UNIT –II (SEM-I)

Cell biology (also **cellular biology** or **cytology**) is a branch of biology that studies the structure, function, and behavior of cells.[1][2] All living organisms are made of cells. A cell is the basic unit of life that is responsible for the living and functioning of organisms.[3] Cell biology is the study of the structural and functional units of cells. Cell biology encompasses both prokaryotic and eukaryotic cells and has many subtopics which may include the study of cell metabolism, cell communication, cell cycle, biochemistry, and cell composition. The study of cells is performed using several microscopy techniques, cell culture, and cell fractionation. These have allowed for and are currently being used for discoveries and research pertaining to how cells function, ultimately giving insight into understanding larger organisms. Knowing the components of cells and how cells work is fundamental to all biological sciences while also being essential for research in biomedical fields such as cancer, and other diseases. Research in cell biology is interconnected to other fields such as genetics, molecular genetics, molecular biology, medical microbiology, immunology, and cytochemistry.

History

[edit]

Cells were first seen in 17th-century Europe with the invention of the compound microscope. In 1665, Robert Hooke referred to the building blocks of all living organisms as "cells" (published in *Micrographia*) after looking at a piece of cork and observing a cell-like structure;[4][5] however, the cells were dead. They gave no indication to the actual overall components of a cell. A few years later, in 1674, Anton Van Leeuwenhoek was the first to analyze live cells in his examination of algae. Many years later, in 1831, Robert Brown discovered the nucleus. All of this preceded the cell theory which states that all living things are made up of cells and that cells are organisms' functional and structural units. This was ultimately concluded by plant scientist Matthias Schleiden[5] and animal scientist Theodor Schwann in 1838, who viewed live cells in plant and animal tissue, respectively.[3] 19 years later, Rudolf Virchow further contributed to the cell theory, adding that all cells come from the division of pre-existing cells.[3] Viruses are not considered in cell biology – they lack the characteristics of a living cell and instead are studied in the microbiology subclass of virology.[6]

Techniques

[edit]

Cell biology research looks at different ways to culture and manipulate cells outside of a living body to further research in human anatomy and physiology, and to derive medications.The techniques by which cells are studied have evolved. Due to advancements in microscopy, techniques and technology have allowed scientists to hold a better understanding of the structure and function of cells. Many techniques commonly used to study cell biology are listed below:[7]

- Cell culture: Utilizes rapidly growing cells on media which allows for a large amount of a specific cell type and an efficient way to study cells.[8] Cell culture is one of the major tools used in cellular and molecular biology, providing excellent model systems for studying the normal physiology and biochemistry of cells (e.g., metabolic studies, aging), the effects of drugs and toxic compounds on the cells, and mutagenesis and carcinogenesis. It is also

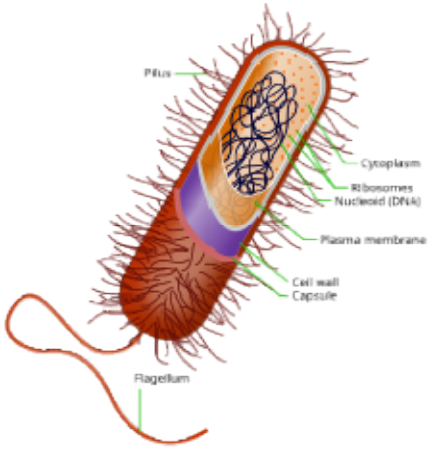
used in drug screening and development, and large scale manufacturing of biological compounds (e.g., vaccines, therapeutic proteins).

- Fluorescence microscopy: Fluorescent markers such as GFP, are used to label a specific component of the cell. Afterwards, a certain light wavelength is used to excite the fluorescent marker which can then be visualized.[8]
- Phase-contrast microscopy: Uses the optical aspect of light to represent the solid, liquid, and gas-phase changes as brightness differences.[8]
- Confocal microscopy: Combines fluorescence microscopy with imaging by focusing light and snap shooting instances to form a 3-D image.[8]
- Transmission electron microscopy: Involves metal staining and the passing of electrons through the cells, which will be deflected upon interaction with metal. This ultimately forms an image of the components being studied.[8]
- Cytometry: The cells are placed in the machine which uses a beam to scatter the cells based on different aspects and can therefore separate them based on size and content. Cells may also be tagged with GFP-fluorescence and can be separated that way as well.[9]
- Cell fractionation: This process requires breaking up the cell using high temperature or sonification followed by centrifugation to separate the parts of the cell allowing for them to be studied separately.[8]

Cell types

[edit]

Main article: Cell types



A drawing of a prokaryotic cell

There are two fundamental classifications of cells: prokaryotic and eukaryotic. Prokaryotic cells are distinguished from eukaryotic cells by the absence of a cell nucleus or other membrane-bound organelle.[10] Prokaryotic cells are much smaller than eukaryotic cells, making them the smallest form of life.[11] Prokaryotic cells include Bacteria and Archaea, and lack an enclosed cell nucleus. Eukaryotic cells are found in plants, animals, fungi, and protists. They range from 10 to 100 μm in diameter, and their DNA is contained within a membrane-bound nucleus. Eukaryotes are organisms containing eukaryotic cells. The four eukaryotic kingdoms are **Animalia, Plantae, Fungi, and Protista.**[12]

