotide is named after the base it containes.
A nucleotide containing ribose has three phosphate groups attached to it, that can give enormous amounts of energy when they are disconnected.
The most fundamental role of nucleotides is the storage and retrieval of biological information.
RNA contains the bases G,C,A and U. It is based on ribose.
DNA contains the bases G,C,A and T. It is based on desoxyribose.
The RNA normally appears in a single chain, as the DNA appears in a double chain. This double chain is anti-parallel and holds together by hydrogen bonding between the bases. The G pairs with the C and the A pairs with the T/U.
The DNA and RNA transmit and store the hereditary information.

Each polymer grows by the addition of a monomer to the end of the chain through a condensation reaction. This is done with enzymes, to make sure that the right monomer is added. A polymer chain is not structured randomly, but specifically. As you can see there are millions of ways to combine the monomers, but only one is ask for at that particular time.

Long chains are flexible so that it can take on many shapes, or conformations.
Noncovalent bonds within the polymer, maybe weaker bonds, but give the polymer structure, that can't be changed. These bonds are formed by the ionic bond, hydrogen bond and the Van der Waals bond (an electrical attraction when two atoms come close together). Another force that is noncovalent is performed by the 3d-structure of water, which forces the polymer together so that it doesn't disrupt the network of water molecules. This is called hydrophobic interaction.

ESSENTIAL CONCEPTS

1. Living cells obey the same chemical and physical laws as nonliving things. Like all other forms of matter, they are composed of atoms, which are the smallest units of chemical elements.

2. Atoms are made of smaller particles. The nucleus of an atom containes protons, which are positively charged, and uncharged neutrons. The nucleus is surrounded by a cloud of negatively charged electrons.
3. The number of electrons in an atom is equal to the number of the protons in its nucleus. The nuclei of different isotopes of the same element contain the same number of protons but a different number of neutrons.
4. Living cells are made up of a limited number of elements, six of which -CHNOPS- make up 99% of their mass.
5. The number and arrangement of its electrons determine the chemical properties of an atom. An atom is most stable when all of its electrons are at their lowest possible energy level and when each electron shell is completely filled with electrons.
6. Chemical bonds form between atoms as electrons move to reach a more stable arrangement. Clusters of two or more atoms held together by chemical bonds are known as molecules.
7. When an electron jumps from one atom to another, two ions of opposite charge are formed; ionic bonds are formed by the mutual attraction of these charged atoms.
8. A covalent bond is formed when a pair of electrons is shared between adjacent atoms. If two pairs of electrons are shared, a double bond is formed.
9. Living organisms contain a distinctive set of small carbon-based molecules that are essentially the same for every living species. The main categories are sugars, fatty acids, amino acids and nucleotides.
10. Sugars are a primary source of chemical energy for cells and can be incorporated into polysaccharides for energy storage.
11. Fatty acids are also important for energy storage, but their most essential function is in the formation of cell membranes.
12. Polymers consisting of amino acids constitute the remarkably diverse and versatile macromolecules known as proteins.
13. Nucleotides play a central part in energy transfer and are the subunits from which the informational macromolecules, DNA and RNA, are made.
14. Macromolecules are intermediate both in size and in complexity between small molecules and cell organelles. They have many remarkable properties that are not easily deduced from the subunits from which they are made.
15. Macromolecules are made as polymers of subunits by repetitive condensation reactions. Their remarkable diversity arises from the fact that each macromolecule has a unique sequence of subunits.
16. Weak noncovalent bonds form between different regions of a macromolecule. These can cause the macromolecule to fold up into a unique three-dimensional shape, as seen most conspicuously in proteins.

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Chapter 3: Energy, catalysis and biosynthesis

The first law of thermodynamics states that energy can be converted from one form to another, but can not be created or destroyed.

The second law of thermodynamics expresses that in the universe (or in an isolated system) the degree of order can only increase, the quantity to measure this disorder is called entropy, the cell is not an isolated system and therefore is creating order with the use of energy from the environment, heat is released to the environment en thereby (creating disorder) total entropy increases.

Two opposing streams of chemical reactions occurring in cells, constitute metabolism:
- catabolic pathways: breakdown molecules, forming building blocks (generating energy)
- anabolic pathways: synthesis of molecules (use energy)

All animals live from energy stored within chemical bonds of molecules made by other organisms, plants in turn trap energy directly from sunlight, photosynthesis (plants and photosynthetic bacteria): magnetic energy in sunlight is converted into chemical bond energy.

The reaction of photosynthesis take place in 2 stages:
- first stage: energy from sunlight is captured and stored in chemical bond energy in specialised small molecules that act as carriers of energy and reactive chemical groups
- second stage: molecules that serve as energy carriers are used to help drive a carbon fixation process in which sugars are manufactured from carbon dioxide gas and water

$$light\ energy + CO_2 + H_2O \rightarrow sugars + O_2 + heat\ energy$$

All animal and plant cells are powered by chemical energy stored in chemical bonds of organic molecules, a cell is able to obtain energy from sugars or other organic molecules by allowing their carbon and hydrogen atoms to combine with oxygen to produce CO_2 and H_2O, a process called respiration.

Reduction and oxidation, electrons are transferred from one atom to another (always occur simultaneously), when a molecule in a cell picks up an electron it often picks up an proton (H^+), the net effect is the addition of an hydrogen atom to the molecule:
- oxidation: the removal of electrons, number of C-H bonds decrease, dehydrogenation
- reduction: the addition of electrons, number of C-H bond increase, hydrogenation

$$A + e^- + H^+ \rightarrow AH$$

A molecule requires an activation energy before it can undergo a chemical reaction, the kick of the energy barrier is greatly aided by a class of proteins, enzymes, each enzyme binds tightly, with the active site, to one or two molecules, called substrates, a substance that can lower the activation energy is termed a catalyst (they allow a much larger proportion of the random collision with surrounding molecules).

Cells must build highly ordered energy-rich molecules from small and simple ones, this is done through enzymes that directly couple energetically favourable reactions, which release energy and produce heat, to energetically unfavourable reactions, which produce biological order.

ΔG (G: free energy) measures the amount of disorder created in the universe when a reaction takes place, energetically favourable reaction are those that decrease free energy, they have a negative ΔG and create disorder, energetically unfavourable reactions, with a positive ΔG by themselves create order in the universe, these reaction can only take place if they are coupled to a second reaction with a negative ΔG so large that the ΔG of the entire process is negative.

For a reversible reaction: A → ← B, a large excess of A over B will tend to drive the reaction in the direction A → B, therefore the ΔG becomes more negative for the transition A → B (and more positive for the transition B → A) as the ratio of A to B increases, ΔG for a given reaction can thereby be written as the sum of 2 parts: the first, standard free-energy change (ΔG°) depends on the intrinsic characters of the reacting molecule; the second depends on their concentrations.

Chemical equilibrium is reached when the concentration effect just balances the push given to the reaction by ΔG°, so that there is no net change of free energy to drive the reaction in either direction, ΔG = 0.

Energy is stored as chemical bond energy in a small set of activated carrier molecules, which contain one or more energy rich bonds, the activated carriers store energy in an easily exchangeable form, either as a readily transferable chemical group or as high energy electrons, they can serve a dual role as a source of both energy and chemical groups in biosynthetic reactions, these molecules are also called coenzymes, the most important of the activated carrier molecules are ATP and (the closely related) NADH/NADPH.

A large part of the free energy that is released by oxidation is captured in a chemical useful form (rather than being released as heat), this is achieved by means of coupled reaction, coupling mechanisms require enzymes and are fundamental to all energy transactions of the cell, enzymes couple an energetically favourable reaction (such as oxidation of foodstuffs) to an energetically unfavourable reaction (such as the generation of an activated carrier molecule), as a result the amount of heat released by the oxidation reaction is reduced by exactly the amount of energy that is stored in the energy-rich covalent bonds of the activated carrier molecule.

ATP (adenosine triphosphate) serves as a convenient and versatile store of energy to drive a variety of chemical reactions, ATP is synthesised in an energetically unfavourable phosphorylation reaction in which a phosphate group is added to ADP (adenosine

diphosphate), the hydrolysis of ATP is energetically favourable, the generated ADP is then available for another round of the phosphorylation reaction, the energetically favourable reaction of ATP is coupled to many otherwise unfavourable reactions through which other molecules are synthesised.

A frequent type of reaction (that is needed for biosynthesis) is where 2 molecules, A and B, are joined to produce A-B in the energetically unfavourable condensation reaction, there is an indirect pathway that allows A-H and B-OH to form A-B, in which the coupling of ATP hydrolysis makes the reaction go, Here energy from ATP hydrolysis is used to convert B-OH to a higher energy intermediate compound, which then reacts with A-H to give A-B.

$$A\text{-}H + B\text{-}OH \rightarrow A\text{-}B + H_2O$$

NAD^+ (nicotinamide adenine dinucleotide) and $NADP^+$ (nicotinamide adenine dinucleotide phosphate) are the most important electron and hydrogen atoms carriers, NAD^+ and $NADP^+$ each pickup a packet of energy corresponding to 2 high energy electrons plus a proton (H^+) becoming NADH (reduced) and NADPH (reduced), NADH and NADPH are effective donors of their hydride ion to other molecules, the transfer is accompanied by a large negative free energy change.

NADPH and NADH bind as substrate to different types of enzymes, thus the 2 types of carriers are used to deliver electrons (or hydride ions) to different destinations, NADPH operates chiefly with enzymes that catalyse anabolic reactions (supplying high energy electrons needed to synthesise energy rich biological molecules, NADH has a special role as an intermediate in the catabolic system of reaction that generate ATP through the oxidation of food molecules.

Coenzyme A carries an acetyl group in a readily transferable linkage and in the activated form is known as acetyl CoA, it is used to ad 2 carbon units in the biosynthesis of larger molecules.

The activated carriers are usually generated in reaction coupled to ATP hydrolysis, therefore energy that enables their groups to be used for biosynthesis ultimately comes from the catabolic reactions that generate ATP.

Macromolecules are made up of subunits (monomers) that are linked together in a condensation reaction, in which the constituents of a water molecule (OH + H) are remover from the 2 reactants, the reverse reaction occurs by the enzyme-catalysed addition of water (hydrolysis), the condensation step depends on energy from nucleoside triphosphate hydrolysis, the O-H group that will be removed in the condensation reaction is first activated by becoming involved in a high energy linkage to a second molecule.

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Chapter 3: Energy, Catalysis and Biosynthesis

Each cell can be viewed as a tiny chemical factory, performing many thousands of reactions every second.
The catabolic pathway breaks down foodstuffs into smaller molecules, creating energy and building blocks, the cell needs.
The anabolic or biosynthetic pathway uses the energy to form other molecules that the cell needs.
These two reactions constitute the metabolism.

Catalysis and the use of energy by cells

Biological order is made possible by the release of heat energy by cells
The amount of disorder in a system is called entropy, the greater the disorder the greater the entropy. A cell is not an isolated system; it takes energy from its environment in the form of food. Heat is energy in its most disordered form.
Energy can transformed from one form to another, but cannot be created or destroyed.

Photosynthetic organisms use sunlight to synthesize organic molecules
Solar energy enters the world by photosynthesis by plants and bacteria. They use the energy derived from sunlight to form building blocks from atoms.
Light energy + CO_2 + H_2O → sugars + O_2 + heat energy
The sugars are the source for the chemical bond energy and are used for making other molecules.

Cells obtain energy by the oxidation of organic molecules
Energy is extracted from food molecules by a process of gradual oxidation or controlled burning. Respiration is the process of making carbon dioxide and water from carbon, hydrogen and oxygen. This is the opposite of photosynthesis. Oxygen is released by photosynthesis, and is used by almost all other organisms.
Biosphere is all the living organisms on earth.

Oxidation and reduction involve electron transfer
The word oxidation is used in the process of electron transfer from one atom to the other. It means the removing of electrons. Reduction is the adding of electrons. These terms are also used when a covalent bond is made between two atoms.
Hydrogenation reactions are reductions because they involve an electron. Reduction is occurring if the number of C-H bonds increases.

Enzymes lower the barriers that blocks chemical reactions
Free energy is energy that can be harnessed to do work or to drive chemical reactions. A spontaneous reaction occurs in the energetically most favorable way. The molecules however need activation energy to make the reaction. This activation energy helps the molecules to get over a barrier. Enzymes help the molecules to get over the barrier needed for the reaction. An enzyme adds itself to a substrate and this bond lowers the activation-energy. Catalysts are the reactions that occur when an enzyme is used. Enzymes are also highly selective so that only the needed reaction occurs. Each enzyme has an active site to which the substrate is added. Enzymes remain unchanged and can therefore be used many times.

How enzymes find their substrates: the importance of rapid diffusion
Both enzymes and substrates are in small numbers in the cell. Rapid binding is capable because of the enormously fast at the molecular level. The enzymes will explore the cells by diffusion. A substrate moves faster than an enzyme. When the two meet a complex is formed, called an enzyme-substrate complex. Many weak bonds are formed to sustain the complex.

The free-energy change for a reaction determines when it can occur
Energetically unfavorable reactions produce biological order. Free energy called G is of value when a change is made. This is noted down as ΔG. A negative G is an energetically favorable reaction. Energetically unfavorable reactions have a positive G.

The concentration of reactants influences DG
ΔG is not only dependent on the energy stored in each individual molecule but also on the concentration of the molecules.
$\Delta G = \Delta G^0 + 0.616 \ln (B): (A)$
There is a chemical equilibrium when $\Delta G = 0$.

For sequential reactions, DG^0 values are additive
For more than one reaction, the ΔG is jut simply added. An unfavorable reaction can be done by first making a favorable reaction, which frees energy. As long as the ΔG^0 is negative all the reactions can be made.

Activated carrier molecules and biosynthesis
In most cases the energy is stored as chemical bond energy in a small set of activated carrier molecules, which contain one or more energy-rich covalent bonds. The activated carriers store the energy in an easily exchangeable form. These are sometimes referred to as coenzymes. The most important carrier molecules are ATP, NADH and NADPH.

The formation of an activated carrier is coupled to an energetically favorable reaction
Enzyme catalyzed reactions make sure that the energy is bond in a chemically useful form. This is done by coupled reaction, in which an unfavorable reaction is done with the energy. In this way less energy is wasted.

ATP is the most widely used activated carrier molecule
ATP is used as a versatile and convenient store of energy. This way it is able to drive chemical reactions in the cell. It gives away its energy by hydrolyzing to ADP. Mostly the phosphor group is added to another molecule.

Energy stored in ATP is often harnessed to join two molecules together
Hydrolyzing the unfavorable reactions is mostly done and with the help of ATP.
$A\text{-}H + B\text{-}OH \rightarrow A\text{-}B + H_2O$
ATP lets go its phosphor group and converts into ADP + Pi.

NADH and NADPH are important energy carriers
NAD^+ and $NADP^+$ each pick up a packet of energy containing two electrons and a proton (H^+) and become NADH and NADPH. The hydrogen atom and the two electrons are removed from the substrate. The H is transferred because of a free energy change. NADH and NADPH are different and bind to different substrates and are bond by different enzymes. NADPH is used by anabolic reactions and NADH is used by catabolic reactions.

There are many other activated carrier molecules in cells
The activated carriers are usually generated in reactions coupled to ATP hydrolysis.

The synthesis of biological polymers requires an energy input

Molecules are made from subunits that are linked together by a condensation reaction. The reverse reaction is done by enzymes and is called hydrolysis. There are also limits to what each activated carrier can do.

Essential concepts

1. Living organisms are able to exist because of a continual input of energy. Part of this energy is used to carry out essential functions- such as maintenance, growth and reproduction- and the remainder is lost in the form of heat.
2. The primary source of energy for most living organisms is the sun. Plants and photosynthetic bacteria use solar energy to produce organic molecules from carbon dioxide. Animals obtain food by eating plants or by eating animals that feed on plants.
3. Each of the many hundreds of chemical reactions that occur in a cell is specifically catalysed by an enzyme. Large numbers of different enzymes work in sequence to perform chains of reactions called metabolic pathways each performing a particular function in the cell.
4. Catabolic reactions break down food molecules through oxidative pathways and release energy. Anabolic pathways build up the many complex molecules needed by the cell and require an energy input. Both the building blocks and the energy required are obtained by catabolism in animal cells.
5. Enzymes catalyse reactions by binding to particular substrate molecules in a way that lowers the activation energy required for making and breaking the specific covalent bonds.
6. The only chemical reactions possible are those that increase the total amount of disorder in the universe. The free energy change for a reaction, ?G, measures this disorder, and must be less than zero for a reaction to proceed.
7. The free energy change for a chemical reaction, ? G, depends on the concentration of the reacting molecules and may be calculated from these concentrations if the equilibrium constant K of the reaction (or the standard free energy change $?G^0$ for the reactants) is known.
8. By creating a reaction pathway that couples an energetically favourable reaction to an energetically unfavourable reaction enzymes cause otherwise impossible reactions to occur.
9. A small set of activated carrier molecules, in particular, ATP, NADH and NADPH, plays a central part in these coupling events. ATP carries high-energy phosphate groups whereas NADH and NADPH carry high-energy electrons.
10. Food molecules provide the carbon skeletons for the formation of larger molecules. The covalent bonds of these larger molecules are typically produced in reactions coupled to energetically favourable bond changes in activated carrier molecules such as ATP and NADPH.

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Chapter 4: How cells obtain energy from food

In a food molecule such as glucose is oxidised to CO_2 an H_2O in a single step, it releases an amount of energy many times larger than any carrier molecule could capture, instead cells use enzymes to carry out the oxidation in a highly controlled series of reactions: the glucose molecule is degrade step by step, paying out energy in small packets to activated carrier molecules by means of coupled reactions.
Animal cells make ATP in 2 ways, one is by a series of enzyme catalysed reactions in the cytosol that ends in the partial oxidation of the food molecules, the second takes place in mitochondria and uses the energy from activated carrier molecules to drive ATP production.