They both reproduce through binary fission. Bacteria, the most prominent type, have several different shapes, although most are spherical or rod-shaped. Bacteria can be classed as either gram-positive or gram-negative depending on the cell wall composition. Gram-positive

bacteria have a thicker peptidoglycan layer than gram-negative bacteria. Bacterial structural features include a flagellum that helps the cell to move,[13] ribosomes for the translation of RNA to protein,[13] and a nucleoid that holds all the genetic material in a circular structure.[13] There are many processes that occur in prokaryotic cells that allow them to survive. In prokaryotes, **mRNA synthesis** is initiated at a promoter sequence on the DNA template comprising two consensus sequences that recruit RNA polymerase. The prokaryotic polymerase consists of a core enzyme of four protein subunits and a σ protein that assists only with initiation. For instance, in a process termed conjugation, the fertility factor allows the bacteria to possess a pilus which allows it to transmit DNA to another bacteria which lacks the F factor, permitting the transmittance of resistance allowing it to survive in certain environments.[14]

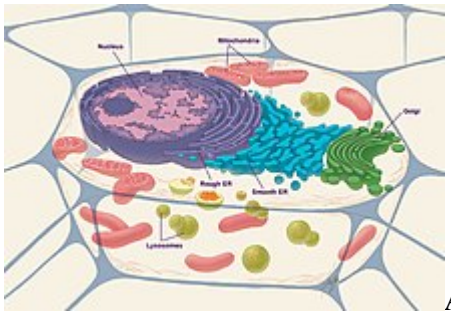
Structure and function

[edit]

Structure of eukaryotic cells

[edit]

Main article: Eukaryote



A diagram of an animal cell

Eukaryotic cells are composed of the following organelles:

- Nucleus: The nucleus of the cell functions as the genome and genetic information storage for the cell, containing all the DNA organized in the form of chromosomes. It is surrounded by a nuclear envelope, which includes nuclear pores allowing for the transportation of proteins between the inside and outside of the nucleus.[15] This is also the site for replication of DNA as well as transcription of DNA to RNA. Afterwards, the RNA is modified and transported out to the cytosol to be translated to protein.[16]
- Nucleolus: This structure is within the nucleus, usually dense and spherical. It is the site of ribosomal RNA (rRNA) synthesis, which is needed for ribosomal assembly.
- Endoplasmic reticulum (ER): This functions to synthesize, store, and secrete proteins to the Golgi apparatus.[17] Structurally, the endoplasmic reticulum is a network of membranes found throughout the cell and connected to the nucleus. The membranes are slightly different from cell to cell and a cell's function determines the size and structure of the ER.[18]
- Mitochondria: Commonly known as the powerhouse of the cell is a double membrane bound cell organelle.[19] This functions for the production of energy or ATP within the cell. Specifically, this is the place where the Krebs cycle or TCA cycle for the production of NADH and FADH occurs. Afterwards, these products are used within the electron transport chain (ETC) and oxidative phosphorylation for the final production of ATP.[20]
- Golgi apparatus: This functions to further process, package, and secrete the proteins to their destination. The proteins contain a signal sequence that allows the Golgi apparatus to

recognize and direct it to the correct place. Golgi apparatus also produce glycoproteins and glycolipids.[21]

- Lysosome: The lysosome functions to degrade material brought in from the outside of the cell or old organelles. This contains many acid hydrolases, proteases, nucleases, and lipases, which break down the various molecules. Autophagy is the process of degradation through lysosomes which occurs when a vesicle buds off from the ER and engulfs the material, then, attaches and fuses with the lysosome to allow the material to be degraded.[22]
- Ribosomes: Functions to translate RNA to protein. it serves as a site of protein synthesis.[23]
- Cytoskeleton: Cytoskeleton is a structure that helps to maintain the shape and general organization of the cytoplasm. It anchors organelles within the cells and makes up the structure and stability of the cell. The cytoskeleton is composed of three principal types of protein filaments: actin filaments, intermediate filaments, and microtubules, which are held together and linked to subcellular organelles and the plasma membrane by a variety of accessory proteins.[24]
- Cell membrane: The cell membrane can be described as a phospholipid bilayer and is also consisted of lipids and proteins.[13] Because the inside of the bilayer is hydrophobic and in order for molecules to participate in reactions within the cell, they need to be able to cross this membrane layer to get into the cell via osmotic pressure, diffusion, concentration gradients, and membrane channels.[25]
- Centrioles: Function to produce spindle fibers which are used to separate chromosomes during cell division.

Eukaryotic cells may also be composed of the following molecular components:

- Chromatin: This makes up chromosomes and is a mixture of DNA with various proteins.
- Cilia: They help to propel substances and can also be used for sensory purposes.[26]

Cell metabolism

[edit]

Cell metabolism is necessary for the production of energy for the cell and therefore its survival and includes many pathways and also sustaining the main cell organelles such as the nucleus, the mitochondria, the cell membrane etc. For cellular respiration, once glucose is available, glycolysis occurs within the cytosol of the cell to produce pyruvate. Pyruvate undergoes decarboxylation using the multi-enzyme complex to form acetyl coA which can readily be used in the TCA cycle to produce NADH and $FADH_2$. These products are involved in the electron transport chain to ultimately form a proton gradient across the inner mitochondrial membrane. This gradient can then drive the production of ATP and H_2O during oxidative phosphorylation.[27] Metabolism in plant cells includes photosynthesis which is simply the exact opposite of respiration as it ultimately produces molecules of glucose.