- *stage 1*: digestion, occurs either in intestine outside cells or in specialised organelle within cells, foods are broken down into their monomer subunits, after digestion the small organic molecules enter the cytosol of he cell
    - proteins – amino acids
    - polysaccharides – sugars
    - fats – fatty acids and glycerol
- *stage 2*: glycolysis, converts each molecule into 2 smaller molecules of pyruvate, sugars other than glucose are similarly converted to pyruvate after their conversion to one of the sugar intermediates in this glycolitic pathway, 2 types of activated carrier molecules produced: ATP en NADH, the pyruvate then passes from the cytosol into mitochondria, there each pyruvate molecule is converted into CO_2 plus a 2 carbon acetyl group which becomes attached to coenzyme A (CoA) forming acetyl CoA, another activated carrier molecule large amount of acetyl CoA are also produced by the stepwise breakdown and oxidation of fatty acids derived from fats, which are carried in the bloodstream, imported into cells as fatty acids and moved in the mitochondria for acetyl CoA production
- *stage 3*: citric acid cycle, the acetyl group in acetyl CoA is linked to coenzyme A through a high energy linkage and is therefore easily transferable to other molecules, after its transfer to the 4 carbon molecule oxaloacetate, the acetyl group enters the citric acid cycle, the acetyl group is oxidised to CO_2 and large amounts of electron carrier NADH are generated,
- *stage 4:* oxidative phosphorylation, the high energy electrons form NADH are passed along an electron transport chain within the mitochondrial inner membrane, where the energy released by their transfer is used to drive a process that produces ATP and consumes O_2

Glycolysis produces ATP without involvement of O_2, glycolysis involves a sequence of 10 separate reactions, each producing different sugar intermediate and each catalysed by a different enzyme, although no O_2 is involved oxidation occurs, in that electron are removed by NAD^+ (producing NADH) from some of the carbon derived from the glucose molecule, at end of glycolysis there is a net gain of 2 ATP for each glucose molecule and 2 molecules of NADH are formed.

For many anaerobic organisms glycolysis is the principal source of the cell's ATP, this is also true for certain animal tissue (skeletal muscle), in anaerobic conditions the pyruvate and the NADH electrons stay in the cytosol, the pyruvate is converted to products excreted from the cell (ethanol and CO_2 in yeast or lactate in muscle), in this process the NADH gives up its

electrons and us converted back into NAD^+, anaerobic energy yielding pathways are called fermentations.

Steps 6 and 7 in the glycolysis account for the net yield of 2 ATP and 2 NADH molecules per molecule of glucose, the 2 central reactions convert the 3 carbon sugar intermediate glyceraldehydes phosphate into phosphoglycerate, a carboxyl acid (this entails the oxidation of an aldehyde group to a carboxyl acid group), the overall reaction releases enough free energy to convert a molecule of ADP to ATP and to transfer 2 electrons from the aldehyde to NAD^+ to from NADH, while still releasing enough heat to the environment to make the overall reaction energetically favourable.

The chemical reactions are guided by 2 enzymes, the first (glyceraldehydes phosphate dehydrogenase) forms a short liver covalent bond to the aldehyde through a reactive SH-group on the enzyme and catalyses its oxidation while still in the attached state, the reactive enzyme-substrate bond is then displaced by an inorganic phosphate ion to produce a high energy phosphate intermediate, which is released from the enzyme, this intermediate binds to the second enzyme (phosphoglycerate kinase) which catalyses the energetically unfavourable transfer of the high energy phosphate just created ADP, forming ATP and completing the process of oxidising an aldehyde to a carboxyl acid.

In aerobic metabolisms the pyruvate produced by glycolysis is rapidly decarboxylated by a giant complex of 3 enzymes, the pyruvate dehydrogenase complex, the products of pyruvate decaborxylation are a molecule of CO_2 (waste product), a molecule of NADH an acetyl CoA, the enzyme complex is located in the mitochondria of eucaryotic cells.

The enzymes that degrade the fatty acids derived from fats likewise produce acetyl CoA in mitochondria, each molecule of fatty acid activated molecule fatty acetyl CoA is broken down completely by a cycle of reactions that trims 2 carbons at a time from its carboxyl end, generating on molecule of acetyl CoA for each turn of the cycle, a molecule of NADH and a molecule of $FADH_2$ are also produced in this process.

The citric acid cycle, tricarboxyl acid cycle or the Krebs cycle accounts for about 2/3 of the total oxidation of carbon compounds in most cells, and its major end products are CO_2 and a high energy form of NADH, CO_2 is released as a waste product while the high energy electrons from NADH are passed to a membrane bound electron transport chain, eventually combining with O_2 to produce H_2Ode cycle does not use the O_2, it helps NADH to get rid of its electrons and thus generate the NAD^+ that is needed to keep the cycle going.

The result of the citric acid cycle is the complete oxidation of acetyl CoA into CO_2, the acetyl group is not oxidised directly, it is transferred from acetyl CoA to a larger 4 carbon molecule, oxaloacetate, to form the 6 carbon tricarboxylic acid (citric acid), the citric acid molecule is then gradually oxidised and the energy of this oxidation is harnessed to produce energy rich carrier molecules, the 8 reaction forms a cycle because at the end oxaloacetate is regenerated and enters a new turn of the cycle.

Each turn of the cycle also produces one molecule of $FADH_2$ from FAD and one molecule of GTP from GDP, like NADH, $FADH_2$ is a carrier for high energy electrons and hydrogen (will be used subsequently like NADH in the oxidative phosphorylation), GTP is a close relative of ATP.

The oxygen atoms required to make CO_2 from the acetyl groups entering the citric acid cycle are supplied by H_2O in stead of O_2 (molecular oxygen), 3 molecules of water are split in each cycle ant the oxygen atoms of some of them are ultimately used to form CO_2, some amino acids pass from the cytosol into mitochondria, where they are also converted into acetyl CoA or one of the other intermediates of the citric acid cycle, the citric acid cycle also produces starting points for important biosynthetic reactions, like producing the vital carbon containing intermediates such as oxaloacetate and α-ketoglutarate.

In the last step, the oxidative phosphorylation, the electron carriers NADH and $FADH_2$ transfer electrons that they have gained when oxidising other molecules to the electron transport chain, is embedded in the inner membrane of the mitochondrion, passing along specialised electron acceptor and donor molecules the electrons fall to successfully lower energy states, the energy they release in this process is used to drive H^+ ions (protons) across the membrane, a gradient of H^+ ions is thereby generated, this serves as a source of energy to drive a variety of energy requiring reactions, e.g. generation of ATP from ADP.

Fatty acids are stored as fat droplets composed of water-insoluble triacylglycerol, largely in specialised fat cells, sugar is stored as glucose subunits in the large branched polysaccharide glycogen, which is present as small granules in the cytoplasm of many cells, the oxidation of one gram of fat releases about twice as much energy as the oxidation of a gram of glycogen.

Essential Cell Biology

Chapter 4: How cells obtain energy from food

Molecules are degraded step by step to obtain all the energy that comes free.

The breakdown of sugars and fats
ATP is made in two different ways. One is in the cytosol and one is in mitochondria.

Food molecules are broken down in three stages to produce ATP
Large molecules have to be broken down before the cells can use them. Digestion can be done in our intestines or in lysosomes. Polymers are broken down in monomers. From there they enter the cytosol.
Glycolysis is the conversion of glucose in its monomers. Glucose is made by the aerobe phosphorylation. Energy is packed and transported to other places where it is of use. A lot of energy is released by the cell as heat.

Glycolysis is a central ATP-producing pathway
Glycolysis is the splicing of glucose and it produces ATP. All of the reactions that occur in the glycolysis are catalyzed by enzymes. Oxidation is used because electrons are involved. The energy is stored in carrier molecules or released as heat.

Fermentations allow ATP to be produced in the absence of oxygen
For anaerobic molecules glycolysis is the principal source of the cells ATP. This is also true for tissues that have limited oxygen. NAD^+ is formed to help with the glycolysis.
These anaerobe pathways are called fermentations.

Glycolysis illustrates how enzymes couple oxidation to energy storage
The hydrolysis of glucose into two pyruvates creates enough energy to make ATP out of ADP and to make NADH from NAD^+.

Sugars and fast are both degraded to acetyl CoA in mitochondria
In the oxidative phosphorylation lots of oxygen is needed.
The produced pyruvate is decarboxylated by a gigantic complex of three enzymes called the pyruvate dehydrogenase complex. The products are a CO_2, a NADH and CoA.
This is likewise with fatty acids.
Sugars and fats provide the most energy.
Most of all these reactions take place in mitochondria.

The citric acid cycle generates NADH by oxidizing acetyl groups to CO_2
In absence of oxygen cells produce lactic acid and ethanol. They produce CO_2 and H_20 when oxygen is there. This is due to the citric acid cycle. Its main products are CO_2 and NADH. The oxygen is needed for NADH to release the hydrogen and form water. The NAD^+ is needed to keep the cycle going. The energy produced is kept in activated carriers. Each cycle also produces a $FADH_2$ and a GTP. The GTP produces the ADP into an ATP. The $FADH_2$ carries electrons and hydrogen and is used in the oxidative phosphorylation.
At each cycle from the citric acid cycle three water molecules are spliced off.

Electron transport drives the synthesis of the majority of the ATP in most cells
The energy that is released when the food was digested is captured in NADH and $FADH_2$ and they takes these electrons to electron transport chain. The electrons fall into lower states and energy is released. The H^+ are driven through the membrane. This creates a source of energy. ATP is this way generated from ADP. The hydrogen then diffuses with the oxygen into the mitochondria again and produces molecules of water. This is called oxidative phosphorylation.

Storing and utilizing food

Organisms store food molecules in special reservoirs
To compensate for long periods of fasting, animals store food within their cells.
Fatty acids are stored as droplets in cytoplasm.
Sugar is stored as glucose subunits in glycogen, which is present in small granules.
Fat is a major storage for energy.

Many biosynthetic pathways begin with glycolysis or the citric acid cycle
Catabolism provides the building blocks and the energy. A lot of the produced products are used as blocks for the cell instead of finishing the cycle. These choices that have to be made are very carefully made.

Metabolism is organized and regulated
The metabolic balance is very stable. A cell will always attempt to correct the mistake, to get back into balance. The cycle is controlled by many control mechanisms.

Essential concepts

1. Glucose and other food molecules are broken down by controlled stepwise oxidation to provide chemical energy in the form of ATP and NADH.
2. Three distinct stages in the breakdown of food molecules can be distinguished: glycolysis (which occurs in the cytosol), the citric acid cycle (in the mitochondrial matrix) and oxidative phosphorylation (on the inner mitochondrial membrane).
3. The reactions of glycolysis degrade the six-carbon sugar glucose to the two molecules three-carbon sugar pyruvate, producing small numbers of molecules of ATP and NADH.
4. In the presence of oxygen pyruvate is converted into acetyl CoA plus CO_2. The citric acid cycle then converts the acetyl group into acetyl CoA and CO_2 and H_2O. In eucaryotic cells these reactions occur in mitochondria. Much of the energy of oxidation released in these oxidation reactions is stored as high-energy electrons in the carriers NADH and $FADH_2$.
5. The other major energy source in food is fat. The fatty acids produced from fats are imported into mitochondria and oxidized to acetyl CoA molecules. These acetyl CoA molecules are than further oxidized through the citric acid cycle, just like the acetyl CoA derived from pyruvate.
6. NADH and $FADH_2$ pass the electrons they are carrying to an electron transport chain in the inner mitochondrial membrane, where a series of electron transfers is then used to drive the formation of ATP. Most of the energy captured during the breakdown of food molecules is harvested during this process of oxidative phosphorylation.
7. Cells store food molecules in special reservoirs. Glucose subunits are stored as glycogen in animals and as starch in plants; both animals and plants store food as fats.

The food reservoir produced by plants is major sources of food for animals, including us.

8. Molecules ingested as food are used not only as sources of metabolic energy but also as raw material for biosynthesis. Thus many intermediates of glycolysis and the citric acid cycle are starting points for pathways that lead to the synthesis of proteins, nucleic acids and other specialized molecules of the cell.
9. The many thousands of different reactions carried out simultaneously by a cell are closely coordinated, enabling the cell to adapt and continue to function under a wide range of external conditions.

Essential Cell Biology

Chapter 5: Protein structure and function

Proteins are the building blocks off a cell and execute almost all cell functions. We first must learn to understand how proteins work, before we will know how the human body works. Because proteins have many different functions, they have many different forms.

The shape and structure of proteins

There are 20 different sorts of amino acids in a protein. A protein therefore is made of many different amino acids. They link through a peptide bond. This forms the backbone. Many side-chains give their attaching amino acid unique properties. Every protein has his unique amino acid sequence. This creates many sorts of proteins. This backbone is flexible, but the noncovalent bonds between the backbone and the side chains make a structure. Hydrogen bonds, ionic bonds and Van Der Waals bonds form these bonds. Also, chains tend to be forced together in a watery environment. The hydrophobic chains will go inside the ball to avoid the water. Hydrophilic chains will situate themselves near the water so that they can form hydrogen bonds with the water.

Proteins fold in into a conformation of lowest energy

A protein has a determined three-dimensional structure, due to the sequence of the amino acids. All the information required for the folding of the protein is in the sequence of the amino acids. The conformation will slightly change when the protein interacts with other molecules in the cell. The folding of the protein can be done by the protein itself, but is generally assisted by the molecular chaperones. They help the protein to fold during the most energetically favorable folding pathway. They also prevent the joining of two wrong chains.

Proteins come in a wide variety of complicated shapes

Methods have been developed to open cells, purify proteins and determining the sequence of the amino acids. It is easier now because they can sequence DNA, this way they can determine the order of the nucleotides in the DNA that determine the protein sequence. At present the only way to discover the precise folding pattern of any protein is by experiment, using either X-ray or nuclear magnetic resonance methods.

The a helix and the ß sheet are common folding patterns

These two patterns result from hydrogen bonding between the N-H and C=O groups in the polypeptide backbone. They do not involve the side chains.
The core of many proteins contains extensive regions of ß sheet. This forms a rigid structure held together by hydrogen bonds.
The a helix is generated when a single polypeptide chain turns around itself to make a rigid cylinder. A hydrogen bond is made after every 4^{th} peptide bond, making another peptide bond.
Proteins in the cell membrane have these a helixes. Also the backbone, which is hydrophilic, is bend into an a helix.
When these helixes wrap around each other a coiled-coil is formed. This forms when the chains have most of the hydrophobic sides on one side.

Proteins have several levels of organization

Even a small molecule is build from thousands of precisely oriented covalent and noncovalent bonds. A protein exists of different kinds of structures.

Primary structure = the amino acid sequence
Secondary structure = the a helixes and the ß sheets
Tertiary structure = the three-dimensional structure
Quaternary structure = the complex of more than one protein

The protein domain is the structure from which many more proteins can be built. Different domains are often associated with different functions. One protein can have many different domains held together by unstructured lengths of polypeptide chain.

Few of the many possible polypeptide chains will be useful
There are a lot of different combinations possible, because the amino acids do not need to be on the same place every time. But in cells the proteins show stability. This is because the other conformations are not biologically necessary. Natural selection terminates them.
The proteins are so precisely built that the change of even a few atoms can disrupt the structure and thereby cause a catastrophically loss of function.

Proteins can be classified into families
Many present-day proteins can be grouped into protein-families, with each family member having an amino acid sequence and a three-dimensional conformation that closely resembles all the other family members. But they all carry out a distinct function in an organism.

Larger protein molecules often contain more than one polypeptide chain
Noncovalent bonds allow proteins to bond to each other. This is able at the binding sites. The polypeptide chains of this protein are called subunits.
An example of a protein where this is done is hemoglobin.

Proteins can assemble into filaments, sheets or spheres
A filament is a long helical structure formed from many molecules of a protein.
All the information to obtain a complicated structure is in the macromolecules themselves.

A helix is a common structural motif in biological structures
It is very rare for units to assemble in a straight line, so normally a helix is formed. This is because the subunits want to attach to each other every time in exactly the same way.

Some types of proteins have elongated fibrous shapes
Some proteins have roles in the cell, which require that each protein molecule span a large distance. These are the fibrous proteins. They are especially abundant outside the cell, where they form the gel-like extra cellular matrix. Collagen is an example, but so is elastin.

Extra cellular proteins are often stabilized by covalent cross-linkages
Proteins are exposed to extra cellular conditions, so to help maintain their form they form disulfide bonds. These are formed as proteins are exported from the cells. They do not change the form, but secure it. Proteins do not need these bonds inside the cell.

How proteins work
Every shape indulges a specific function.

Proteins bind to other molecules

All proteins bind to other molecules, but this is always a specific bond. Each protein can only bond to those specific molecules of the thousands it meets. These molecules are the ligands of the protein.
They can only bond when numerous noncovalent bonds are formed, because one is too weak. The surfaces of the ligand and the protein must match. This matching area is the binding site. It works like a keyhole and the key that comes with it. Small changes can ruin the structure and it will become impossible to form this connection. Due to rapid movements bonds can be formed between molecules if they have matching surfaces.
If they have matching surfaces they can form bonds for a long period of time.

The binding sites of antibodies are especially versatile

Antibodies, or immunoglobulins are proteins produced by the immune system in response to foreign molecules. The antibody inactivates the target or marks it for destruction. Antibodies recognize these antigens, but each antigen has a specific antibody, so there will have to be lots of different antibodies. The antibodies are Y-shaped which is the binding site.

Binding strength is measured by the equilibrium constant

Different antibodies bind to their ligands with different strength. Antibody-ligand complexes are formed, but these can also be broken again by thermally induced motion. They will come to a steady state, equilibrium. Both binding and unbinding will be done, in the same quantity. The concentrations form a good measure, the equilibrium constant K. It becomes larger as the strength increases.

Enzymes are powerful and highly specific catalysts

Many proteins only bond to an antigen, that is their task and then it is fulfilled. For enzymes however this task is very important. They bond with one or more ligands called substrates and convert them into products. Enzymes only speed up reactions. They are not used up. They make sure life is possible. Enzymes work in teams; the product of the first enzyme is the substrate of the second enzyme. This way, the cell gets all it needs.

Lysozyme illustrates how an enzyme works

Lysozyme catalyses the cutting of polysaccharide chains in the cell walls of bacteria. It uses hydrolysis (adding a water molecule) to break two sugar groups. The free energy becomes less. This process has to be catalyzed, because the energy threshold is too big. In order to add the water molecule the substrate has to be in the transition state. Than the activation energy must be supplied, through collisions, to enable the process.
An enzyme has a surface (active site) that fits onto the surface of the substrate and they form a complex. This active site is a kind of groove. The needed activity is lowered and water is added between the two sugar groups. The substrate now has the water molecule, and the enzyme lets go.
The bonding of the enzyme to the substrate also proceeds by many noncovalent bonds.
The activation energy is lowered by this following system: One part of the substrate is situated just outside the enzyme, so that it is distorted from its most stable conformation. The bond is also held close to two amino acids with acidic side chains. This lowers the activation energy.
The active site of an enzyme contains precisely positioned atoms that speed up a reaction by using charged groups to alter the distribution of electrons in the substrates.

V_{max} and K_M measure enzyme performance

A substrate is bonded to an enzyme, a chemical reaction breaks the substrate in two pieces and then the enzyme lets the two pieces go. These pieces are now ready for another reaction.
If there is more substrate added the enzyme-substrate-complexes will increase linearly. However more enzymes make a bond so at a particular time the maximum amount of bonds have taken place, V_{max}.
The turnover number (number of molecules that are bond) can be between 1-10000.
K_M is the concentration of substrate at which the enzyme works at half its maximum speed (at 0.5 V_{max}). A high value means strong bonding.

Tightly bound small molecules add extra functions to proteins

Proteins often need nonprotein molecules to perform functions that would be difficult or impossible to do using only amino acids. Sometimes small molecules are bonded forever to the protein. This slightly modifies the protein so that it can perform the duty.
Enzymes with a catalytic function have a metal bonded to them. They can also have an organic molecule bonded to them.

The catalytic activities of enzymes are regulated

Many enzymes work at the same time. This makes a gigantic web of reaction, where each product is the substrate of the next enzyme. The enzyme therefore must adjust constantly to the molecules it encounters so that it does not make the wrong bonds.
If a lot of end products are made, they start to bond to the enzyme, so that they will slow down. This is called feedback inhibition. This is called negative regulation; it prevents an enzyme from acting.
Positive regulation is when an enzyme is stimulated to make a reaction.

Allosteric enzymes have two binding sites that interact

An enzyme has two different binding sites, one active site that recognizes the substrates, and a second site that recognizes the regulatory molecule. These two sites communicate.
The interaction of the two sites on the protein depends on conformational change. The bonding at one site means a slight change in structure.
An inhibitor could take one place and cause a change to the active center of the protein so that no other bonds can take place.
Most proteins are allosteric.

A conformational change can be driven by protein phosphorylation

To regulate a proteins function, phosphate groups can be added to the amino acid side chains. Because a phosphate group carries two negative charges a lot is altered of the protein.
Removing the phosphor group the protein resumes its original structure.
This reversible protein phosphorylation controls the activity of many different types of proteins in eucaryotic cells. Both the attachment as the removal of the phosphor is done under influence of a catalyst. The energy needed for this process comes from ATP.

GTP-binding proteins can undergo dramatic conformational changes

Binding a guanine nucleotide controls the activity of these proteins. The active GTP-bond is turned into a GDP-bond, which is inactive. This process is reversible. The reverse reaction is mostly done under the influence of a signal from the cell. The loss of this single phosphate group gives an enormous change in the shape of the protein.

Motor proteins produce large movements in cells

Their major function is to move other molecules. It can move along a DNA string by undergoing a lot of changes. This is reversible, so that it can move to the other side as well. Without an input of energy a protein can only move aimlessly. Making one of the changed shapes irreversible prevents this. Because a great deal of free energy is released when ATP or GTP is hydrolyzed it is very unlikely that the nucleotide binding protein will undergo a reverse shape change. This can all take place very rapidly.

Proteins often form large complexes that function as protein machines

Ten or more enzymes often catalyze processes at the same time, and these enzymes form a protein machine. Coordinated movements of the protein machine make sure that this can all be done.

These protein machines were invented by the cell to accomplish any task they had to do. This is much more efficient.

Essential concepts

1. Living cells contain an enormous diverse set of protein molecules, each made as a linear chain of amino acids covalently linked together.
2. Each type of protein has a unique amino acid sequence that determines both its three-dimensional shape and its biological activity.
3. The folded structure of a protein is stabilized by noncovalent interactions between different parts of the polypeptide chain.
4. Hydrogen bonds between the neighboring regions of the polypeptide backbone can give rise to regular folding patterns, known as a helices and ß sheets.
5. The structure of many proteins can be subdivided into smaller globular regions of compact three-dimensional structure known as protein domains.
6. The biological function of a protein depends on the detailed chemical properties of its surface and how it binds to other molecules, called ligands.
7. Enzymes are protein that first bind tightly to specific molecules, called substrates, and then catalyze the making and breaking of covalent bonds in these molecules.
8. At the active site of an enzyme, the amino side chains of the folded protein are precisely positioned so that they favor the formation of the high-energy transition states that the substrates must pass through to react.
9. The three-dimensional structure of many proteins has evolved so that the binding of a small ligand can induce a significant change in the protein shape.
10. Most enzymes are allosteric proteins that can exist in two conformations that differ in catalytic activity and the enzyme can be turned on or off by ligands that bind to a distinct regulatory site to stabilize either the active or the inactive conformation.
11. The activities of most enzymes within the cell are strictly regulated. One of the most common forms of regulation is feedback inhibition, in which an enzyme early in a metabolic pathway is inhibited by it's binding to one of the pathway's end products.
12. Many thousands of proteins in a typical eucaryotic cell are regulated either by cycles of phosphorylation and dephosphorylation, or by the binding and hydrolysis of GTP by a partner GTP-binding protein.
13. The hydrolysis of ATP to ADP by motor proteins produce directed movements in the cell.
14. Assemblies of allosteric proteins in which conformational changes are coordinated to perform complex cellular functions form highly efficient protein machines.

Essential Cell Biology

Chapter 6: DNA

Cells store, retrieve and translate the genetic instructions. The information is passed on to the daughter cells at cell division and the reproductive cells. The instructions are stored in the genes.
The information is copied a million times without any flaws (most of the time).

Genetic instructions consist primarily of the information for making proteins. These proteins determine almost entirely the properties and functions of a cell.
DNA was identified as the likely carrier of genetic information in 1940. Later the structure of DNA is retrieved and the replication is figured out.

Each cell can transcript DNA and can repair DNA when it is broken. Nevertheless mutations do occur. This mutation can be good. For thousands of year's changes in DNA made us what we are now. But a mutation is more likely to be bad. Inherited diseases are made, it can cause cancer, and so on.

The structure and function of DNA
Genes are carried on chromosomes that are situated in the nucleus. They become visible as the cell begins to divide.
Chromosomes consist of DNA and proteins. The DNA is because of its chemical simplicity, its structure and chemical properties ideal.

Genes are made of DNA
Adding DNA to a bacterium changes its properties and is given to the next generation.

A DNA molecule consists of two complementary chains of nucleotides
The first X-ray diffraction results indicated that DNA was composed of two strands wound into a helix. Each chain is made of 4 nucleotide subunits. The two chains are held together by hydrogen bonds, between the bases.
A nucleotide is made out of a sugar (desoxyribose), a phosphate and a base. DNA has four different bases, being Adenine, Thymine, Guanine and Cytosine. These bases form a backbone.
The bases are situated on the inside of the helix, so that they can form hydrogen bonds together. A always pairs with T, and G always pairs with C. This enables the pairs to packed in the energetically most favorable arrangement. To make sure the bases bond with their partner, the strands have to be antiparallel.

The structure of DNA provides a mechanism of hereditary
Information is copied and the DNA-strands are divided into the two daughter cells. Each base can be seen as a letter in a four-letter alphabet. Organisms differ from one another, because their DNA sequence is different.
DNA has the code for constructing proteins that is secured in the base sequence.

The complete set of information in the DNA is called genome.
At each cell division, the cell must copy its genome in order to pass the information to the daughter cells.

DNA replication

Each strand can act as a template, or mould, because it is exactly opposite of its other strand. This makes an exact copy of the other strand. This way a cell is able to replicate his DNA before passing it on.
DNA replication produces two complete double helices from the original DNA molecule. Each daughter cell has one old strand and one new strand.

DNA synthesis begins at replication origins

Initiator proteins that bind to the DNA strands and pry the two strands apart begin the process of DNA replication. The hydrogen bonds are not difficult to break, because the protein only breaks a few at the time.
The position at which the DNA is opened is called a replication origin. They are marked by a specific nucleotide sequence. There are many origins on one genome. This allows the replication to take place at more than one place, which speeds up the process. They work as a protein machine.

New DNA synthesis occurs at replication forks

Y-shaped junctions in the DNA are replication forks, the replication is moving along the DNA.
DNA-polymerase synthesizes new DNA by using an old strand as a template. Nucleotides have phosphate groups, which supply the energy for the making of the new strand. DNA-polymerase stays attached to the DNA to make more strands.

The replication fork is asymmetrical

The fork is asymmetrical because one strand is running in a direction, but the other strand is running in the opposite direction. DNA polymerase can only add nucleotides on one end of the strands, the 3' to 5'. But there is no protein that can go in the 5' to 3' direction. This is solved by a backstitching maneuver. The 5' strand is made in separate pieces. This is done by DNA-polymerase by working backwards. The pieces are later stitched together to form the other strand. This discontinuous strand is called a lagging strand; the continuous strand is called a leading strand.

DNA polymerase is self-correcting

It makes only 1 error in every 10^7 nucleotide pairs. Less stable base pairs, like G – T and A – C can be made as well. But these base pairs can destroy the cell, so polymerase can correct these mistakes. This is called proofreading. The polymerase checks every former base pair when it starts to make a new pair. If the former pair is wrong, polymerase cuts the wrong bond and tries again. A polymerase can only proceed in the 5' to 3' direction.

Short lengths of RNA act as primers for DNA synthesis

Another enzyme can start a complete new DNA strand by producing RNA. The DNA strand is only used as a template. It has a 3' end and a starting place for DNA polymerase. It is a primer for DNA synthesis. Primase synthesizes the RNA. It is virtually the same kind of strand. Only ribose is used instead of desoxyribose, and it contains the base Uracil instead of Thymine.
For the leading strand, a RNA primer is only needed to make a start, and then DNA polymerase can take over. But on the lagging strand new primers are needed every time because the strand is discontinued.
The DNA is formed until it reaches another RNA primer. The RNA primer disappears and a connection is made between the two strands of DNA.

A nuclease breaks apart the RNA primer, repair polymerase replaces the RNA with DNA and DNA ligase joins the parts together.
There are many mistakes in RNA, but because DNA replaces the RNA and because this is done by polymerase, all the mistakes are corrected.

Proteins at a replication fork cooperate to form a replication machine
Helicase is at the head of this machine. It is a protein that uses the energy of ATP hydrolysis to speed along the DNA opening the double helix as it moves.
Single-strand binding protein clings to the single strand and prevents it from becoming a base pair again.
Sliding clamp keeps the DNA polymerase attached to the DNA strand.

DNA repair
Organism adapt to their environment. The environment has changing conditions over the years. Genetic change is almost always detrimental. In order to survive and reproduce the organism must be genetically stable. Correcting the mistakes that are made in the copying of the DNA also does this

Changes in the DNA are the cause of mutations
A permanent change in the DNA is called a mutation. Since the structure and activity of a protein depend on its amino acid sequence, a protein with an altered sequence may function poorly or not at all. This shows that it is very important to protect reproductive cells against mutation. This cell divides itself many times, and it can even be passed on to the next generation. Nucleotide changes that occur in somatic cells can give rise to variant cells, some of which grow in an uncontrolled fashion at the expense of the other cells in the organism. This can cause cancer.

A DNA mismatch repair system removes replication errors that escape from the replication machine
The cell has a backup system, called DNA-mismatch-repair. This system is dedicated to correct the rare mistakes that are made. If a nucleotide is left uncorrected, the mismatch will result in a permanent mutation in the next round of DNA mutation. If the mistake is recognized later, the proteins remove the DNA strand that has the error and synthesizes a new strand. Having a damaged mismatched repair gene predisposes a person to cancer.

DNA is continually suffering damage in cells
DNA is continually undergoing thermal collisions with other molecules. These often result in major chemical changes in the DNA. This causes depurination (loss of A and T bases) and deamination (loss of an amino group from Cytosine in DNA to make Uracil). The ultraviolet radiation in sunlight is also damaging to the DNA. Usually these things can be repaired, if not these can have enormous consequences.

The stability of genes depend on DNA repair
Different enzymes catalyze the different repair systems. If one strand of the DNA is damaged, the information is not lost. The information is in the other strand, but just in the opposite order. The repairing of damaged DNA will be done in these three steps:

1. The damaged DNA is recognized and removed by one of the variety of different nucleases, which cleave the covalent bonds that join the damaged nucleotides to the rest of the DNA molecule, leaving a small gap on one strand of the DNA double helix in this region.

2. A repair DNA polymerase binds to the 3' hydroxyl end of the cut DNA strand. Then it fills the gap by making a complementary copy of the information stored in the undamaged strand. Although a different enzyme from the DNA polymerase that replicates DNA, a repair DNA polymerase synthesizes DNA strands in the same way. For example it synthesizes chains in the 5' to 3' direction and has the same type of proofreading activity to ensure that the template strand is accurately copied. In many cells, this is the same enzyme that fills the gap left after the RNA primers are removed in normal DNA replication.
3. When the repair DNA polymerase has filled the gap, a breaks remains in the sugar-phosphate backbone of the repaired strand. This nick in the helix is sealed by DNA ligase; the same enzyme that joins the lagged strand DNA fragments during DNA replication.

Step 1 uses different kinds of enzymes, depending on the damage that is done to the DNA.

The high fidelity with which DNA is maintained means that closely related species have protein with very similar sequences.
Because of the remarkable preservation of DNA the changes to it come very slowly throughout the evolution. The DNA sequence of a whale and a man are very similar.

Essential concepts

1. Life depends on stable and compact storage of genetic information.
2. Very long DNA molecules, encoded in the lineair sequence of nucleotides A, C, G and T, carry genetic information.
3. A molecule of DNA is in the form of a double helix composed of a pair of complementary strands of nucleotides held together by hydrogen bonds between G and C, A and T.
4. Each strand of DNA has a polarity due to the linkage of alternating sugars and phosphates in its backbone. The two strands of DNA molecule run antiparallel- that is, in opposite orientations.
5. Each of the two DNA strands can act as a template for the synthesis of the other strand. A DNA double helix thus carries the same information in each of its strands.
6. A DNA molecule is duplicated (replicated) by the polymerization of new complementary strands onto each of the old strands of the DNA double helix. This process of DNA replication, in which two identical DNA molecules are formed from the original molecule, enables the genetic information to be copied and passed on from cell to daughter cell and from parent to offspring.
7. As a DNA molecule replicates, its two strands are pulled apart to form one or more Y-shaped replication forks. The enzyme DNA polymerase, situated in the fork, lays down a new complementary DNA strand on each parental strand, thereby making two new double helical molecules.
8. DNA polymerase replicates a DNA template with remarkable fidelity, making less than one error in every 10^7 bases read. This is possible because the enzyme removes its own polymerization errors as it moves along the DNA (proofreading).
9. Since DNA polymerase can synthesize new DNA in only one direction, only one of the strands in the replication fork, the leading strand, can be replicated in a continuous fashion. On the lagging strand DNA is synthesized by the polymerase in a discontinuous backstitching process, making short fragments of DNA that are later joined up by the enzyme DNA ligase to make a single continuous DNA strand.
10. The proofreading feature of DNA polymerase makes it incapable of starting a new DNA chain. DNA synthesis is primed by a RNA polymerase, called primase that

makes short lengths of RNA, called primers that are subsequently erased and replaces with DNA.

11. DNA replication requires the cooperation of many proteins, which form a multienzyme replication machine, situated at the replication fork, that catalyses DNA synthesis.
12. Errors in the replication of DNA and chemical reactions that damages the nucleotides in DNA cause changes in the nucleotide sequence of DNA. If these changes were not efficiently corrected they would give rise to mutations, many of which would be harmful to the organism. Genetic information can be stored stably in DNA sequences only because a variety of DNA repair enzymes continuously scan the DNA and correct replication mistakes and replace damaged nucleotides. DNA can be repaired easily because one strand can be corrected using the other strand as a template.
13. The rare copying mistakes that slip through the replication machinery are dealt with by the mismatch repair proteins, which monitors new DNA and repair copying mistakes. The overall accuracy of DNA replication, included mismatch repair is one mistake by 10^7 nucleotides copied.
14. DNA damage caused by chemical reactions and ultraviolet irradiation is corrected by a variety of enzymes that recognize damaged DNA and excise a short stretch of the DNA strand that contains it. A repair DNA polymerase that uses the undamaged strand as a template resynthesizes the missing DNA. DNA ligase reseals the DNA to complete the repair process.

Essential Cell Biology

Chapter 7: from DNA to protein

The hereditary information is encoded in the nucleotide sequence. The DNA code has been deciphered and the language can be read. “Proteins are the principal constituents of cells and determine not only their structure but also their functions. Each type of protein has his unique amino acid sequence.
When a particular protein is needed, the nucleotide sequence is first copied into another type of nucleic acid, called RNA. These RNA pieces are used as template for the protein that is needed.
Transcription is the copying of DNA to RNA.
Translation is the use of information from the RNA to make a protein.

From DNA to RNA
Transcription and translation is the way a call expresses its genes. Because there can be more than one copy of this particular gene the reproduction can be much faster.

Portions of DNA sequence are transcribed into RNA
A cell starts by copying the necessary part of DNA, the gene, into a nucleotide sequence of RNA. This is called transcription. This RNA is made of ribose and the bases Guanine, Cytosine, Adenine and Uracil. RNA is also single stranded. It is able to form many different structures, allowing it to perform more duties in the cell.

Transcription produces RNA complementary to one strand of DNA
One of the two strands of DNA is the template. The amino acid sequence of RNA is also determined by the sequence of DNA, binding the complementary nucleotides. This RNA strand does not remain bonded to the DNA strand. The double helix of the DNA is restored. The RNA is also much shorter than the DNA strand. RNA polymerases are the enzymes that carry out the transcription. The RNA chain grows in the 5’ to 3’ way and the energy that is needed is distracted from the ATP, GTP, CTP or UTP. More than one strand of RNA is synthesized at the same time.
Also RNA polymerase differs from DNA polymerase, because RNA polymerase catalyzes the bonds between ribonicleotides and it cannot proofread. RNA polymerase can thus start a chain without a primer.
RNA does not need to be as accurate as the forming of DNA because it is not the definite storage place of the hereditary information.

Several types of RNA are produced in cells
The RNA molecules copied from the DNA strand are collectively called messenger RNA, or mRNA.
Ribosomal RNA, or rRNA is the core of the ribosome, on which the mRNA is translated into a protein and transfer RNA, or tRNA, select the amino acid and hold them at their place of the ribosome. This way, the amino acids are placed into a protein.
RNA can carry the information for one or a few proteins.

Signals in DNA tell RNA polymerase where to start and finish
RNA polymerase binds tightly when it encounters a site called a promoter. This promoter contains a sequence of nucleotides indicating the starting point for RNA synthesis. RNA polymerase can recognize this sequence even when the DNA is bonded into a double helix.

When the RNA binds to the promoter it opens up the DNA a bit and starts to synthesize the RNA strand. This synthesis is made until the polymerase encounters a stop site, called the terminator. The polymerase stops and lets both the DNA and the RNA go.
The sigma factor of the polymerase helps to recognize the promoter and lets go after 10 bonded nucleotides. The polymerase bonds with the sigma factor after the terminator.
The transcription can only proceed in the 5' to 3' direction.