Cell signaling

[edit]

Further information: Cell signaling

Cell signaling or cell communication is important for cell regulation and for cells to process information from the environment and respond accordingly. Signaling can occur through direct cell contact or endocrine, paracrine, and autocrine signaling. Direct cell-cell contact is when a receptor on a cell binds a molecule that is attached to the membrane of another cell. Endocrine signaling occurs through molecules secreted into the bloodstream. Paracrine signaling uses molecules diffusing between two cells to communicate. Autocrine is a cell sending a signal to

itself by secreting a molecule that binds to a receptor on its surface. Forms of communication can be through:

- Ion channels: Can be of different types such as voltage or ligand gated ion channels. They allow for the outflow and inflow of molecules and ions.
- G-protein coupled receptor (GPCR): Is widely recognized to contain seven transmembrane domains. The ligand binds on the extracellular domain and once the ligand binds, this signals a guanine exchange factor to convert GDP to GTP and activate the G-α subunit. G-α can target other proteins such as adenyl cyclase or phospholipase C, which ultimately produce secondary messengers such as cAMP, Ip3, DAG, and calcium. These secondary messengers function to amplify signals and can target ion channels or other enzymes. One example for amplification of a signal is cAMP binding to and activating PKA by removing the regulatory subunits and releasing the catalytic subunit. The catalytic subunit has a nuclear localization sequence which prompts it to go into the nucleus and phosphorylate other proteins to either repress or activate gene activity.[27]
- Receptor tyrosine kinases: Bind growth factors, further promoting the tyrosine on the intracellular portion of the protein to cross phosphorylate. The phosphorylated tyrosine becomes a landing pad for proteins containing an SH2 domain allowing for the activation of Ras and the involvement of the MAP kinase pathway.[28]

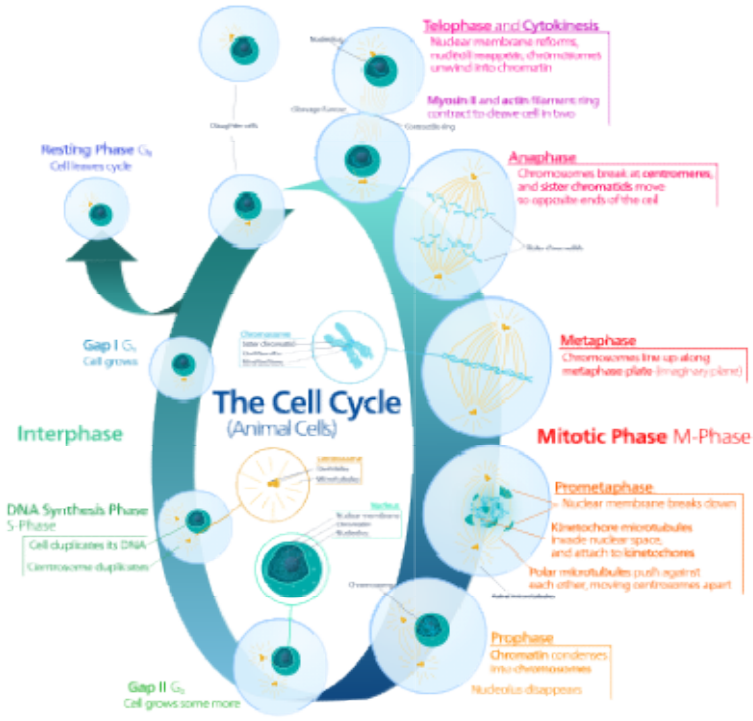
Growth and development

[edit]

Eukaryotic cell cycle

[edit]

Main article: Cell cycle



The process of cell division in the animal cell cycle

Cells are the foundation of all organisms and are the fundamental units of life. The growth and development of cells are essential for the maintenance of the host and survival of the organism. For this process, the cell goes through the steps of the cell cycle and development which involves cell growth, DNA replication, cell division, regeneration, and cell death.

The cell cycle is divided into four distinct phases: G1, S, G2, and M. The G phase – which is the cell growth phase – makes up approximately 95% of the cycle. The proliferation of cells is instigated by progenitors. All cells start out in an identical form and can essentially become any type of cells. Cell signaling such as induction can influence nearby cells to determinate the type of cell it will become. Moreover, this allows cells of the same type to aggregate and form tissues, then organs, and ultimately systems. The G1, G2, and S phase (DNA replication, damage and repair) are considered to be the interphase portion of the cycle, while the M phase (mitosis) is the cell division portion of the cycle. Mitosis is composed of many stages which include, prophase, metaphase, anaphase, telophase, and cytokinesis, respectively. The ultimate result of mitosis is the formation of two identical daughter cells.

The cell cycle is regulated in cell cycle checkpoints, by a series of signaling factors and complexes such as cyclins, cyclin-dependent kinase, and p53. When the cell has completed its growth process and if it is found to be damaged or altered, it undergoes cell death, either by apoptosis or necrosis, to eliminate the threat it can cause to the organism's survival.[29]

Cell mortality, cell lineage immortality

[edit]

The ancestry of each present day cell presumably traces back, in an unbroken lineage for over 3 billion years to the origin of life. It is not actually cells that are immortal but multi-generational cell lineages.[30] The immortality of a cell lineage depends on the maintenance of cell division potential. This potential may be lost in any particular lineage because of cell damage, terminal differentiation as occurs in nerve cells, or programmed cell death (apoptosis) during development. Maintenance of cell division potential over successive generations depends on the avoidance and the accurate repair of cellular damage, particularly DNA damage. In sexual organisms, continuity of the germline depends on the effectiveness of processes for avoiding DNA damage and repairing those DNA damages that do occur. Sexual processes in eukaryotes, as well as in prokaryotes, provide an opportunity for effective repair of DNA damages in the germ line by homologous recombination.[30][31]

Cell cycle phases

[edit]

The cell cycle is a four-stage process that a cell goes through as it develops and divides. It includes Gap 1 (G1), synthesis (S), Gap 2 (G2), and mitosis (M). The cell either restarts the cycle from G1 or leaves the cycle through G0 after completing the cycle. The cell can progress from G0 through terminal differentiation. Finally, the interphase refers to the phases of the cell cycle that occur between one mitosis and the next, and includes G1, S, and G2. Thus, the phases are:

- **G1 phase**: the cell grows in size and its contents are replicated.
- **S phase**: the cell replicates each of the 46 chromosomes.
- **G2 phase**: in preparation for cell division, new organelles and proteins form.
- **M phase**: cytokinesis occurs, resulting in two identical daughter cells.

- **G0 phase**: the two cells enter a resting stage where they do their job without actively preparing to divide.[32]

Pathology

[edit]

Main article: Cytopathology

The scientific branch that studies and diagnoses diseases on the cellular level is called cytopathology. Cytopathology is generally used on samples of free cells or tissue fragments, in contrast to the pathology branch of histopathology, which studies whole tissues. Cytopathology is commonly used to investigate diseases involving a wide range of body sites, often to aid in the diagnosis of cancer but also in the diagnosis of some infectious diseases and other inflammatory conditions. For example, a common application of cytopathology is the Pap smear, a screening test used to detect cervical cancer, and precancerous cervical lesions that may lead to cervical cancer.[33]

Cell cycle checkpoints and DNA damage repair system

[edit]

The cell cycle is composed of a number of well-ordered, consecutive stages that result in cellular division. The fact that cells do not begin the next stage until the last one is finished, is a significant element of cell cycle regulation. Cell cycle checkpoints are characteristics that constitute an excellent monitoring strategy for accurate cell cycle and divisions. Cdks, associated cyclin counterparts, protein kinases, and phosphatases regulate cell growth and division from one stage to another.[34] The cell cycle is controlled by the temporal activation of Cdks, which is governed by cyclin partner interaction, phosphorylation by particular protein kinases, and de-phosphorylation by Cdc25 family phosphatases. In response to DNA damage, a cell's DNA repair reaction is a cascade of signaling pathways that leads to checkpoint engagement, regulates, the repairing mechanism in DNA, cell cycle alterations, and apoptosis. Numerous biochemical structures, as well as processes that detect damage in DNA, are ATM and ATR, which induce the DNA repair checkpoints[35]

The cell cycle is a sequence of activities in which cell organelles are duplicated and subsequently separated into daughter cells with precision. There are major events that happen during a cell cycle. The processes that happen in the cell cycle include cell development, replication and segregation of chromosomes. The cell cycle checkpoints are surveillance systems that keep track of the cell cycle's integrity, accuracy, and chronology. Each checkpoint serves as an alternative cell cycle endpoint, wherein the cell's parameters are examined and only when desirable characteristics are fulfilled does the cell cycle advance through the distinct steps. The cell cycle's goal is to precisely copy each organism's DNA and afterwards equally split the cell and its components between the two new cells. Four main stages occur in the eukaryotes. In G1, the cell is usually active and continues to grow rapidly, while in G2, the cell growth continues while protein molecules become ready for separation. These are not dormant times; they are when cells gain mass, integrate growth factor receptors, establish a replicated genome, and prepare for chromosome segregation. DNA replication is restricted to a separate Synthesis in eukaryotes, which is also known as the S-phase. During mitosis, which is also known as the M-phase, the segregation of the chromosomes occur.[36] DNA, like every other molecule, is capable of undergoing a wide range of chemical reactions. Modifications in DNA's sequence, on the other hand, have a considerably bigger impact than modifications in other

cellular constituents like RNAs or proteins because DNA acts as a permanent copy of the cell genome. When erroneous nucleotides are incorporated during DNA replication, mutations can occur. The majority of DNA damage is fixed by removing the defective bases and then re-synthesizing the excised area. On the other hand, some DNA lesions can be mended by reversing the damage, which may be a more effective method of coping with common types of DNA damage. Only a few forms of DNA damage are mended in this fashion, including pyrimidine dimers caused by ultraviolet (UV) light changed by the insertion of methyl or ethyl groups at the purine ring's O6 position.[37]

Mitochondrial membrane dynamics

[edit]