Eucaryotic RNAs undergo processing in the nucleus
Bacterial DNA lies directly exposed to the cytoplasm where the ribosomes lie.
In a eucaryotic cell the DNA is contained within the nucleus. So this mRNA must first be transported to the cytoplasm. This RNA undergoes many processing steps. The unprocessed RNA is called primary transcript.
These processes are RNA capping (a modification of the 5' end of the primary transcript. A guanine with a methyl group is added) or polyadenylation (provides mRNA with a special structure at the 3' end. First some nucleotide sequences are cut off and then adenine nucleotides are added). These two processes are thought to stabilize the mRNA and to help the transport through the membrane.

Eucaryotic cells are interrupted by noncoding sequences
RNA has to undertake another step before it is functional. Also the RNA seemed to be getting shorter in the nucleus. Discovered was that only 5% of the produced RNA reached the cytoplasm? This is explained by the discovery that the coding sequence is interrupted by a noncoding sequence called introns. The useful coding sequence called exons is shorter than the introns. The exons are also a small fraction of the synthesized RNA.

Introns are removed by RNA splicing
First a long RNA, the primary transcript, is formed containing introns and exons. Capping and polyadenylation remove the introns sequences, and the exons are stitched together. This process is called RNA splicing. The RNA has become an mRNA and can leave the nucleus and is translated into a protein.
The introns contain short nucleotide sequences, which work as cues to the removal. The splicing enzymes are called small nuclear ribonucleoprotein particles, which also rejoins the RNA chain by the exons.
The introns form a lariat and will be degenerated in the nucleus.
It is thought that the introns were of use in the early days, that they speeded up processes, like making proteins. Many proteins in this day work together like protein domains.

The cell eventually degrades mRNA molecules
Every mRNA is eventually degraded in the cell to single nucleotides. The lifetime of an mRNA differs per cell and per function. This lifetime helps the cell to regulate the protein amount.

The earliest cells may have had introns in their genes
Making a RNA chain with both introns and exons means that the cell has to maintain a large genome. Smaller genomes allowing faster DNA replication could have contributed to the loss of introns. This fast translation could also mean smaller introns.

From RNA to protein
Information from DNA is first copied into RNA and than into a protein. This poses the coding problem: How is the sequence of RNA translated into the sequence of the amino acid chain?

An mRNA sequence is decoded in sets of three nucleotides
Translation is the conversion of the information in the RNA into a protein. This translation takes place in the genetic code. This is done by groups of three nucleotides, which gives us 64 combinations. However there are only 20 amino acids, so the other 44 resemble a similarly protein as another code.
Each three nucleotides are called a codon. A codon is specific for an amino acid.
Only mitochondria have a different system.

tRNA molecules match amino acids to codons in mRNA
The translation of mRNA to a protein depends on adaptor molecules that can recognize and bind both to the codon and to the amino acid. These are called tRNA.
The RNA folds like a cloverleaf, by the forming of hydrogen bonds.
A tRNA molecule has an anticodon that forms a bond with mRNA. The tRNA also forms a bond with the amino acid, which is done at the 3' site. Many codons differ only in their third nucleotide so that they can form a bond with a wrong amino acid, called a wobble.

Specific enzymes couple tRNAs to the correct amino acid
In order to read the genetic code cells make many different tRNA molecules. Recognition and attachment of the correct amino acid depends on enzymes called aminoacyl-tRNA synthetases. There are different synthetase enzymes for all different amino acids. This is all done by the use of ATP as an energy source. The amino acid is coupled to the 3' end of the tRNA.

The RNA message is decoded on ribosomes
Ribosomes are composed of one large unit and one small unit. The rRNA brings the small unit and the large unit together.
The small unit matches the tRNA and the mRNA together. The large unit catalysis the formation of the peptide bonds that link the amino acids together.
A ribosome moves along the mRNA translating the codons and using the tRNA to add each amino acid to the sequence.
The two units of the ribosome separate when the synthesis of the protein is complete.

A ribosome contains 4 binding places, one for the mRNA and three for the tRNA. These three places are called the A, P and E place. The tRNA bonds tightly if his codon forms hydrogen bonds with the A or P place. The tRNA molecules are hereby forced to form bonds with the mRNA molecule.
A new amino acid is bonded to tRNA and bonds to the A-site. The polypeptide chain is uncoupled from the former tRNA and attached to the new tRNA with the new amino acid. This new bond takes place at the A-site. The entire chain moves along a place now, putting the new chain on the p-site. This process is catalyzed by peptidyl transferase. The tRNA at the e-site dissociates.

Codons in mRNA signal where to start and to stop protein synthesis
The first step is very important and a mistake could mean a useless protein. The translation of an mRNA begins with the codon AUG. The initiator tRNA always carrying Met bonds on this place. Met could later be removed. This first tRNA has initiation factors with it and can make a strong bond with the small particle of the ribosome. Than the larger part of the ribosome adds itself and the process of synthesis can begin. The first tRNA searches for the first AUG to bond with it.

The end of the synthesis is marked by three different codons, UAA, UAG or UGA. These are called the stop codons. They signal the ribosome to stop the translation. Releasing factors bind to these stop codons and a water molecule is added instead of a new amino acid. This causes the release of the carboxyl group of the growing peptide, which causes it to let go of the ribosome. The peptide chain goes into the cytoplasm. The mRNA is also released and the two units of the ribosome are separated.

Proteins are made on polyribosomes
Many ribosomes attach themselves to a single mRNA to speed up the process of synthesis.

Carefully controlled protein breakdown helps regulate the amount of each protein in a cell
Cells regulate the amounts of protein by breaking them in their amino acids. Each protein has a different lifetime. The enzymes that degrade proteins (proteolysis) are known as proteases. They break the chain into small pieces and eventually in single amino acids. Proteolytic pathways are the lifetime planners of an enzyme. They also remove damaged proteins. Lysosomes also degrade the proteins that need to be broken down. Most proteins are degraded by proteasomes. It's a kind of tube, the protein goes in the tube in one piece, and comes out in single amino acid molecules. Proteasomes work primarily on the proteins that have been marked for destruction. The binding of a small protein called ubiquitin does this. Others proteins that have to be broken have a very short sequence and resemble the ubiquitin.

There are many steps between DNA and protein
The making of a protein depends on a lot of steps and the efficiency with which these steps are carried out.

RNA and the origins of life
To understand the processes as they occur now we have to understand how they occurred in the years of evolution. RNA is believed to be the first genetic carrier.

Simple biological molecules can form under prebiotic conditions
The circumstances on earth in the beginning of time, was very good for the forming of nucleotides. This happened and the nucleotides were bonded by condensation although the climate was very watery. These chains could catalyze themselves.

RNA can both store information and catalyze chemical reactions
Polynucleotides needed the ability to replicate themselves in order to create. RNA can be used as a template to produce more RNA. But without catalysts the polymer formation is slow, error-prone and inefficient. This is solved when appeared that RNA can work as a catalyst itself. This could have allowed RNA to play the central role in the origin of life. The RNA molecule can also fold into a unique three-dimensional pattern, due to the amino acid sequence.
RNAs with catalytic properties are called ribozymes.

RNA is thought to predate DNA in evolution
The earliest cells of the evolution had their hereditary information stalled in the RNA and not in DNA. Ribose is an easier structure and possesses all the elements that were on the early earth. DNA came later but proved to be more suited; the chain was far more stable. DNA was also easier to repair having Thymine instead of Uracil. Uracil is made out of Cytosine.

Essential concepts

1. The flow of genetic information in all living cells is DNA → RNA → protein. The conversion of the genetic instructions in DNA into RNAs and proteins is called gene expression.
2. To express the genetic information carried in DNA, The nucleotide sequence of a gene is first transcribed into RNA. The enzyme RNA polymerase catalyzes transcription. Nucleotide sequences in the DNA molecule indicate to the RNA polymerase where to start and stop transcribing.
3. RNA differs in several respects from DNA. It contains the sugar ribose instead of desoxyribose and the base Uracil instead of Thymine. RNAs in cells are synthesized as single stranded molecules, which often folds up into precise three-dimensional shapes.
4. Cells make several different functional types of RNA, including mRNA, which carries the instructions for making proteins; rRNA, which is a component of ribosomes; and tRNA, which acts as an adaptor molecule in protein synthesis.
5. In eucaryotic DNA, most genes are split into a number of smaller coding regions, called exons, interspersed with noncoding regions, called introns.
6. When a eucaryotic gene is transcribed from DNA into RNA, both the exons and introns are copied to produce the primary RNA transcript.
7. Introns are removed from primary RNA transcripts in the nucleus by the process of RNA splicing. In a reaction catalyzed by small ribonucleoprotein complexes from the primary transcript and the exons are joined together. The mRNA then moves to the cytoplasm.
8. Translation of the nucleotide sequence of mRNA into a protein takes place in the cytoplasm on large ribonucleoprotein assemblies called ribosomes. These attach to the mRNA and move stepwise along the mRNA chain, translating the message into a protein.
9. The nucleotide sequence in mRNA is read in sets of three nucleotides (codons), each codon corresponding to one amino acid.
10. The correspondence between amino acids and codons is specified by the genetic code. The possible combinations of the 4 different nucleotides in RNA give 64 different codons in the genetic code. Most amino acids are specified by more than one codon.
11. tRNA acts as an adaptor molecule in protein synthesis. Enzymes called aminoacyl-tRNA synthatases link amino acids to their appropriate tRNAs. Each tRNA contains a sequence of three nucleotides, the anticodon, which matches a codon in mRNA by complementary base pairing between codon and anticodon.
12. Protein synthesis begins when a ribosome assembles at an initiation codon AUG in mRNA a process that is regulated by proteins called initiation factors. The completed protein chain is released from the ribosome when a stop codon UAA, UAG, UGA is reached.
13. An rRNA molecule in the large ribosomal subunit probably catalyzes the stepwise linking of amino acids into a polypeptide chain.
14. The degradation of protein in the cell is carefully controlled. Some proteins are degraded in the cytosol by large protein complexes called proteasomes.
15. From our knowledge of present day organisms and the molecules they contain, it seems likely that living systems began the evolution of RNA molecule that could catalyze their own replication.
16. It has been proposed that, as cells evolved, the DNA double helix replaced RNA as a more stable molecule for storing increased amounts of genetic information, and proteins replaced RNAs as major catalytic and structural components.

17. The flow of information in present day living cells is DNA → RNA → protein, with RNA serving primarily as a go-between. Some important reactions, however, are still catalyzed by RNA; these are thought to provide a glimpse into the ancient, RNA-based world.

Essential Cell Biology

Chapter 8: Chromosomes and gene regulation

Genes are used selectively, which is called gene expression. This causes cell specialization. Cell differentiation is caused by changes in the gene expression. The DNA is folded inside the nucleus in such a way that the necessary genes are available.

The structure of eucaryotic chromosomes

Special proteins fold DNA in exactly the right way. Transcription, replication and repair are still necessary.

Eucaryotic DNA is packaged into chromosomes

A chromosome is a string DNA with the folding proteins. Also called a chromatin. The maternal and paternal chromosomes are one pair of homologous chromosomes. Only nonhomologous are the sex chromosomes. DNA hybridization is a way to distinguish and match the chromosomes.

Chromosomes exist in different states throughout the life of a cell

The state of the chromosomes varies according to the cell cycle. The highly condensed chromosomes in a dividing cell are called mitotic chromosomes. A mitotic spindle divides them.

Specialized DNA sequences ensure that chromosomes replicate efficiently

The first type of nucleotide sequence acts as a DNA replication origin. Most chromosomes contain more of these sequences so that the replication is done fast. The second sequence is called a centromere, which allows one chromosome to be pulled into a daughter cell. Kinetochore forms a complex between the centromere and the spindle, allowing them to be pulled apart. The third sequence is a telomere, which ables the ends of the chromosomes to be replicated. The ends attract the enzymes telomerase, which add the multiple copies of the DNA to the end of the chromosomes. They also protect the DNA from digesting enzymes.

Nucleosomes are the basic units of chromatin structure

Chromosomes that are ready for mitosis are folded up into the highly condensed mitotic chromosomes. Replication and transcription have ceased.
The first packing level of a chromosome is the nucleosome. It is like a bead in a string. The DNA is wounded twice around the core of the protein. The chromosome between two nucleosomes is called linker-DNA. The core of protein is made of 8 histone proteins. Nucleosome means the core and the linker DNA.
The histones are positively charged. This way they can easily bind to the negatively charged sugar phosphate groups on the backbone of the DNA.
Through histone the chromosomes becomes a chromatin.

Chromosomes have several levels of DNA packing

Tight packing of the nucleosomes gives the 30nm fiber. At the stage of mitosis the 30nm fiber is packed in a loop so it becomes visible under the microscope. When packing the DNA, the RNA synthesis stops.

Interphase chromosomes contain both condensed and more extended forms of chromatin

After mitosis the chromosomes unpack. They are now interphase chromosomes. Some parts are more extended for synthesis. Unfolding has to do with gene expression. Heterochromatin

is highly condensed, concentrated around the centromere and the ends of the chromosomes. It is inactive. Euchromatin is active chromatide and mostly unfolded.

Position effects on gene expression reveal differences in interphase chromosomes packing
Expressions of genes that are dependable of their location are termed position effects.

Interphase chromosomes are organized within the nucleus
Interphase chromosomes are also organized within the nuclear envelope. Both the membranes of the envelope have support by protein filaments. Most apparent chromosome organization is in the nucleolus, where the genes for rRNA are located.

Gene regulation
Differentiation between cells is because of different gene expression. A cell has the entire code of an organism.

Cells regulate the expression of their genes
The universal proteins (proteins every cell has) are called housekeeping proteins. The genes that encode them are housekeeping genes.
A cell can control proteins:

1. How often is this gene transcribed
2. How the primary RNA transcript is sliced/processed
3. Selecting mRNA for translation
4. (In) Activating the proteins

Transcription is controlled by proteins binding to regulatory DNA sequences
The promoter for synthesis starts at an initiation site. Regulatory DNA sequences are able to switch the gene on or off. For their effect these sequences have to be recognized by gene regulatory proteins. They bond to the DNA. Proteins mostly work in pairs.

Repressors turn genes off and activators turn them on
Genes transcribed on a single mRNA are called operons. This is mostly found in bacteria's, not in eucaryotes. The promoter has an operator site, which blocks RNA polymerase. The repressor has to bind with tryptophan and binds to the operator and the gene is switched off. Binding tryptophan to the repressor causes a slight structural change and this way the repressor can bind to the operator. No tryptophan proteins are transcribed (negative terugkoppeling). Unregulated gene expression is called constitutive gene expression. A RNA is always made but in low quantities.
Activators also act as promoters. A protein also stimulates its function first so that it can bind to the DNA.

Initiation of eucaryotic gene transcription is a complex process
Differences between bacteria and eucaryotes:

1. Eucaryotic cells have three types of RNA polymerase called I, II and III. They transcribe different genes. Bacterial cells only have one RNA polymerase.
2. Eucaryotic RNA polymerase needs the help of general transcription factors at the promoter to let polymerase start working. Bacteria do not need these factors.
3. Eucaryotic cells have activators and repressors that influence transcription even far away from the promoter. In bacterias they have to be near the promoter.
4. Eucaryotic transcription initiation is also reliable for folding.

Eucaryotic genes are regulated by combinations of proteins
Regulatory proteins can control transcription even if they are far away from the promoter. Proteins work together to express a gene by combinatorial control. Negative and positive proteins are added up and this decides the fate of the gene.

The expression of different genes can be coordinated by a single protein
Bacteria coordinate the expression of more genes at once by forming an operon with a single promoter. Eucaryotic cells have a protein that can activate different genes because they have the same binding site.

Combinatorial control can create different types
Regulatory proteins have influence on the differentiation of cells. Muscles have cells that are formed by the fusion of cells, and are called myoblasts. Muscles have the special actin and myosin proteins for the contraction. All of these proteins are switched on as the myoblast begins to fuse. These proteins are also in potential muscle cells and hereby help the differentiation. The dramatic differences between the cell types are produced by differences in gene expression.

Stable patterns of gene expression can be transcribed to daughter cells
Once a cell is differentiated it will stay this way. Also the daughter cells will become the same type of cell. Some will never ever divide again. VB. Muscle cells and neurons.
The gene expression is passed on to the daughter cell. A positive feedback loop makes sure that the daughter cell develops in the right way. A key gene regulatory protein activates the transcription of its own gene in addition. Another way is by the faithful propagation of a condensed chromatin structure from parent to daughter cell.

The formation of an entire organ can be triggered by a single gene regulatory protein
The regulatory protein can switch on or off sets of genes. The action of one regulatory protein can turn on a cascade of regulatory proteins, whose actions may result in forming an organized group of many different types of cells.

Essential concepts

1. The genetic material of a eucaryotic cell is contained within one or more chromosomes, each formed from a single enormous long DNA molecule that contains many genes.
2. The DNA in a chromosome contains, in addition to genes, many replication origins, one centromere and two telomeres. These sequences ensure that the chromosome can be replicated efficiently and passed on to daughter cells.
3. Chromosomes in eucaryotic cells consist of DNA tightly bound to a roughly equal mass of specialized proteins. These proteins fold up the DNA into a more compact form so that it can fit into a cell nucleus. The complex of DNA and proteins in chromosomes is called chromatin.
4. The proteins associated with DNA include the histones, which pack up DNA into a repeating array of DNA-protein particles called nucleosomes.
5. Nucleosomes pack together, with the aid of histone H1 molecules, to a 30 nm fiber. This fiber can be further coiled and folded.
6. Some forms of chromatin are so highly compacted that the packaged genes are transcriptionally silent. This is the case for all genes in the chromosomes during nuclear division (mitosis) when the chromosomes become highly condensed.

7. Specific regions of chromosomes, termed heterochromatin, are also condensed and inactive even in nondividing cells. Genes artificially moved into regions of heterochromatin are often silenced.
8. A typical eucaryotic cell expresses only a fraction of its genes, and the distinct types of cells in multicellular organisms arise because different sets of genes are expressed as a cell differentiates.
9. Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of transcription is the most important point of control.
10. The transcription of individual genes is switched on and off in cells by gene regulatory proteins. These act by binding to short stretches of DNA called regulatory DNA sequences.
11. Although each gene regulatory protein has unique features, most bind to DNA using one of a small number of protein structure motifs. The precise amino acid sequence that is folded into the motif determines the particular DNA sequence that is recognized.
12. RNA polymerase binds to the DNA and initiates transcription at a site called the promoter.
13. In bacteria, regulatory proteins usually bind to regulatory DNA sequences close to the RNA polymerase binding site and either activates or repress transcription of the gene. In eucaryotes, these regulatory DNA sequences are often separated from the promoter by many thousands of nucleotide pairs.
14. To initiate transcription, eucaryotic RNA polymerases require the assembly of a complex of general transcription factors at the promoter. Eucaryotic gene regulatory proteins are thought to act by affecting the assembly process, speeding it up (for activators) and slowing it down (for repressors).
15. In eucaryotes, the expression of a gene is generally controlled by a combination of gene regulatory proteins.
16. In multicellular plants and animals, the production of different gene regulatory proteins in different cell types ensure the expression of only those genes appropriate to that type of cell.
17. A single gene regulatory protein, if expressed in the appropriate precursor cell, can trigger the formation of specialized cell type or even an entire organ.