Mitochondria are commonly referred to as the cell's "powerhouses" because of their capacity to effectively produce ATP which is essential to maintain cellular homeostasis and metabolism. Moreover, researchers have gained a better knowledge of mitochondria's significance in cell biology because of the discovery of cell signaling pathways by mitochondria which are crucial platforms for cell function regulation such as apoptosis. Its physiological adaptability is strongly linked to the cell mitochondrial channel's ongoing reconfiguration through a range of mechanisms known as mitochondrial membrane dynamics, including endomembrane fusion and fragmentation (separation) and ultrastructural membrane remodeling. As a result, mitochondrial dynamics regulate and frequently choreograph not only metabolic but also complicated cell signaling processes such as cell pluripotent stem cells, proliferation, maturation, aging, and mortality. Mutually, post-translational alterations of mitochondrial apparatus and the development of transmembrane contact sites among mitochondria and other structures, which both have the potential to link signals from diverse routes that affect mitochondrial membrane dynamics substantially,[36] Mitochondria are wrapped by two membranes: an inner mitochondrial membrane (IMM) and an outer mitochondrial membrane (OMM), each with a distinctive function and structure, which parallels their dual role as cellular powerhouses and signaling organelles. The inner mitochondrial membrane divides the mitochondrial lumen into two parts: the inner border membrane, which runs parallel to the OMM, and the cristae, which are deeply twisted, multinucleated invaginations that give room for surface area enlargement and house the mitochondrial respiration apparatus. The outer mitochondrial membrane, on the other hand, is soft and permeable. It, therefore, acts as a foundation for cell signaling pathways to congregate, be deciphered, and be transported into mitochondria. Furthermore, the OMM connects to other cellular organelles, such as the endoplasmic reticulum (ER), lysosomes, endosomes, and the plasma membrane. Mitochondria play a wide range of roles in cell biology, which is reflected in their morphological diversity. Ever since the beginning of the mitochondrial study, it has been well documented that mitochondria can have a variety of forms, with both their general and ultra-structural morphology varying greatly among cells, during the cell cycle, and in response to metabolic or cellular cues. Mitochondria can exist as independent organelles or as part of larger systems; they can also be unequally distributed in the cytosol through regulated mitochondrial transport and placement to meet the cell's localized energy requirements. Mitochondrial dynamics refers to the adaptive and variable aspect of mitochondria, including their shape and subcellular distribution.[36]

Autophagy

[edit]

Main article: Autophagy

Autophagy is a self-degradative mechanism that regulates energy sources during growth and reaction to dietary stress. Autophagy also cleans up after itself, clearing aggregated proteins, cleaning damaged structures including mitochondria and endoplasmic reticulum and eradicating intracellular infections. Additionally, autophagy has antiviral and antibacterial roles within the cell, and it is involved at the beginning of distinctive and adaptive immune responses to viral and bacterial contamination. Some viruses include virulence proteins that prevent autophagy, while others utilize autophagy elements for intracellular development or cellular splitting.[38] Macro autophagy, micro autophagy, and chaperon-mediated autophagy are the three basic types of autophagy. When macro autophagy is triggered, an exclusion membrane incorporates a section of the cytoplasm, generating the autophagosome, a distinctive double-membraned organelle. The autophagosome then joins the lysosome to create an autolysosome, with lysosomal enzymes degrading the components. In micro autophagy, the lysosome or vacuole engulfs a piece of the cytoplasm by invaginating or protruding the lysosomal membrane to enclose the cytosol or organelles. The chaperone-mediated autophagy (CMA) protein quality assurance by digesting oxidized and altered proteins under stressful circumstances and supplying amino acids through protein denaturation.[39] Autophagy is the primary intrinsic degradative system for peptides, fats, carbohydrates, and other cellular structures. In both physiologic and stressful situations, this cellular progression is vital for upholding the correct cellular balance. Autophagy instability leads to a variety of illness symptoms, including inflammation, biochemical disturbances, aging, and neurodegenerative, due to its involvement in controlling cell integrity. The modification of the autophagy-lysosomal networks is a typical hallmark of many neurological and muscular illnesses. As a result, autophagy has been identified as a potential strategy for the prevention and treatment of various disorders. Many of these disorders are prevented or improved by consuming polyphenol in the meal. As a result, natural compounds with the ability to modify the autophagy mechanism are seen as a potential therapeutic option.[40] The creation of the double membrane (phagophore), which would be known as nucleation, is the first step in macro-autophagy. The phagophore approach indicates dysregulated polypeptides or defective organelles that come from the cell membrane, Golgi apparatus, endoplasmic reticulum, and mitochondria. With the conclusion of the autophagocyte, the phagophore's enlargement comes to an end. The auto-phagosome combines with the lysosomal vesicles to formulate an auto-lysosome that degrades the encapsulated substances, referred to as phagocytosis.[41]

Notable cell biologists

[edit]

- Jean Baptiste Carnoy
- Peter Agre
- Günter Blobel
- Robert Brown
- Geoffrey M. Cooper
- Christian de Duve
- Henri Dutrochet
- Robert Hooke
- H. Robert Horvitz
- Marc Kirschner
- Anton van Leeuwenhoek
- Ira Mellman
- Marta Miączyńska[42]