Essential Cell Biology

Chapter 10: DNA technology

Recombinant DNA, gene splicing and genetic engineering make it possible to create chromosomes with combinations that would never be created by nature. It can also manipulate genes.
We are going to study recombinant DNA technology.

How DNA molecules are analyzed

Genetic information was encoded in the nucleotide sequence of DNA. Restriction nucleases catalyzes the reaction by hydrolyzing a phosphodiester bond in a nucleic acid. They only cut at particular sites, marked by the sequence.

Restriction nucleases cut DNA molecules at specific sites
These nucleases only cleave the DNA at certain places marked by a specific nucleotide sequence. They will always give the same set of DNA fragments.

Gel electrophoresis separates DNA fragments of different sizes
The DNA fragments need to be separated. Gel electrophoresis separates the fragments based on their length. DNA is negatively charged so they move towards the positive electrode. The larger parts move more slow because they are more attached to the gel. DNA is usually invisible, unless they are stained in some way. This is done by fluorescent molecules or radiotopes.
A physical map is where the DNA is characterized by charting landmarks along the DNA fragments.
A restriction map is where the cutting sites of the DNA fragments are shown. It can reveal differences between closely related DNA's.

The nucleotide sequence of DNA fragments can be determined
DNA polymerase is used to make copies of the DNA fragments. This is done in vitro under specific circumstances.

Nucleic acid hybridization

The weak hydrogen bonds between the two DNA strands can be broken at 90 degrees Celsius, or putting it in an extreme pH surrounding.
Renaturation or hybridization is the reassemble of two strands when the temperature lowers or the pH returns to normal. The hydrogen bonds are restored. They however need complementary nucleotide sequences.

DNA hybridization facilitates the prenatal diagnosis of genetic disease
A DNA probe is a short single stranded DNA sequence that is used in hybridization reactions to detect nucleic acid molecules containing a complementary sequence. Some diseases are caused by one single mutation in a genome, but can now be detected in fetuses. Searching all the nucleotides is possible with DNA hybridization.
For a prenatal diagnosis some DNA is extracted from fetal cells. Two probes are used, one for the good sequence and one for the mutation sequence. Because we cannot repair mistakes in the genes, these people will have an increased risk of cancer.

In situ hybridization locates nucleic acid sequences in cells or on chromosomes
Probes are used with nucleic acid sequences when the DNA is still in the cell. This prevents the potential loss of very important information. This is called in situ hybridization. This is used for the detection of sequences of DNA in chromosomes or RNA in cells. It can also reveal the distribution of RNA from the nucleus to the cytoplasm. This helps with the understanding in gene expression.

DNA cloning
All of the above mentioned procedures are used to clone an individual stretch of DNA. It is used to make many identical copies of a particular needed part of DNA. First however we need to isolate this particular part of DNA.

DNA ligase joins DNA fragments together to produce a recombinant DNA molecule
The enzyme DNA ligase reseals the two DNA strands after repair or transcription. Once the two DNA strands are joined the cell cannot tell that they were once separated and the cell will treat the resulting DNA as one molecule.

Bacterial plasmids can be used to clone DNA
There are some different ways to clone a gene.
To clone within a rapidly dividing bacterium. It copies the introduced DNA as well. A bacterial plasmid is used as a carrier for the introduced DNA and helps it to stay in the cell. This cloning vector is circular DNA, and it contains a replication origin. The introduction DNA is placed in the bacterium and the bacterium can start growing. Later the pieces are cut out again and many copies of the needed DNA are made.

Human genes are isolated by DNA cloning
People with hemophilia A suffer for uncontrolled bleeding. The production of pure Factor VIII using recombinant DNA technology is significant for the treatment.
The first step in cloning a DNA sequence is making the DNA sequences shorter so that they are more manageable. The DNA is cut up in fragments. These fragments are cloned. The fragments are obtained in a genomic library. DNA probes are used to detect a particular part of DNA. If a gene does not have any introns it is easy to detect them when you have the right probe. Introns make the DNA longer and this makes it harder. Another library is constructed, cDNA (complementary DNA).

The cDNA libraries represent the mRNA produced by a particular tissue
The DNA in this library is not genomic but copied from mRNA's. To make this library all of the mRNA in a tissue is extracted and DNA copies are made. This cDNA is copied to make the library. The cDNA libraries are different for different organs due to the different mRNA's that are needed in the organ.

Hybridization allows even distantly related genes to be identified
Because related genes are so much alike it is easy to identify a family member once a gene has been isolated. This is by using the sequence of the first gene as hybridization probes.

The polymerase chain reaction amplifies the selected DNA sequences
The polymerase chain reaction is a much cheaper way to clone DNA. This is entirely done in vitro without the use of cells. A given nucleotide sequence can rapidly be copied.

PCR copies the DNA template by DNA polymerase. Primers are added at the place that needs to be replicated. PCR is extremely sensitive. It can detect a single copy of DNA sequence in a sample by amplifying it so much that it becomes detectable after staining.
PCR is used in three ways:

1. PCR can be used to clone a part of DNA. The original template can be DNA or mRNA, so a genomic copy or a cDNA copy is made.
2. PCR is also used to detect viral infections at very early stages. Sequences complementary to the viral genome are used as primers.
3. PCR has a great potentiality in forensic medicine. It can work in a very small sample and still make a DNA fingerprint.

DNA engineering
All this has provided new ways to study the function of genes, RNA and molecules and proteins.

Completely novel DNA molecules can be constructed
To make a library, one of the two DNA molecules is the vector, derived from a bacterial plasmid or virus and the other molecule is either fragment DNA or cDNA. By joining the fragments of DNA sequence a wanted gene can be made.

Rare cellular proteins can be made in large amounts using cloned DNA
DNA cloning and genetic engineering made it possible to produce large amounts of very rare proteins. This is usually done by expressions vectors, which include gene regulatory and promoter DNA sequences necessary to enable the fusion with a new piece of DNA and to let it be transcribed. In this way large amounts of the necessary protein are synthesized. These proteins have to be pured before they can be used.

RNAs can be produced by transcription in vitro
DNA technology can be used to make large amounts of RNA once its gene has been isolated. The synthesis can be done best in vitro without the other RNA's.

Mutant organisms best reveal the function of a gene
Neither the nucleotide sequence nor the three-dimensional structure can say what the protein does. Mutants that lack a particular protein show best what the protein does. Also damaged or altered proteins that can be switched on and off by altering the temperature can show the function of the protein.
Mutants are made in vitro and are put inside the cell.
Site directed mutagenesis is when the protein is altered. This reveals some functions of the protein.

Transgenic animals carry engineered genes
To insert the mutant gene inside an organism reveals the effect it has. These organisms with altered genes are called transgenic organisms. Sometimes the good gene is replaced by the mutant gene. This is done in homologous organisms.
The normal gene can also still be there.
The gene can be replaced if the cells are still germ like.

Essential concepts

1. Recombinant DNA technology has revolutionized the study of the cell, making it possible for researchers to pick out any gene at will from the thousands of genes in a cell and, after an amplification step, to determine the exact molecular structure of the gene.
2. A crucial element in this technology is the ability to cut a large DNA molecule into a specific and reproducible set of DNA fragments using restriction nucleases, each of which cuts the DNA double helix at only a particular nucleotide sequence.
3. DNA fragments can be separated from one another on the basis of size using gel electrophoresis.
4. Techniques are now available for rapidly determining the nucleotide sequence of ant isolated DNA fragment.
5. The complete nucleotide sequence of the genome of several single celled organisms (including several bacteria and yeast) are not known. Those of more complex organisms (the nematode worm, Drosophila, several plants and even humans) are anticipated in the next decade.
6. Nucleic acid hybridization can detect any given DNA or RNA sequence in a mixture of nucleic acid fragments. This technique relies on the fact that a single strand of DNA or RNA will form a double helix only with another nucleic acid strand of the complementary nucleic acid strand.
7. Single stranded DNA's of known sequences and labeled with fluorescent dyes or radioisotopes are used as probes in hybridization reactions. Nucleic acid hybridization can be used to detect the precise location of genes in chromosomes, or RNA in cells and tissues.
8. DNA strands of any desired sequence up to about 120 nucleotides can be made by chemical (nonenzymatic) synthesis in the laboratory.
9. DNA cloning techniques enable a DNA sequence to be selected from millions of other sequences and produced in unlimited amounts in pure forms.
10. DNA fragments can be joined together in vitro using DNA ligase to form recombinant DNA molecules not found in nature.
11. The first step in a typical cloning procedure is to insert the DNA fragment to be cloned into a DNA molecule capable of replication, such as a plasmid or a viral genome. This recombinant DNA molecule is then introduced into a rapidly dividing host cell, usually a bacterium, so that the DNA is replicated at each cell division.
12. A collection of cloned fragments of chromosomal DNA representing the complete genome of an organism is known as a genomic library. The library is often maintained as clones of bacteria, each clone carrying a different DNA fragment.
13. cDNA libraries contain closed DNA copies of the total mRNA of a particular cell type or tissue. Unlike genomic DNA clones, cloned cDNAs contain only protein-coded sequences; they lack introns, gene regulatory sequences, and promoters. They are thus more suitable for use when the cloned gene is to be expressed to make a protein.
14. The polymerase chain reaction (PCR) is a powerful form of DNA amplification that is carried out in vitro using a purified DNA polymerase. PCR requires a prior knowledge of the sequence to be amplified, since two synthetic oligonucleotide primers must be synthesized that bracket the portion of DNA to be replicated.

15. Cloned genes can be permanently inserted into the genome of a cell of an organism by the technique of genetic engineering. Cloned DNA can be altered in vitro to create mutant genes to order and then reinserted into a cell or an organism to study gene function.
16. Genetic engineering has far-reaching consequences. Bacteria, yeasts and mammalian cells can be engineered to synthesize a particular protein from any organism in large quantities, thus making it possible to study otherwise rare or difficult-to-isolate proteins.

Essential Cell Biology

Chapter 11: Membrane structure

A cell is held together by a plasma membrane. Fatty lipids make it. Transport through protein molecules. The membrane grows with the cell. They serve as a barrier between two different spaces. The proteins are responsible for giving an organelle its function.
A membrane is formed by a lipid bilayer.

The lipid bilayer
How does it behave in a watery environment?

Membrane lipids form bilayers in water
Lipids have a hydrophilic head and a hydrophobic tail. Most of the lipids are phospholipids. They are linked with a phosphate group. The most common phospholipid is phosphatidylcholine. It has a choline attached to the phosphate group. These molecules are amphipatic.
The hydrophilic head is pointed towards the water of the cell and the hydrophobic tails are formed together. A tear will be eliminated because it is energetically unfavorable. Eventually a ball is formed.

The lipid bilayer is a two-dimensional fluid
The phospholipids can move within the bilayer. Flip-flop, the exchange of phospholipids between monolayers, does not occur often. Phospholipids do rotate around their axis. They also exchange places with their neighbors.

The fluidity of a lipid bilayer depends on its composition
The movement of the phospholipids is important for the function of the membrane. A short carbon tail increases the fluidity. The tail also has C=C bonds, it is unsaturated. This forms kinks and makes the phospholipids more fluid.
The length and saturation can be altered.
Fluidity is necessary for the diffusion of proteins, interaction of proteins and cell signaling.
Cholesterol stiffens the bilayer by going in the openings of the bilayer.

The lipid bilayer is asymmetrical
This is due to the different selection of phospholipids and the exact positioning of the proteins. Enzymes form the bilayer. Flippase makes the selection, and gives the membrane its unique phospholipid sequence.

Lipid asymmetry is generated inside the cell
Membrane synthesis takes place in the E.R. These pieces are then transported and attached to the membrane. Cytosolic side is on the inside of the cell. Noncytosolic layer is on the outside. Glycolipids are situated on the noncytosolic half. The sugar groups are on the exterior of the cell.
Inositol phospholipids are for the signaling of the cell, but are located on the cytosolic half.

Lipid bilayers are impermeable to solutes and irons
The hydrophobic interior forms the barrier for the hydrophilic molecules. Small, hydrophobic molecules can diffuse quickly.

1. Small non-polar molecules dissolve rapidly in the bilayer and diffuse easily.
2. Uncharged polar molecules diffuse fast if they are small.
3. Ions and charged molecules cannot be diffused because of their attraction to water. Membrane transport proteins transport these.

Membrane proteins
The proteins carry out the membrane functions. They account for the transport, anchors, receptors and enzymes. Proteins reflect the function of the membrane.

Membrane proteins associate with the lipid bilayer in various ways

1. Many membrane proteins lie through the bilayer. It also has hydrophobic and hydrophilic regions.
2. Some proteins are only on the outside, attached by bonding
3. Some are only in one layer.

Proteins have unique orientations in the membrane.

A polypeptide chain usually crosses the bilayer as an a-helix
Proteins are connected to each other by amino acids with hydrophobic side chains within the bilayer. The amino acid backbone is hydrophilic so hydrogen bonds have to be made in the hydrophobic layer. A a-helix is formed. If the chain crosses the bilayer once they are receptors.
Proteins that have to transport water (soluble molecules) cross the membrane a number of times. ? -helices are formed and they together form an aqueous pore.
Transport can also be done through ß-sheets, which have a ß-barrel at the top. (Porinprotein)

Membrane proteins can be solubilized in detergents and purified
Detergents can separate proteins from the membrane. They have only one tail, which is hydrophilic. In water they form micelles. They remove the protein by bonding with it. They also bond the phospholipids together.

The complete structure is known for very few proteins
Standard method is X ray crystallography. Some bacterial proteins get their energy from sunlight. The retinal, a molecule, absorbs the light, and changes, which causes the bilayer to change. An H+ is transported. The retinal than bonds a new H+ and the process continue. The H+ is used for ATP generating.

The plasma membrane is reinforced by the cell cortex
Membranes are strengthened by proteins, which form a network called the cell cortex. An abnormality in the spectrin (a rod of amino acids) is responsible for fewer red blood cells.

The cell surface is coated with carbohydrate
Glycoproteins have sugars linked to them called oligosaccharides. Proteoglycans have polysaccharide chains attached. These are all located on the noncytosolic side. This forms a sugarcoating called glycocalyx. It helps to protect the cell. The slimy surface is necessary for

transport between the cells. These sugars also provide recognitions of the cell and adhesion. This also makes infections noticeable.

Cells can restrict the movement of membrane proteins
Proteins can move within their layer, but they are also confined within a way. These areas are called membrane domains. This can be done by forces outside the cell, inside the cell or by barriers.
An apical surface is the side that is connected to the external environment.
A basal surface is the surface that is attached to other tissues.
A lateral surface is the surface that is attached to one kind of tissue.
A tight junction creates a seal between the cell membranes. Diffusion between the cells has become impossible.

Essential concepts

1. Cell membranes enable cells to create barriers that confine particular molecules to specific compartments.
2. Cell membranes consist of a continuous double layer of lipid molecules in which proteins are embedded.
3. The lipid bilayer provides the basic structure and barrier function of all cell membranes.
4. Membrane lipid molecules have both hydrophobic and hydrophilic regions. They assemble spontaneously into bilayer when placed into water, forming closed compartments that reseal if torn.
5. There are three major classes of membrane lipids molecules: phospholipids, sterols and glycolipids.
6. The lipid bilayer is fluid, and individual lipid molecules are able to diffuse within their own monolayer; they do not however flip for one layer to the other.
7. The two layers of the lipid bilayer have a different lipid composition, reflecting the different functions of the two faces of a cell membrane.
8. Cells adjust their membrane fluidity by modifying the lipid composition of their membranes.
9. The lipid bilayer is impermeable to all ions and large polar molecules, but it is permeable to small non-polar molecules such as oxygen and carbon dioxide and to very small polar molecules such as water.
10. Membrane proteins are responsible for most of the functions of a membrane, such as the transport of small water-soluble molecules across the lipid bilayer.
11. Trans-membrane proteins extend across the lipid bilayer but are attached to one or the other side of the membrane either by noncovalent association with other membrane proteins or by covalent attachments to lipids.
12. Many of the proteins and some of the lipids exposed on the surface of cells have attached chains of sugars, which help protect and lubricate the cell surface and are involved in cell-cell recognition.
13. An attached framework of proteins supports most cell membranes. An example is the meshwork of fibrous proteins forming the cell cortex underneath the plasma membrane.
14. Although many membrane proteins can diffuse rapidly in the plane of the membrane, cells have ways of confining proteins to specific membrane domains and of immobilizing particular proteins by attaching them to intracellular or extra cellular macromolecules.

Essential Cell Biology

Chapter 12: Membrane transport

Many molecules must be able to pass the membrane if the cell wants to stay alive. Some can easily diffuse through the bilayer, but most of them have to be transported by membrane transport enzymes. This makes sure that only the needed molecules enter the cell.
There are two classes of transport enzymes:

1. Carrier proteins, binds a solute on one side and drops it on the other by a change in conformation of the carrier protein.
2. Channel proteins, form tiny hydrophilic pores in the membrane and diffusion can take place. They can let through ions.

The ion concentrations inside a cell are very different from those outside
Ions are very important to living cells. They maintain the osmotic value, and play a central key in nerve cells. Na is on the outside of the cell and K is on the inside of the cell. Cl balances the Na; the K is balanced by fixed anions. Negatively charged molecules.

Carrier proteins and their functions
They are required for the transport of small organic molecules. It is highly specific, transporting only one type of molecule.
Membrane transport proteins are believed to be both. The transport is done through a channel created by multiple *a*-helices.
Both proteins discriminate. The channel protein discriminates on base of size and charge. A carrier protein only transports those molecules it can bond to. This binding is specific.

Solutes cross membranes by passive or active transport
Movement of molecules from a high concentration to a low concentration occurs spontaneously. This movement is called passive.
To move the solute against the concentration gradient a transport enzyme has to work, it costs energy. This is called active transport.

Electrical forces as well as concentration gradients can drive passive transport
A carrier protein has two conformations, one with the binding site at the exterior of the cell and one with the binding place one the interior of the cell. This way, processes can be regulated. The concentration gradient regulates the process. This protein does not determine the transport direction itself, and so the process is done passively.
For electrically charged molecules an extra force comes in to play. Membranes have a voltage across them. This is called the membrane potential. The electrochemical gradient regulates the passive transport of charged molecules.

Active transport moves solutes against their electrochemical gradients
Cells carry out active transport in three main ways:

1. Coupled transporters, the uphill transport of one solute is combined with the downhill transport of another solute
2. ATP-driven pumps, couple uphill transport to the hydrolysis of ATP.
3. Light-driven pump, couple uphill transport to the energy from light.

The ATP driven pump has the main role in active transport.

Animal cells use the energy of ATP hydrolysis to pump out Na+
The Na+ pump hydrolyses ATP to ADP. It also couples the inward transport of Na+ to the outward transport of K+. This gives it the name Na+-K+ pump. This takes 30% of all the made ATP. The inside of a cell has a negative charge; so positive ions want to move in to the cell. This force is strong due to the concentration gradient and the electrochemical gradient.

The Na^+-K^+ pump is driven by the transient addition of a phosphate group
The pump is a couple transporter.
(zie boek blz. 379)

Animal cells use the Na+ gradient to take up nutrients actively
Coupled transporters use the energy from the first transport for the second transport as well. The transport is called symport if the molecules are transported in the same direction and it is called antiport if the transport is done in opposite directions.
A carrier protein that only transports one solute across the membrane in different directions is called a uniport. These proteins are used to maintain all sorts of processes, such as the osmotic value.

The Na+-K+ pump helps maintain the osmotic balance of animal cells
Water diffuses to make the concentrations equal. This is done from diffusing water from the low concentration to the high concentration and is called osmosis. The driving force is osmotic pressure. Without counteracting forces, the water will diffuse into the cell causing it to swell. Na^+ and Cl^- balance the concentration in the cell, preventing the cell to swell. The cell has to keep pumping the solutes outside the cell, because of the electrochemical gradient. This pumping is done by the Na^+-K^+ pump.

Intracellular Ca^{2+} concentrations are kept low by Ca^{2+} pumps
Ca is inside the cytosol, but not as plentiful as Na. It is crucial that Ca stays at its place, because binding with other molecules can mean altering its function. A flow of Ca into the cell is often a signal for e.g. muscle contraction. Low concentrations of free Ca in the cytosol means high sensitivity. The Ca pump, that works, maintains the Ca concentration very similar to the K-Na pump.

H^+ gradients are used to drive membrane transport in plants, fungi and bacteria
H^+ gradients are used to drive solutes into the cell. An H^+ pump pumps the H^+ outside the cell disrupting the homeostasis. This causes the cell to take inside many sugars and amino acids. The H^+ is also used to keep the interior of some organelles acid, which is critical to their function.

Ion channels and the membrane potential
Channel proteins are hydrophilic channels through the membrane. They allow the passive movement of water-soluble molecules through the membrane.
Some proteins form gap-junctions between two cells.
Most channel proteins are ion-channeling proteins.

Ion channels are ion selected and gated
Ion channels are different from other channels because they show two great differences:

1. They are ion selective, depending on the diameter and shape of the channel, and on the charged amino acids. The ions lose all their water molecules going through.

2. Ion channels are also not continuously open. They are gated. This way they can control the amounts of ions that are transported.
3. They work much faster than normal channels, up to a thousand ions per second.
4. There can only be passive transport.

An ion flow changes the membrane potential, which influences the entire cell, giving a signal. The membrane potential is the basis of all the electrical activity.

Ion channels randomly snap between open and closed states

Patch-clamp recording measures the electric current flow in a single channel. It is possible to see the affects of the changing in the membrane potential to the opening of the channels. The channel changes its conformation by random thermal movement of the molecules in its environment.

Essential concepts:

1. The lipid bilayer of cell membranes is highly impermeable to most water-soluble molecules and all ions. Membrane transport enzymes carry out transfer of nutrients, metabolites, and ions across the plasma membrane.
2. Cell membranes contain a variety of transport proteins each of which is responsible for transferring a particular type of solute across the membrane. There are two classes of membrane transport proteins-carrier proteins and channel proteins.
3. The electrochemical gradient represents the net driving force on an ion due to its concentration gradient and the electric field.
4. In passive transport an uncharged solute moves spontaneously down its concentration gradient, and a charged solute (ion) moves spontaneously down its electrochemical gradient. In active transport an uncharged solute or an ion is transported against its concentration or electrochemical gradient in an energy-requiring process.
5. Carrier proteins bind specific solutes (inorganic ions, small organic molecules or both) and transfer them across the lipid bilayer by undergoing conformational changes that exposes the solute binding site first on one side of the membrane and then on the other.
6. Carrier proteins can act as pumps to transport a solute uphill against its electrochemical gradient using the energy provided by ATP hydrolysis, by a downhill flow of Na^+ or H^+ ions, or by light.
7. The Na^+-K^+ pump in the plasma membrane of animal cells is an ATPase that actively transports Na^+ out of the cell and K^+ in, maintaining the steep Na^+ gradient across the plasma membrane that is used to drive other active transport processes and to convey electrical signals.
8. Channel proteins form aqueous pores across the lipid bilayer through which solutes can diffuse. Whereas transport by carrier proteins can be active or passive, transport by channel proteins is always passive.
9. Most channel proteins are selective ion channels that allow inorganic ions of appropriate size and charge to cross the membrane down the electrochemical gradient. Transport through ion channels is at least 1000 times faster than transport through any known carrier protein.

Essential Cell Biology

Chapter 14: Intracellular compartments and transport

Processes must be done separately or the process cannot be done fully. To organize the chemical reactions, cells have two different strategies:

1. To assemble all the enzymes those are needed for a particular reaction into one protein complex.
2. To confine different metabolic processes and the required proteins within membrane bounded compartments.

Membranes have a selective permeable barrier. Each compartment contains a unique set of proteins. These proteins are transported to the compartment by protein sorting. This depends on the amino acids sequence.
Communication between cells is done through vesicles. They pinch off from one cell and move through the cytosol to melt with another cell. This is called vesicular transport.

Membrane bounded organelles
Internal membranes divide the cytosol. Reactions that occur within the membranes will occur without disturbance. Each compartment has a unique set of organelles.

Eucaryotic cells contain a basic set of membrane bounded organelles
The cytosol contains varies of organelles:

1. A double membrane, the envelope, bound the nucleus. It is in contact with the cytosol through pores.
2. The E.R. is a continuous membrane and forms the nuclear envelope as well. It synthesizes new membrane. If the E.R. has ribosomes attached to it is called rough E.R. Smooth E.R. is rare, but it is for detoxification and steroid hormone synthesis.
3. The Golgi apparatus receives proteins and lipids from the E.R., modifies them and ships them off again.
4. Lysosomes are digestive enzymes. They break down disposable material.
5. Endosomes sort out the ingested molecules and recycles them back to the plasma membrane.
6. Peroxisomes have a single membrane and contain enzymes for oxidative reactions.
7. Mitochondria have a double membrane and produces ATP.

Organelles that are attached to the cytoskeleton stay more or less in the same place. Centrifuging can separate them.

Membrane bounded organelles evolved in different ways
Compartments probably evolved in stages. The first cells are to believe to be bacterial, because they are simple and self-sufficient. Internal membranes probably originated from invagination of the plasma membrane. Mitochondria were believed to live in symbiosis with the cell at first and later consumed by the cell. This also explains the double membrane of the mitochondria.

Protein sorting
A cell has to duplicate its organelles before dividing. The organelles grow, are divided and then each transported into another daughter cell. There must always be enough lipids and proteins for degrading or making new organelles. The mitochondria, chloroplasts, peroxisomes and the nucleus get the proteins directly from the cytosol. The other organelles get the proteins through the ER. Proteins enter the ER direct from the cytosol. Some stay and

some are transported as vesicles. First to the Golgi and then to the other organelles. Proteins made in the cytosol are dispatched to different locations in the cell according to specific address labels that they contain in their amino acid sequence.

Proteins are imported into organelles by three mechanisms
Almost all proteins are made by ribosomes in the cytosol and are than transported into organelles. The amino acid sequence is a sorting signal that directs the proteins to the organelle. Proteins without a sorting signal stay in the cytosol as a residue. It is difficult for organelles to import proteins because of their membranes, but three answers were found:

1. Nucleus → proteins are transported through the nuclear pores, which are selective gates. They actively transport macromolecules, but diffuse small molecules freely.
2. ER, mitochondria, chloroplasts or peroxysomes → proteins are transported through these membranes by protein translocators in the membrane. Proteins must unfold and sneak through.
3. From ER to other organelle → ferried by transport vesicles. Vesicles become loaded with proteins from the lumen (interior space) of a compartment as they pinch off from its membrane. Fusing with another membrane unloads the cargo.

Signal sequences direct proteins to the correct compartment
The signal sequence is often removed from the protein if the sorting is done. The signal sequences specifying the same destination can vary greatly even though they have the same function: physical properties, such as hydrophobicity or the placement of charged amino acids, often appears to be more important for the function than the exact amino acid sequence.

Proteins enter the nucleus through nuclear pores
The inner nuclear membrane contains proteins that act as binding sites for the chromosomes and the nuclear lamina (protein filaments for support of the nucleus). The nuclear envelope has pores. These are the gates to the nucleus. Each pore contains one or more water filled channels, through which small water-soluble molecules can pass freely. Larger molecules cannot pass the pores unless they have the right sorting signal. The transport from the cytosol through the pores is done by nuclear import receptors. The energy comes from GTP hydrolysis. The nuclear import receptor always returns to the cytosol for reuse. Proteins do not have to unfold to get through the nuclear pores.

Proteins unfold to enter mitochondria and chloroplasts
They both have a double membrane and synthesize ATP. They both make their own proteins, because they carry genomes. But they also get proteins from the cytosol. These proteins can be transported through the double membrane where the two membranes come together. The protein unfolds is transported and the sorting signal is cleaved off. This is done with the help of chaperone proteins. Transport in the organelles is done by another sorting signal. Water-soluble lipid-carrying proteins transport lipids.

Proteins enter the ER being synthesized
The ER transports proteins to other organelles. Vesicles do the transport. Water-soluble proteins are translocated to the ER lumen and further transported. Prospective transmembrane proteins are embedded in the ER membrane where they either stay or go to another organelles membrane. Proteins that enter the ER are mostly not completely synthesized. This requires that the ribosomes be attached to the ER creating rough ER. They are attached to the cytosolic side. There are also free ribosomes in the cytosol.

Soluble proteins are released into the ER lumen
The ER signal sequence has two components:

1. Signal recognition particle (SRP)→ is in the cytosol and binds to the signal sequence when its exposed on the ribosome
2. SRP receptor → is in ER membrane. When it bonds with SRP this piece is chopped off and the protein synthesis recommences. The proteins go through the translocation channel into the lumen.

The signal sequence also opens the translocation channel. The signal is cleaved off and degraded.

Start and stop signals determine the arrangement of a transmembrane protein in the lipid bilayer
Some proteins remain in the ER as transmembrane proteins. The first amino terminal sequence initiates translocation. A stop transfer sequence embeds the protein in the membrane by a a helix.
The amino acid stop sequence is cut off. Once anchored the protein does not change its orientation. Sometimes an internal sequence starts the translocation. This is not removed afterwards. This is the case with multipass membrane proteins.

Vesicular transport
The transport through the ER (vesicular transport) always goes to the Golgi first. It is a sort of communication between organelles. Proteins and lipids undergo chemical changes to stabilize the protein structure.

Transport vesicles carry soluble proteins and membrane between compartments
A secretory pathway leads from the biosynthesis of proteins on the ER, into the ER, through the Golgi to the cell surface.
An endocytic pathway is responsible for the ingestion and degrading of extra cellular molecules. From plasma membrane to endosomes to lysosomes. A vesicle is specific in its bonding and transport.

Vesicle budding is driven by the assembly of a protein coat
Vesicles have a protein coat and are called coated vesicles. After transport the coat is released and it can fuse with the distinctive organelle. The coat shapes the vesicle and helps with the onward transport.
Clathrin-coated-vesicles → protein clathrin on the coat. Comes from the Golgi and forms the plasma membrane. At the plasma membrane each vesicle starts as a clathrin coated pit. The clathrin starts to form a ball on the membrane (on the cytosolic side) and this is the start of the vesicle. Dynamin assembles around the neck of each pit, hydrolyses its GTP and thereby pinching off the vesicle. Adaptins bind the coat to the vesicle membrane and selects the cargo molecules. Cargo receptors recognize the cargo and binds to it.

The plasma membrane and the Golgi have different adaptins as different pathways.

The specifity of vesicle docking depends on SNARE's
If the distance is short the vesicles diffuse, if the distance is long they are helped by motor proteins. The vesicle has to recognize and dock with its target. SNARE's give the vesicle membrane and the target membrane a specifity, a bonding place for that particular vesicle. When docked the vesicle fuses with the membrane and not only delivers its cargo, but also fuses its membrane. To fuse a water molecule must be displaced from the hydrophilic surface of the membrane. This of course has to be catalyzed to form the fusion complex.

Secretory pathways
Exocytosis is when a vesicle fuses with the plasma membrane. The vesicle has the route ER, Golgi, cell surface for this process. Along its route the vesicle is modified. This process is also monitored.

Most proteins are covalently modified in the ER
Proteins are modified as they enter the ER by S-S. It helps to stabilize the structure. They are mostly converted into glycoproteins by glycosylation with the help of enzymes. The oligosaccharides protect the protein, retain it in the ER and guide it to the right organelle. The oligosaccharides also form the glycocalyx. The side chain is already formed and it is attached in the whole, to the lipid dolichol and transferred to the NH_2 group of asparagines.

Exit from the ER is controlled to ensure protein quality
Proteins that have to stay in the ER have an ER retention signal. Most proteins however have to go to other organelles by vesicle transport. Exit from the ER is highly selective. Wrong proteins bind to chaperone proteins and stay in the ER. The protein than has to correct the wrong or is degraded.
Cystic fibrosis produces a plasma membrane transport protein that is misfolded. Because it is retained in the ER it has consequences.

Proteins are further modified and sorted in the Golgi apparatus
The Golgi is situated near the nucleus. It exists of flattened sacs. The number of sacs varies per cell. Each stack (all the sacs) has an entry (cis) and an exit (trans) face. The cis points to the ER and the trans to the plasma membrane. Transport to, in, and from the Golgi is through vesicles. They enter at the cis side. Proteins are again sorted, making sure that they land in the right place. The oligosaccharide groups are modified again.

Secretory proteins are released from the cell by exocytosis
Vesicles bud from the Golgi to the plasma membrane to supply it with new lipids and proteins (exocytosis pathway). This is for the growth of the cell or secretion of proteins. Regulated exocytosis pathways are only found in cells that are destined for secretion. They produce e.g. hormones, which are transported through secretory vesicles. These proteins aggregate and this is the recognition mark. Aggregation also makes sure that much more proteins can fit the secretion vesicle.

Endocytic pathways
Molecules ingested by the cell are transported through endocytic vesicles. The material ultimately comes in the lysosomes for digestion. The metabolites are freed into the cytosol where they are used. Pinocytosis involves the ingestion of fluid and very small vesicles. Phagocytosis involves the ingestion of larger particles. The vesicles are called phagosomes. Specialized phagocytic cells normally do this.

Specialized phagocytic cells ingest large particles

Phagocytosis is a way of feeding. The food is digested in the lysosomes. Phagocytic cells defend us against infection. Particles must first bind to the receptors of the cell, and some receptors recognize antibodies. Phagocytic cells also remove damaged/dead cells.

Fluid and macromolecules are taken up by pinocytosis

Exocytosis and endocytosis are in homeostasis in the cell. The endocytic pathway first goes to the endosomes. Clathrin-coated vesicles normally do it. Fluid intake is balanced by fluid loss.

Receptor mediated endocytosis provides a specific route into animal cells

The endocytosis is not specific. It will take any cargo. Receptor mediated endocytosis is when vesicles are filled with macromolecules that bonded with receptors.
VB. Cholesterol that is needed for new membrane is transported in the bloodstream by LDL. The LDL bonds with the receptors. Through vesicle transport they are delivered to the endosomes. The acid environment causes the LDL-receptor-bond to break and LDL goes to the lysosomes. There the cholesterol is released and delivered in the cytosol.
People that have arteriosclerosis have a defective LDL system.

Endocytosed macromolecules are sorted in the endosomes

There are early endosomes and late endosomes. Their environment is acidic by a H^+ pump. Endosomes also sort out the vesicles:

1. Most are returned to the same plasma membrane part
2. Some travel to lysosomes
3. Some go to a different part of plasma membrane by transcytosis.

Lysosomes are the principal sites of intracellular digestion

Lysosomes are sacs carrying hydrolytic enzymes for digestion. They need an acidic environment (pH5). The enzymes cannot work in the cytosol (pH7.2). Maintained by an H^+ pump. Lysosomes have a unique membrane. It has transport proteins for moving the particles to the cytosol. The enzymes are made in the ER. Lysosomes can also digest other organelles. The organelle is enclosed by membrane from the ER creating an autophagosome, which fuses with the lysosome.

Essential concepts

1. Eucaryotic cells contain many membrane-bounded organelles, including a nucleus, ER Golgi, lysosomes, endosomes, mitochondria, chloroplasts (in plant cells) and peroxisomes.
2. Cells make new membrane bounded organelles by enlarging existing ones, which then divide.
3. Most organelle proteins are made in the cytosol and transported into the organelle where they function. Sorting signals in the amino acid sequence guide the proteins to the right organelle; proteins that function in the cytosol have no signals and remain where they are made.

Essential Cell Biology

Chapter 15: Cell communication

In a multicellular organism, cells must coordinate their behavior in many different ways.

General principles of cell signaling
The process of converting information is called signal transduction. A molecule is produced by a signaling cell and detected by a target cell, by a receptor protein. Cell signaling consists of reception and transduction.

Signals can act over long or short range
Hormones are signaling molecules secreted into the bloodstream. Cells that produce hormones are endocrine cells.
Paracrine signaling → the signal molecule stays near the cell that secreted it and they act as local mediators. Vb. Wound healing (inhibit cells)
Neuronal signaling → messages are delivered over private lines. Each electrical impulse stimulates the synapses to secrete a pulse of a chemical signal called a neurotransmitter.
Contact-dependant signaling → between two cells contact is made through signaling molecules in their plasma membranes (immuunsystem).

Each cell responds to a limit set of signals
A cell must respond selectively to the mixture of signals. This depends on the receptors the cell has. The signals are used to control the behavior of the cell in two ways:

1. Binding to a receptor, the molecule can change the target cell or some of the organelles. This depends on the type of cell.
2. The different receptors on the cell can make the cell sensitive for more than one reaction. This can cause serious reactions. Signals used in a different combination can get control over the cell.