- Peter D. Mitchell
- Rudolf Virchow
- Paul Nurse
- George Emil Palade
- Keith R. Porter
- Ray Rappaport
- Michael Swann
- Roger Tsien
- Edmund Beecher Wilson
- Kenneth R. Miller
- Matthias Jakob Schleiden
- Theodor SchwannYoshinori OhsumiJan Evangelista PurkyněJan Evangelista Purkyněi

Adenosine triphosphate (**ATP**) is a nucleotide[2] that provides energy to drive and support many processes in living cells, such as muscle contraction, nerve impulse propagation, and chemical synthesis. Found in all known forms of life, it is often referred to as the "molecular unit of currency" for intracellular energy transfer.[3]

When consumed in a metabolic process, ATP converts either to adenosine diphosphate (ADP) or to adenosine monophosphate (AMP). Other processes regenerate ATP. It is also a precursor to DNA and RNA, and is used as a coenzyme. An average human adult processes around 50 kilograms daily.[4]

From the perspective of biochemistry, ATP is classified as a nucleoside triphosphate, which indicates that it consists of three components: a nitrogenous base (adenine), the sugar ribose, and the triphosphate.

Structure

[edit]

ATP consists of an adenine attached by the #9-nitrogen atom to the 1′ carbon atom of a sugar (ribose), which in turn is attached at the 5' carbon atom of the sugar to a triphosphate group. In its many reactions related to metabolism, the adenine and sugar groups remain unchanged, but the triphosphate is converted to di- and monophosphate, giving respectively the derivatives ADP and AMP. The three phosphoryl groups are labeled as alpha (α), beta (β), and, for the terminal phosphate, gamma (γ).[5]

In neutral solution, ionized ATP exists mostly as ATP^{4-}, with a small proportion of ATP^{3-}.[6]

Metal cation binding

[edit]

Polyanionic and featuring a potentially chelating polyphosphate group, ATP binds metal cations with high affinity. The binding constant for Mg^{2+} is (9554).[7] The binding of a divalent cation, almost always magnesium, strongly affects the interaction of ATP with various proteins. Due to the strength of the ATP-Mg^{2+} interaction, ATP

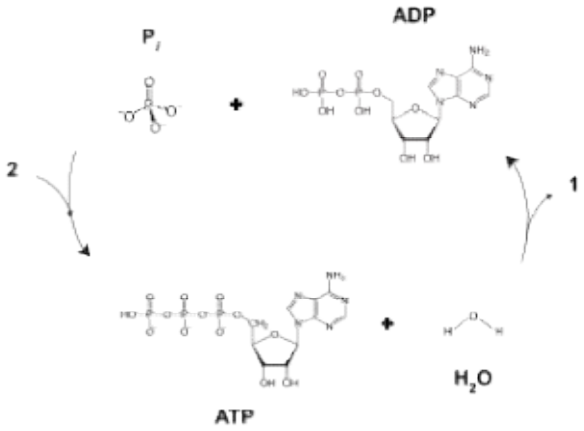
exists in the cell mostly as a complex with Mg^{2+} bonded to the phosphate oxygen centers.[6][8]

A second magnesium ion is critical for ATP binding in the kinase domain.[9] The presence of Mg^{2+} regulates kinase activity.[10] It is interesting from an RNA world perspective that ATP can carry a Mg ion which catalyzes RNA polymerization.[*citation needed*]

Chemical properties

[edit]

Salts of ATP can be isolated as colorless solids.[11]



The cycles of synthesis and degradation of ATP; 2 and 1 represent input and output of energy, respectively.

ATP is stable in aqueous solutions between pH 6.8 and 7.4 (in the absence of catalysts). At more extreme pH levels, it rapidly hydrolyses to ADP and phosphate. Living cells maintain the ratio of ATP to ADP at a point ten orders of magnitude from equilibrium, with ATP concentrations fivefold higher than the concentration of ADP.[12][13] In the context of biochemical reactions, the P-O-P bonds are frequently referred to as *high-energy bonds*.[14]

Reactive aspects

[edit]

The hydrolysis of ATP into ADP and inorganic phosphate

$$ATP^{4-}(aq) + H_2O(l) = ADP^{3-}(aq) + HPO^{2-}(aq) + H^{+}(aq)$$

releases 20.5 kilojoules per mole (4.9 kcal/mol) of enthalpy. This may differ under physiological conditions if the reactant and products are not exactly in these ionization states.[15] The values of the free energy released by cleaving either a phosphate (P_i) or a pyrophosphate (PP_i) unit from ATP at standard state concentrations of 1 mol/L at pH 7 are:[16]

$$ATP + H_2O \rightarrow ADP + P_i \quad \Delta G^{\circ\prime} = -30.5 \text{ kJ/mol } (-7.3 \text{ kcal/mol})$$

ATP + H
$_2$O → AMP + PP$_i$ $\Delta G^{\circ\prime}$ = −45.6 kJ/mol (−10.9 kcal/mol)

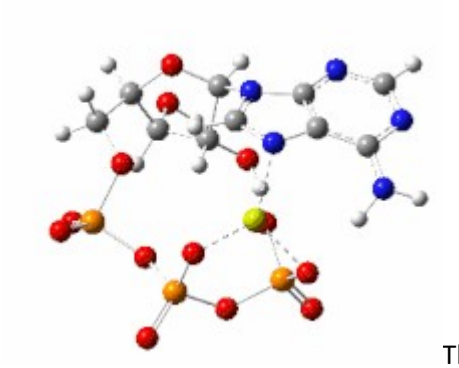
These abbreviated equations at a pH near 7 can be written more explicitly (R = adenosyl):