Receptors relay signals via intracellular signaling pathways
Mostly the target molecule is a receptor protein. It receives the signal and generates a new intracellular signal in response. The message is transported this way. The final outcome is the response of the cell. These intracellular signaling molecules have several crucial functions:

1. Transfer the signal
2. Transform the signal
3. Amplify the signal
4. Distribute the signal
5. Modulate the signal (outside interference)

Some signal molecules can cross the plasma membrane
Large and hydrophilic signal molecules cannot pass the plasma membrane. Receptors lie in the membrane to attach to the signal molecules.
Small, hydrophobic signaling molecules can diffuse across the plasma membrane and the receptors are on the inside of the cell. These receptors are gene regulatory proteins or enzymes. The steroid hormones and thyroid hormones are the best known. The receptors for these hormones lie in the inactivated cell. When the hormone is attached to the receptor, the structure changes and the specific sequence in the DNA is transcribed.

Nitric oxide can enter cells to activate enzymes directly
A quick reaction is done by the activation of an enzyme instead of first producing one. NO does this. It causes smooth muscle cells of the blood vessels to relax so that more blood can go through them. Vb. Erection.
NO can quickly diffuse from one cell to another. The most common target of NO is guanylate cyclase, which catalyzes the formation of cyclic GMP, which evokes a response in the cell.

There are three main classes of cell-surface receptors
Most signaling molecules are unable to pass the plasma membrane. Receptors are on the outside of the cell. There are three large families:

1. Ion-channel-linked receptors → a flow of ions produces an electrical effect.
2. G-protein-linked receptors → an activated form of a membrane-bounded protein may diffuse activating a cascade of effects.
3. Enzyme-linked receptors → enzyme activity is switched on through the receptor and creates further signals.

Many drugs and poisons also act in this way.

Ion-channel-linked receptors convert chemical signals into electrical ones
These are used by the nervous system; they transduce a chemical signal, in the form of a pulse, directly to an electrical signal. The channel lets through ions, which go through the channel because of the electrochemical gradient. The membrane potential is changed.

Intracellular signaling cascades as a series of molecular switches
Enzyme-linked receptors start a cascade of activating signaling molecules, which are mostly proteins. They serve as messengers and can also alter the signal. Most signaling molecules behave as switches. A signal turns them on and they stay on until another signal turns them off. These signals are mostly phosphor groups, added by kinase and disattached by phosphatase. Others are the GTP-GDP binding proteins.

G-protein-linked receptors
Despite the diversity of the signal molecules that bind to them, all G-protein-linked receptors have a similar structure. These are all seven-pass-transmembrane-receptor-proteins.

Stimulation of G-protein-linked receptors activates G-protein subunits
When a signaling molecule is attached the G receptor changes its structure it can interact with a G protein.
A G protein is constructed by three subunits, the a, ß and ?. Unstimulated the a has a GDP bonded. When activated the GDP is replaced by GTP and the a unit is turned loss from the other two units. The two proteins can than activate other molecules and are themselves turned off by GTP hydrolyze. The two units of the complex make one complex again.

Some G proteins regulate ion channels
The target proteins for G proteins are ion channels or membrane bounded enzymes. This is done by the same principle discussed earlier.

Some G proteins activate membrane-bound enzymes
The most frequent target enzymes for G proteins are adenylate cyclase. This produces cyclic AMP. There are G proteins that stimulate enzyme activity and those that suppress enzyme activity. These intracellular signaling molecules are called second messengers.

The cyclic AMP pathway can activate enzymes and turn on genes
The a unit of G proteins mostly stimulate the activation of adenylate cyclase and thus the activation of cyclic AMP. It can carry signals to their organelles. Different target cells respond very differently to the rise of cyclic AMP. Not all effects are as fast as the others. Cyclic AMP exerts the various effects by activating A-kinase. Other target cells are activated.

The pathway through phospholipase C results in a rise in intracellular Ca^{2+}
G proteins also activate the membrane bound enzyme phospholypase C that act on the inositol phospholipids. Phospholipase C generates two different messenger molecules. These are IP_3 and DAG. These are important for the signaling inside the cell.
IP_3 goes to the ER and opens the Ca^{2+} channel and the Ca^{2+} molecules rush out into the cytosol. The concentration is normally kept very low.
DAG helps to activate the protein kinase C and stays attached to the membrane. It has to bind Ca^{2+} to become active.

A Ca^{2+} signal triggers many biological processes
It has a widespread function as an intracellular messenger. It can influence many sorts of reactions by binding to Ca^{2+} sensitive proteins.
The concentration in the cytosol is normally low. A pump maintains this. This gives a steep electrochemical gradient. When a channel opens the Ca^{2+} rushes out and triggers a reaction.
One of the most common Ca^{2+} binding proteins is calmodulin, which is present in the plasma membrane. It is activated and this activates other molecules. These molecules can be CaM-kinases, which influence the phosphorylating of selected proteins.

Intracellular signaling cascades can achieve astonishing speed, sensitivity and adaptability: photoreceptors in the eye
The photoreceptor cells of the retina produce electrical responses to a sudden flash of light.
Amplification is done when there is not much light.
Adaptation occurs in signaling pathways. A cell can remain sensitive to changes.
Sight and taste both rely on G proteins.

Enzyme linked receptors
They have a role in response to growth factors. Responses are typically slow. It also influences the way a cell moves and changes its shape. They also play a role in the cancer process.

They are also transmembrane proteins that bind to a ligand at the cytosolic side. On the inside it acts as an enzyme or binds a protein that can act as an enzyme, vb tyrosine kinase.

Activated receptor tyrosine kinases assemble a complex of intracellular signaling proteins
Signal molecule binding causes two receptors to form a dimmer, the contact between the tails activates the kinase function. One tail will phosphorylate the other. Signaling complexes are drawn towards the tails. These proteins become active. They all send different signals if they are different proteins and so a complex response is triggered, such as cell proliferation. When the phosphates are removed the signal stops, because the proteins are no longer activated.

Receptor tyrosine kinases activate the GTP-binding protein RAS
Through the phosphorylation of the dimmer receptors, an adaptor protein is attached to the phosphate group. This is activated and activates a RAS-activating protein. When the RAS is activated it changes its GDP for a GTP and now it can promote the cascade of kinases, which will eventually influence the protein activity and the gene expression.
A hyperactive RAS can cause tumors. It stimulates cell proliferation.

ONCOGENES = cancer-promoting genes

PROTO-ONCOGENES = the not mutated version of oncogenes. They are called this way because they can be changed into oncogenes.

Protein kinase networks integrate information to control complex cell behavior
Kinases regulate components of the other signaling pathways as well as components of their own pathway. There is cross talk between different pathways.
Cells have to combine the information from many different sources and have to make up the right response. This is done by cross talk.

Essential concepts

1. Cells in multicellular organisms communicate through a large variety of extra cellular chemical signals
2. Hormones are carried in the blood to distant target cells, but most other extracellular signal molecules act only over a short range. Neighboring cells often communicate through direct cell-surface contacts.
3. Cells are stimulated through an extracellular signal when it binds to and activates a receptor protein. Each receptor protein recognizes a particular signal molecule.
4. Receptor proteins act as transducers converting the signal from one physical form to another,
5. Most extracellular signal molecules cannot pass through the cell membrane; they bind to receptor proteins located on the cell surface. These receptors transduce the signal across the plasma membrane.
6. Small hydrophobic extracellular signal molecules such as steroid hormones and NO can diffuse directly across the plasma membrane; they activate intracellular receptor proteins, which are either gene regulatory proteins or enzymes.
7. There are three main classes of cell-surface receptors: (1) ion-channel-linked-receptors, (2) G-protein-linked-receptors and (3) enzyme-linked-receptors.
8. G-protein-linked receptors and enzyme-linked receptors respond to extracellular signals by initiating cascades of intracellular signaling reactions that alter the behavior of the cell.

9. G-linked protein receptors activate a class of trimeric GTP-binding proteins, which acts as molecular switches, transmitting the signal onward to the interior of the cell for a short period and then switching themselves off by hydrolyzing their bound GTP to GDP.
10. Some G proteins directly regulate ion channels in the plasma membrane. Others activate the enzyme adenylate cyclase, increasing the intracellular concentrations of cyclic AMP. Still other G proteins activate the enzyme phospholipase C, which generates the messenger molecules IP_3 and DAG.
11. IP_3 opens ion channels in the membrane of the ER, releasing a flood of free Ca^{2+} ions into the cytosol. Ca^{2+} itself acts as an intracellular messenger, altering the activity of a wide range of proteins.
12. A rise in cyclic AMP activates protein kinase A while Ca^{2+} and DAG in combination activate protein kinase C.
13. C-kinase and A-kinase phosphorylate selected target proteins on serines and threosines, thereby altering protein activity. Different cell types contain different target proteins and are affected in different ways.
14. In general, stimulating G-protein-linked receptors produces rapid and reversible cell responses.
15. Many enzyme-linked receptors have intracellular protein domains that function as enzymes; most are receptor tyrosine kinases, which are activated by growth factors and phosphorylate tyrosines on selected intracellular proteins.
16. Activated receptor tyrosine kinases cause the assembly of an intracellular signaling complex on the intracellular tail of the receptor; a part of this complex serves to activate RAS, a small GTP-binding protein, which activates a cascade of protein kinases that relay the signal from the plasma membrane to the nucleus.
17. Mutations that stimulate cell proliferation by making RAS hyperactive are a common feature of many cancers.
18. The different intracellular signaling pathways interact, enabling cells to produce an appropriate response to a complex combination of signals. Some combinations of signals enable a cell to survive; other combinations of signals will cause it to proliferate; and in the absence of any signals, most cells will kill themselves.

Essential Cell Biology

Chapter 16: Cytoskeleton

Cytoskeleton is a protein filament network throughout the cytoplasm. It supports the cytoplasm. It can be altered by changes in its environment. The cytoskeleton is the bones and the muscles. It controls the locations of the organelles and provides the transport between them.
It is built of three different proteins: intermediate filaments, microtubules and actin filaments.

Intermediate filaments
Their function is withstanding stress that is given with the cell stretching. Their diameter is between that of actin or myosin. These filaments are very tough. They are found in the cytoplasm of animal cells. They are often anchored to the cell-cell junctions and at the nuclear envelope. They are also the nuclear lamina.

Intermediate filaments are strong and durable
The filaments are twisted strands. Each strand has a NH_2 head and a COOH tail. In between is the rod domain. This rod domain consists of a a helical region, which enables firm dimers. These dimers than form a tetramer by noncovalent bonding. The rods are all the same. The head and tail regions are busy with forming bonds with the cytoplasm-components. These ends do differ in structure.

Intermediate filaments strengthen cells against mechanical stress
Intermediate filaments are abundantly in cells that have mechanical stress as nerve cells and muscles and skin cells. They keep the membrane from tearing.
Intermediate filaments in the cytoplasm can be divided in to three different groups:

1. Keratin filaments in epithelial cells
2. Vimentin and vimentin related cells in connective tissue cells, muscle cells and supporting cells of the nervous system
3. Neurofilaments in nerve cells

A filament is made of polymerization of their protein subunits.
Keratin has the biggest subunit family. Keratin filaments span the interiors of epithelial cells and are connected with each other by cell-cell junctions called desmosomes. These are very important in the cell, because they make sure that cells are able to withstand rupture.
Intermediate filaments also form the lamina, a two-dimensional structure on the inside of the nuclear envelope. It is made of lamins. This lamina disassembles and reforms at every cell division. The proteins called kinases do this. The noncovalent bonds between the strand break and the lamina is divided. Phosphorilation does this.

Microtubules
Long and stiff hollow tubes that can be disassembled for transport. They grow from the centrosome. Organelles can be moved along this network. This determines the place of the membrane bounded organelles and the intracellular transport. They form the mitotic spindle at mitosis. They can also form permanent structures. The organizing function depends on the association of microtubules and accessory proteins.

Microtubules are hollow tubes with structurally distinct ends
They are made from the subunits tubulin. This tubulin is a dimer of a a and a ß unit. A protofilament is a stack of tubulin proteins. The protofilaments together form the microtubule.

A protofilament has a polarity. The tubulin adds more rapidly to the plus end. The polarity is crucial for the transport ability.

A balance of assembly and disassembly maintains microtubules
Free tubulin molecules in the cytoplasm are for the growth of the microtubules. The continue modification of the microtubules is crucial for the function. Some drugs can alter this function causing the cell to stay in mitosis. The inactivation or destruction of the mitotic spindle causes the cell to die. This is used I the treatment of cancer.

The centrosome is the major microtubule-organizing center in animal cells
Centrosomes organize everything about the microtubules. They are located on one side of the nucleus when the cell is not in mitosis. The ? tubule is the starting point of the growth of the microtubules. The minus end of the protofilament is embedded in the centrosome.
Centrioles are made of microtubules embedded in the centrosome.
Cells control the microtubules making by keeping the amount of free tubulin molecules low and creating nucleation sites at the right time.

Growing microtubules show dynamic instability
Microtubules growing from the centrosome undergo changes that are called dynamic instability. The tubes can be enlarged or broken down or even disappear. Each dimer has a GTP bonded to it. This GTP is hydrolyzed to GDP, which is not firmly attached to the chain. If the chain is produced fast enough the hydrolysation cannot destroy the chain, because there are GTP tubules at the end. These GTP tubules at the end form the GTP cap. It prevents depolymerisation.
If GTP hydrolyses before the next molecule is attached the chain will start to disassemble. These freed tubulin molecules are than transported to the cytosol where they exchange the GDP for a GTP.
The chain is stabilized when it reaches a target. This forms a stable link between the centrosome and the target.

Microtubules organize the interior of the cell
Cells adapt their microtubules to the phase their in. Proteins that are bonded to the microtubules when it has reached its target, prevents the microtubules from altering.
They are stabilized and maintain the structure of the cell. Most cells are polarized. It helps to position the organelles, and is for the transport of signals or secretions. Microtubules do not act alone, but with the help of proteins. Motor proteins move along the microtubules. They use the energy of ATP hydrolysis to transport organelles or vesicles along the tracks.

Motor proteins drive intracellular transport
Saltatory movement is the short jerking movements of cells. Motor proteins generate these movements. They bind to the filaments and use the energy from ATP hydrolyses to move along it. They also attach other molecules, which they take with them as cargo.
The motor proteins that move along the cytoplasmic microtubules such as a nerve cell are the kinesins that move from the – to the +, and the dyneins that move from the + to the -. They have heads with a specific structure that binds to the microtubules if it fits. The tail will bind to the cargo. The heads are enzymes that hydrolyze ATP, which is used for the movement along the network.

Organelles move along microtubules
Microtubules and their motor proteins play an important role in the positioning of membrane-bounded organelles. Drugs alter the microtubules and in this way also the position of the organelles. If the drug is removed they will retain their position. Motor proteins do all this.

Actin filaments
These are essential for the movement of the cell. The cells crawl along surfaces. The actin filaments are also unstable, but they can form stable structures as in the muscle. Actin binding proteins enable the filaments to serve their functions. For example the contractile ring is formed out of actin filaments.

Actin filaments are thin and flexible
A filament is a twisted chain of identical actin molecules. The filament has a structural polarity. They are found in cross-linked bundles and networks.

Actin and tubulin polymerize by similar mechanisms
The filaments grow by adding monomers at the end. It is unstable and can disassemble at both ends. The disassembly starts with the hydrolization of ATP in ADP. This reduces the binding strength and the chain disassembles.
The ability to (dis)assemble is necessary for the functions the filaments have to do.

An actin rich cortex underlies the plasma membrane of most eucaryotic cells
The cell cortex is just under the plasma membrane and is made of actin filaments. It supports the outer surface of the cell and gives it mechanical strength. It includes a dense network of actin filaments that are projected into the cytoplasm.

Cell crawling depends on actin
Cells move by crawling over surfaces, rather than by swimming. The molecules in the cell are changed in order to crawl. An organelle as flagellum is responsible. It is done in three different stages:

1. The cell pushes out protrusions at its front
2. These adhere to the cell surface
3. The cell drags itself forward by traction to these anchor points.

All three processes involve actin, but all in a different way. Transmembrane proteins in their plasma membrane known as integrins adhere to molecules in the extracellular matrix or on the surface of another cell over which the moving cell is crawling. The cell attaches itself to a further lying anchor by stretching out and bonds with it. Then it lets its behind go and retracts a bit. The motor proteins that enable this are myosins.

Actin associates with myosin to form contractile structures
All actin dependant motor proteins are of the myosin family. They move along the actin filaments by ATP hydrolyzing. It works closely together in the muscle. There are two different myosins.

1. Myosin I → has one head domain and a tail. The head interacts with actin. The tail varies, creating different myosin I. It sets out the cargo it can take.
2. Myosin II → is located in the muscle. It has two heads and one tail. They form contractile structures with actin filaments. It is a dimer held together by the tail. They work in opposite direction, letting the actin slide one way on one of the two chain, and letting actin slide the other way on the other chain. This is done with muscle contraction.

During muscle contraction actin filaments slide against myosin filaments
Skeletal muscle contracts moving bones in our body. These skeletal muscles are made of fused cells. This fiber is multinucleated. The cytoplasm is made up of myofibrils the contractile elements of the muscle. A myofibril contains a chain if identical contractile units called sacromeres. It gives the myofibril the striped appearance. The thin actin filaments and the thick myosin II filaments do this striping. These filaments overlap each other. Shortening of the sacromeres cause the contraction. When a contraction is needed, the head of the myosin walks along the actin filament. They are pulled together. Relaxation caused by the unattachment of myosin to actin. With contraction each head hydrolyzes an ATP.

Muscle contraction is triggered by a sudden rise in Ca^{2+}
The interaction between myosin and actin only takes place when the skeletal muscle receives a signal from the nervous system. The signal gives an action potential. The signal moves into transverse tubules that extend inward from the plasma membrane around each myofibril. Than it is relayed to the sarcoplasmic reticulum. This is like ER in muscle. It contains a high concentration of Ca^{2+}, which is released when the signal arrives. It goes through the ion channels and interacts with a molecular switch. It changes its shape, which allows myosin to attach to actin. This initiates contraction.
Because the signals arrive at the same time the filaments contact at the same time. It stops when no more signals are given.
Smooth muscles cells need enzymes for the contraction. This is however nonspecific.

Essential concepts

1. The cytoplasm of a eucaryotic cell is supported and spatially organized by a cytoskeleton of intermediate filaments, microtubules and actin filaments.
2. Intermediate filaments are stable ropelike polymers of fibrous proteins that give cells mechanical strength. Some types underlie the nuclear membrane to form the nuclear lamina; others are distributed throughout the cytoplasm.
3. Microtubules are stiff hollow tubes formed by polymerization of tubulin dimer subunits. They are polarized structures with a slower growing minus end and a faster growing plus end.
4. Microtubules are nucleated in, and grow out from, organizing centers such as the centrosome. The minus ends of the microtubules are embedded in the organizing center.
5. Many of the microtubules in a cell are in a labile dynamic state in which they alternate between a growing state and a shrinking state. These transitions known as dynamic instability are controlled by the hydrolyses of GTP bound to tubulin dimers.
6. Actin filaments are helical polymers of actin molecules. They are more flexible than microtubules and are often found in bundles or network associated with the plasma membrane.
7. Actin filaments are polarized structures with a fast and a slow growing end. Their (dis)assembly is controlled by the hydrolysis of ATP tightly bound to each actin monomer.
8. The varied forms and functions of actin filaments in the cells depend on multiple actin binding proteins. These control the polymerization of actin filaments, cross-link the filaments into loose networks or stiff bundles, attach them to membranes, or move them relative to one another.

9. Myosins are motor proteins that use the energy of ATP hydrolysis to move along actin filaments; they can carry organelles along actin-filament tracks or cause adjacent filament s to slide past each other in contractile bundles.
10. A network of actin filaments underneath the plasma membrane forms the cell cortex, which is responsible for the shape and movement of the cell surface, including the movements involved when a cell crawls along a surface.
11. Muscle contraction depends on the sliding of actin filaments along myosin II filaments, driven by the repetitive motion of the myosin heads.

Essential Cell Biology

Chapter 17: Cell division

Cells are generated from cells. The cycle of duplication and division is known as the cell cycle. Nerve cells and muscle cells do not divide. To produce two identical daughter cells the DNA must be exactly copied, and the chromosomes neatly separated. Cell division is largely the job of the cytoskeleton. Nuclear division is called mitosis and cytoplasmic division is called cytokinesis. The forming of an n-cell from a 2n-cell is called meiosis.

Overview of the cell cycle
Duration of the cell cycle differs per cell.

The eucaryotic cell cycle is divided into 4 phases
The mitosis and the cytokinesis are the M phase. In between two M phases is the interphase. The interphase is divided into three different phases:

1. S phase → replication of nuclear DNA
2. G1 phase → gap phase
3. G2 phase → gap phase

During the interphase the cell synthesizes proteins and grows in mass. First sign of the M phase is the condensation of the chromosomes. This helps with the separation into two daughter cells.

The cytoskeleton carries out both the mitosis and the cytokinesis
The mitotic spindle divides the chromosomes. They are pulled to the spindle poles. The contractile ring is responsible for the dividing of the cytosol. The ring contains actin and myosin filaments. It pulls together.

Some organelles fragment at mitosis
The cell also has to inherit all organelles. Mitochondria can divide themselves so that the daughter cells each have the right amount. ER and Golgi break up in small particles and are divided over the two daughter cells.

Mitosis
Before mitosis the chromosomes have doubled. They are bound at a centromere, which is broken at the stage o mitosis. Mitosis is divided into 5 stages:

1. Prophase → chromosomes condense and mitotic spindle begins
2. Prometaphase → nuclear envelope breaks and the spindle binds to the chromosomes
3. Metaphase → the spindle gathers the chromosomes to the equator of the spindle
4. Anaphase → chromatids are split apart and pulled to the opposing poles
5. Telophase → nuclear envelope reassembles

The mitotic spindle starts to assemble in prophase
The centrosomes between the chromatids break and move toward the poles. The mitotic spindle is the set of microtubules in the cell along which the chromatids travel. Microtubules can rapidly grow or shrink and go to all directions from the centrosome.

Chromosomes attach to the mitotic spindle at prometaphase
Prometaphase starts with the break down of the nuclear envelope into small vesicles. The microtubules bind to these vesicles and pull them towards the centrosome. Microtubules bind

to the chromosomes through kinetochores. The chromatids let go at the centromere. The kinetochore binds to the chromatide and to the microtubules. This enables a good dividing. A random microtubule binds to the chromatide. The chromatide is pulled to the spindle pole.

Chromosomes line up at the equator at metaphase
The chromosomes line up at the equator making the metaphase plate. The microtubules try to pull the chromosomes to the spindle pole.

Daughter chromosomes segregate at anaphase
Proteolytic enzymes cut the centromere and the chromatids can move to the spindle pole. The microtubules shorten (anaphase a) and the distance between the spindle poles grows (anaphase b). Motor proteins do the segregation.

The nuclear envelope reassembles at telophase
The chromosomes are split up and a nuclear envelope is build around them. The vesicles cluster around the chromosomes and fuse. The chromosomes decondensate and transcription is possible.

Cytokinesis
Cytokinesis is the process of the cleavage of the cytoplasm. This also divides the organelles.

The mitotic spindle determines the plane of cytoplasmic cleavage
It starts during the anaphase. The cleaving is at 90° on the mitotic spindle. The cell can even adjust its centrosomes. The cell divides symmetrically so they have the same size.

The contractile ring of animal cells is made of actin and myosin
The ring assembles at anaphase. The cleavage is based on the sliding of the filaments against each other. It is broken down during the process. The new cells can than blend with the tissue.

Meiosis
Gametes, cells specialized for sexual reproduction, are haploid. Other cells are diploid (two sets of chromosomes). Meiosis is the process at which the number of chromosomes is halved.

Homologous chromosomes pair off during meiosis
Each cell contains a paternal chromosome and a maternal chromosome. They are homologous (similar but not identical). With meiosis a cell does not get both chromosomes but only one so that a diploid cell can be formed at fertilization. Separation is not done between chromatids but between pairs.

Meiosis involves two cell divisions rather than one
After DNA replication the two chromosome pairs are linked together to a structure called bivalent. As the two daughter cells are formed they are 2n. In this bivalent stage crossing over can occur. Both the nuclear envelope breaks down and the prometaphase starts. The rest is the same as mitosis. Eventually 4 haploid cells are formed.

Nondisjunction = the centromere does not break so one daughter cell misses the chromosomes and the other cell has doubled the chromosomes. Vb. Downsyndrom.

Essential Cell Biology

Chapter 18: Cell-cycle control and cell death

In the cell the control system that ensures the correct progression through the cell cycle by regulating the cell-cycle machinery is the cell-cycle control system. This system has to activate the enzymes and other proteins that have to carry out their task at that time. It also has to deactivate them again. The control system is also responsible for signals from other cells. When the system malfunctions it can result into cancer.

The cell-cycle control system
This was always very mysterious, but when they discovered the separate proteins responsible for specific reaction, they figured out how it was done.

A central control system triggers the major processes of the cell cycle
A central controller triggers each process. The process, through feedback, regulates the controller. Without the feedback an interruption or delay is disastrous. Each phase must be completely over before a new phase can start. The cell-cycle control system can achieve all this through checkpoints. If something goes wrong, the cycle is slowed down.
The cell has a checkpoint for the growth. For growing a cell needs nutrients and other factors of the extra cellular environment.
Actually there is a checkpoint after every phase, so that a cell cannot start a new phase before ending one. The control system can be regulated by signals from other cells.

Cells can dismantle their control systems and withdraw from the cell cycle
Making the cell stop dividing all together is a radical decision a cell has to make. Entering cells into the G_0 phase do this. This is done with nervous tissue and muscle.
Cells only multiply when other cells tell them. If no such signals arrive at the cell it goes into the G_0 phase. They can be pulled out of this stage again if they receive the proper signals.

Control of cell numbers in multi cellular organisms
Difference in bodily size depends on the number of cells. Cell proliferation as well as the survival and death must be regulated by signals from other cells.

Cell proliferation depends on signals from other cells
Cell sin a multi cellular organism only divide when other cells say that it is necessary. For growing it also needs nutrients. These surrounding cells work as stimulance and as a brake. Growth factors are often stimulated to override the brakes.

Animal cells have a build-in limitation of the number of times they will divide
Even though cells are very able to divide again they have a system that keeps them from another division. The number of times a cell will divide depends on the age of the individual. This is called cell senescence. This can also help determine the body size.

Animal cells require signals from other cells to avoid programmed cell death
The signals from other cells are often called survival factors. If cells do not get these the commit suicide. Some parts of our body are even sculpted by this programmed suicide. In some cases the cell number is regulated in this way, so that there are not too many cells.
In an adult the cell death and cell birth is balanced.

Programmed cell death is mediated by an intra cellular proteolytic cascade
Cell necrosis is when a cell dies of damage. The programmed cell death is called apoptosis. The cell does not damage its neighbours. The plasma membrane is altered so that the cell is labelled for destruction by fagocytosis. Proteases cleave the organelles of the cells and kill it in this way.

Cancer cells disobey the social controls on cell proliferation and survival
Cancer is a fault in the DNA that keeps the cell from listening to the signals from the other cells. But also the faults in the DNA are given to the offspring by replication and cells start to divide untamed. A tumour grows. The proliferation genes (stimulus of the cell to grow) and the antiproliferation genes (that are the brakes) are damaged.
A fault in the proliferation gene results in hyperactive grow of the cell. The gene is now called an oncogene. The protein can be abnormally active when a cell, which normally does not produce the protein, produces it, or because the protein is produced in excessive amounts or when the protein has an uncontrolled activity.

Essential concepts

1. The cell-cycle control system coordinates the events of the cell cycle by cyclically switching on the appropriate parts of the cell-cycle machinery and then switching them off.
2. The cell-cycle control system can halt the cycle at specific checkpoints to ensure that the next step in the cycle does not begin before the previous one has finished.
3. Animal cell numbers are regulated by a combination of intra cellular programs and intra cellular interactions (social controls) that control cell proliferation, cell survival and cell death.
4. Animal cells only proliferate if stimulated by growth factors, which activate intra cellular signalling pathways to override the normal brakes that otherwise block cell-cycle progression; this mechanism ensures that a cell divides only when another cell is needed.
5. Most normal animal cells have an internal mechanism of unknown nature that limits the number of times they can divide.
6. Many normal cells die during the lifetime of an animal cell by activating an internal suicide program and killing themselves-a process called programmed cell death or apoptosis.
7. Programmed cell death depends on family of preteolytic enzymes, which are themselves activated by a proteolytic cascade.
8. Most animal cells require continuous signalling from other cells to avoid programmed cell death; this may be a mechanism to ensure that cells survive only when and where they are needed.

Essential Cell Biology

Chapter 19: Tissues

Cells depend on their membrane for survival. Most cells in multicellular organisms are packed in tissues. The cells secrete an extracellular matrix around them. This gives support to the tissue. Cell junctions connect cells.

Extracellular matrix and connective tissues

Animals are predators and must contain tissues for rapid movement; cells must be able to change quickly. Cells need the extracellular matrix for stability, which is more needed in one tissue then in the other.

Animal connective tissues consist largely of extracellular matrix

There are four different types of tissue:

1. Epithelial tissue
2. Connective tissue
3. Nervous tissue
4. Muscle

In connective tissue there is much extracellular matrix that carries the load. There are many forms of connective tissue. A protein called collagen provides the strength.

Collagen provides tensile strength in animal connective tissues

Collagen is a long, stiff, triple-stranded helical structure. These molecules are twisted agai n into collagen fibrils and these pack together in collagen fibers. In skin the producing cells are called fibroblast, in bones they is called osteoblast. These are released by exocytosis.

Cells organize the collagen that they secrete

Collagen fibrils must be correctly aligned to do their job. Collagen is organized in cells by fibroblasts. They organize them into cables. The fibroblasts influence the alignment of the collagen fibers and the collagen fibers affect the distribution of the fibroblasts.

Integrins couple the matrix outside the cell to the cytoskeleton inside it

Fibronective provides a link for the cell to crawl on collagen. The cell bonds to the fibronective by the integrin. Actin filaments are attached to the integrin to withstand the tension.

Gels of polysaccharide and protein fill spaces and resist compression

Proteoglycans resist compression and fill spaces. These are extracellular proteins and are linked to negatively charged glycoaminoglycans (GAG). In different tissues there are different amounts of GAGs. GAGs are strongly hydrophilic and are usually stretched out. Because they are negatively charged they attract Na, which in his turn attracts water. If there is lots of collagen in a tissue the attraction of water by the GAGs create a pressure giving the tissue strength. The proteoglycans form gels. They can also bind growth factors or proteins that serve as signals for the cell. They can also prevent a cell from moving.

Epithelial sheets are cell-cell junctions

If a sheet of cells is many layers thick it is stratified, if it has small high cells, it is columnar, if it has square cells it is called cuboidal and if the cells are very flat it is called squamous.

These are barriers, secrete products, absorb nutrients or detect signals. The epithelial lining has the function for a tissue that the plasma membrane has for a cell.

Epithelial sheets are polarized and rest on a basal lamina
The apical surface is exposed to the air or watery fluid, the basal face is pointed to the interior. The epithelium is supported by a basal lamina. This is made of collagen and a protein called laminin. Integrins can bond to these laminins. This sheet is polarized. This is important for its function. The organization of the sheet maintained by junctions made between the epithelium and the lamina.

Tight junctions make an epithelium leak-proof and separate its apical and basal surfaces
Junctions can provide leak-proof seals, mechanical attachment, or chemical communication. Junctions prevent the pass of small molecules between the cells.

Cytoskeleton linked junctions bind epithelial cells robustly to one another and to the basal lamina
Adherens and desmosome junctions bind the cells in the epithelium. Hemidesmosome junctions bind the epithelium to the lamina.
Adherens and desmosome junctions are build around proteins called cadherens. Two neighboring cadherens bond, in the presence of Ca. Actin filaments are attached to the cadherens and a belt is formed. It is made just below the tight junctions. It gives the cell ability to change. Desmosome junctions bind keratin for strength.
Blisters show that skin has to be attached to the underlying layers. Integrins form the bond between the laminin and the keratin, and are called hemidesmosomes.

Gap junctions allow ions and small molecules to pass from cell to cell
Gap junctions are the final type of junction. The gaps are complexes made of proteins and are called connexons. These go through two plasma membranes and are the passage way for ions and small molecules.

Tissue maintenance and renewal, and its disruption by cancer
Blood vessels lined with endothelial cells supply the oxygen, nutrients and waste disposal. Tissues are also innervated by nerve cells. A tissue is really a mixture of different cell types. Tissue is constantly dying and new tissue is made. The tissue is preserved in three ways:

1. Cell communication ensures that new cells are produced only when they are needed.
2. Selective cell-cell adhesion prevents the cell mixture from becoming unorganized.
3. Cell memory makes sure that cells maintain their character.

Different tissues are renewed at different rates
Cells have different patterns of turn over. Old bone matrix is slowly eaten away by osteoclasts but new matrix is formed by osteoblasts. Life depends on these renewal processes. Ionizing radiation blocks the cell division.

Stem cells are generated continuous supply of terminally differentiated cells
Cells, that need continuous replacement, are unable to divide, they are terminally differentiated. New cells are generated from stem cells. These stem cells can divide without limit. Each daughter cell has a choice, either to stay a stem cell, or to differentiate. Stem cells only produce the cells.
The pattern of cell replacement varies from one stem-cell-based tissue to another. These stem cells make sure that tissues can grow and can be repaired.

Essential Cell Biology

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Mutations in a single dividing cell can cause it and its progeny has to violate the normal controls
A cell must divide when a new cell of its type is needed. It must also live a specific time, only when it is needed. When a single cell is genetically altered and it is able to survive when it has to die, and produces a daughter cell with the same bad behavior and when the tissue becomes distorted, this is called cancer.
With cancer the cell and the daughter cell reproduce in defiance of normal restraints and invade and colonize territories normally preserved for other cells.
A tumor is benign when it divides excessively but does not spread through the tissue. The tumor can be removed by surgery.
A tumor is cancerous when it invades other tissues. This kind of tumor is malignant. The cells can enter the bloodstream or lymphatic vessels and form secondary tumors called metastases. This is very difficult to cure.

Cancer is a consequence of mutation and natural selection within the population of cells that form the body
Cancer is a genetic disease, an alteration in the information of the DNA. Cancer is due to somatic mutations, mutations that occur in scattered individual cells. In contrast to other diseases that are developed form germ cells. Dominant gain-of-function mutations may create oncogenes; these promote the development of cancer. Recessively loss-of-function mutations may delete or inactivate tumor-repressor genes. The tumor cells are given an advantage over the normal cells. The regular structure s upset.

Cancer requires an accumulation of mutations
A mutation is inevitable. This is due to the limitations of the DNA replication system and the DNA repair system. It takes more than a single mutation to make a cancer cell from a normal cell. A cell must undergo a lot of mutations before it is cancerous and than it must undergo more changes to be able to invade other tissues. Mutations develop over many years. By natural selection some tumor cells are favored and they are able to survive.
Somatic mutations normally occur a later age. Germ like mutations are from birth there and only need to come to expression.

Essential concepts

1. Tissues are composed of cells plus extracellular matrix
2. Animal connective tissues provide mechanical support and consists of extracellular matrix with sparsely scattered cells
3. The organic components of the matrix are made by the connective tissue cells embedded in it (called fibroblasts in most connective tissues)
4. In extracellular matrix of animals, tensile strength is provided by a fibrous protein, called collagen
5. Tension is transmitted from the cytoskeleton of the connective tissue cell to the collagen fibers via transmembrane protein, integrin, and an extracellular adaptor protein fibronectin.

6. Glycosaminoglycans (GAGs) complexes with proteins to form proteoglycans, act as space-fillers and provide resistance to compression.
7. GAGs are negatively charged polysaccharides; the cloud of small positive ions that they attract draws water by osmosis, creating a swelling pressure.
8. Cells joined together in epithelial sheets line all external and internal surfaces of the animal body.
9. In epithelial sheets, in contrast to connective tissue, tension is transmitted directly from cell to cell, via cell-cell junctions.
10. Proteins of the cadherin family span the epithelial cell membrane and bind to similar cadherins in the adjacent epithelial cell.
11. At an adherens junction the cadherins are linked intracellularly to actin filaments; at a desmosome junction they are linked to keratin filaments.
12. Actin bundles connected from cell to cell across an epithelium can contract, causing the epithelium to bend.
13. Hemidesmosomes attach the basal face of an epithelial call to the basal lamina.
14. Tight junctions seal one epithelial cell to the next, creating a barrier to diffusion across the epithelium.
15. Gap junctions form channels allowing passage of small molecules and ions from cell to cell.
16. Most tissues in vertebrates are complex mixtures of cell types that are subjected to continual turn over.
17. New terminally differentiated cells are generated from stem cells.
18. Tissue organization is actively maintained through cell communication, selective cell to cell adhesion and cell memory.