$[RO\text{-}P(O)_2\text{-}O\text{-}P(O)_2\text{-}O\text{-}PO_3]^{4-}$ + H
$_2$O → $[RO\text{-}P(O)_2\text{-}O\text{-}PO_3]^{3-}$ + $[HPO_4]^{2-}$ + H^+

$[RO\text{-}P(O)_2\text{-}O\text{-}P(O)_2\text{-}O\text{-}PO_3]^{4-}$ + H
$_2$O → $[RO\text{-}PO_3]^{2-}$ + $[HO_3P\text{-}O\text{-}PO_3]^{3-}$ + H^+

At cytoplasmic conditions, where the ADP/ATP ratio is 10 orders of magnitude from equilibrium, the ΔG is around −57 kJ/mol.[12]

Along with pH, the free energy change of ATP hydrolysis is also associated with Mg^{2+} concentration, from $\Delta G^{\circ\prime}$ = −35.7 kJ/mol at a Mg^{2+} concentration of zero, to $\Delta G^{\circ\prime}$ = −31 kJ/mol at [Mg^{2+}] = 5 mM. Higher concentrations of Mg^{2+} decrease free energy released in the reaction due to binding of Mg^{2+} ions to negatively charged oxygen atoms of ATP at pH 7.[17]



This image shows a 360-degree rotation of a single, gas-phase magnesium-ATP chelate with a charge of −2. The anion was optimized at the UB3LYP/6-311++G(d,p) theoretical level and the atomic connectivity modified by the human optimizer to reflect the probable electronic structure.

Production from AMP and ADP

[edit]

Production, aerobic conditions

[edit]

A typical intracellular concentration of ATP may be 1–10 μmol per gram of tissue in a variety of eukaryotes.[18] The dephosphorylation of ATP and rephosphorylation of ADP and AMP occur repeatedly in the course of aerobic metabolism.[19]

ATP can be produced by a number of distinct cellular processes; the three main pathways in eukaryotes are (1) glycolysis, (2) the citric acid cycle/oxidative phosphorylation, and (3) beta-oxidation. The overall process of oxidizing glucose to carbon dioxide, the combination of pathways 1 and 2, known as cellular respiration, produces about 30 equivalents of ATP from each molecule of glucose.[20]

ATP production by a non-photosynthetic aerobic eukaryote occurs mainly in the mitochondria, which comprise nearly 25% of the volume of a typical cell.[21]

Glycolysis

[edit]

Main article: Glycolysis

In glycolysis, glucose and glycerol are metabolized to pyruvate. Glycolysis generates two equivalents of ATP through substrate phosphorylation catalyzed by two enzymes, phosphoglycerate kinase (PGK) and pyruvate kinase. Two equivalents of nicotinamide adenine dinucleotide (NADH) are also produced, which can be oxidized via the electron transport chain and result in the generation of additional ATP by ATP synthase. The pyruvate generated as an end-product of glycolysis is a substrate for the Krebs Cycle.[22]

Glycolysis is viewed as consisting of two phases with five steps each. In phase 1, "the preparatory phase", glucose is converted to 2 d-glyceraldehyde-3-phosphate (g3p). One ATP is invested in Step 1, and another ATP is invested in Step 3. Steps 1 and 3 of glycolysis are referred to as "Priming Steps". In Phase 2, two equivalents of g3p are converted to two pyruvates. In Step 7, two ATP are produced. Also, in Step 10, two further equivalents of ATP are produced. In Steps 7 and 10, ATP is generated from ADP. A net of two ATPs is formed in the glycolysis cycle. The glycolysis pathway is later associated with the Citric Acid Cycle which produces additional equivalents of ATP.[*citation needed*]

Regulation

[edit]

In glycolysis, hexokinase is directly inhibited by its product, glucose-6-phosphate, and pyruvate kinase is inhibited by ATP itself. The main control point for the glycolytic pathway is phosphofructokinase (PFK), which is allosterically inhibited by high concentrations of ATP and activated by high concentrations of AMP. The inhibition of PFK by ATP is unusual since ATP is also a substrate in the reaction catalyzed by PFK; the active form of the enzyme is a tetramer that exists in two conformations, only one of which binds the second substrate fructose-6-phosphate (F6P). The protein has two binding sites for ATP – the active site is accessible in either protein conformation, but ATP binding to the inhibitor site stabilizes the conformation that binds F6P poorly.[22] A number of other small molecules

can compensate for the ATP-induced shift in equilibrium conformation and reactivate PFK, including cyclic AMP, ammonium ions, inorganic phosphate, and fructose-1,6- and -2,6-biphosphate.[22]

Citric acid cycle

[edit]

Main articles: Citric acid cycle and Oxidative phosphorylation

In the mitochondrion, pyruvate is oxidized by the pyruvate dehydrogenase complex to the acetyl group, which is fully oxidized to carbon dioxide by the citric acid cycle (also known as the Krebs cycle). Every "turn" of the citric acid cycle produces two molecules of carbon dioxide, one equivalent of ATP guanosine triphosphate (GTP) through substrate-level phosphorylation catalyzed by succinyl-CoA synthetase, as succinyl-CoA is converted to succinate, three equivalents of NADH, and one equivalent of $FADH_2$. NADH and $FADH_2$ are recycled (to NAD^+ and FAD, respectively) by oxidative phosphorylation, generating additional ATP. The oxidation of NADH results in the synthesis of 2–3 equivalents of ATP, and the oxidation of one $FADH_2$ yields between 1–2 equivalents of ATP.[20] The majority of cellular ATP is generated by this process. Although the citric acid cycle itself does not involve molecular oxygen, it is an obligately aerobic process because O_2 is used to recycle the NADH and $FADH_2$. In the absence of oxygen, the citric acid cycle ceases.[21]

The generation of ATP by the mitochondrion from cytosolic NADH relies on the malate-aspartate shuttle (and to a lesser extent, the glycerol-phosphate shuttle) because the inner mitochondrial membrane is impermeable to NADH and NAD^+. Instead of transferring the generated NADH, a malate dehydrogenase enzyme converts oxaloacetate to malate, which is translocated to the mitochondrial matrix. Another malate dehydrogenase-catalyzed reaction occurs in the opposite direction, producing oxaloacetate and NADH from the newly transported malate and the mitochondrion's interior store of NAD^+. A transaminase converts the oxaloacetate to aspartate for transport back across the membrane and into the intermembrane space.[21]

In oxidative phosphorylation, the passage of electrons from NADH and $FADH_2$ through the electron transport chain releases the energy to pump protons out of the mitochondrial matrix and into the intermembrane space. This pumping generates a proton motive force that is the net effect of a pH gradient and an electric potential gradient across the inner mitochondrial membrane. Flow of protons down this potential gradient – that is, from the intermembrane space to the matrix – yields ATP by ATP synthase.[23] Three ATP are produced per turn.

Although oxygen consumption appears fundamental for the maintenance of the proton motive force, in the event of oxygen shortage (hypoxia), intracellular acidosis (mediated by enhanced glycolytic rates and ATP hydrolysis), contributes to mitochondrial membrane potential and directly drives ATP synthesis.[24]

Most of the ATP synthesized in the mitochondria will be used for cellular processes in the cytosol; thus it must be exported from its site of synthesis in the mitochondrial matrix. ATP outward movement is favored by the membrane's electrochemical potential because the cytosol has a relatively positive charge compared to the relatively negative matrix. For every ATP transported out, it costs 1 H^+. Producing one ATP costs about 3 H^+. Therefore, making and exporting one ATP requires $4H^+$. The inner membrane contains an antiporter, the ADP/ATP translocase, which is an integral membrane protein used to exchange newly synthesized ATP in the matrix for ADP in the intermembrane space.[25]

Regulation

[edit]

The citric acid cycle is regulated mainly by the availability of key substrates, particularly the ratio of NAD^+ to NADH and the concentrations of calcium, inorganic phosphate, ATP, ADP, and AMP. Citrate – the ion that gives its name to the cycle – is a feedback inhibitor of citrate synthase and also inhibits PFK, providing a direct link between the regulation of the citric acid cycle and glycolysis.[22]

Beta oxidation

[edit]

Main article: Beta-oxidation

In the presence of air and various cofactors and enzymes, fatty acids are converted to acetyl-CoA. The pathway is called beta-oxidation. Each cycle of beta-oxidation shortens the fatty acid chain by two carbon atoms and produces one equivalent each of acetyl-CoA, NADH, and $FADH_2$. The acetyl-CoA is metabolized by the citric acid cycle to generate ATP, while the NADH and $FADH_2$ are used by oxidative phosphorylation to generate ATP. Dozens of ATP equivalents are generated by the beta-oxidation of a single long acyl chain.[26]

Regulation

[edit]

In oxidative phosphorylation, the key control point is the reaction catalyzed by cytochrome c oxidase, which is regulated by the availability of its substrate – the reduced form of cytochrome c. The amount of reduced cytochrome c available is directly related to the amounts of other substrates:

which directly implies this equation:

Thus, a high ratio of [NADH] to [NAD^+] or a high ratio of [ADP] [P_i] to [ATP] imply a high amount of reduced cytochrome c and a high level of cytochrome c oxidase activity.[22] An additional level of regulation is introduced by the transport rates of ATP and NADH between the mitochondrial matrix and the cytoplasm.[25]

Ketosis

[edit]

Main article: Ketone bodies

Ketone bodies can be used as fuels, yielding 22 ATP and 2 GTP molecules per acetoacetate molecule when oxidized in the mitochondria. Ketone bodies are transported from the liver to other tissues, where acetoacetate and *beta*-hydroxybutyrate can be reconverted to acetyl-CoA to produce reducing equivalents (NADH and $FADH_2$), via the citric acid cycle. Ketone bodies cannot be used as fuel by the liver, because the liver lacks the enzyme β-ketoacyl-CoA transferase, also called thiolase. Acetoacetate in low concentrations is taken up by the liver and undergoes detoxification through the methylglyoxal pathway which ends with lactate. Acetoacetate in high concentrations is absorbed by cells other than those in the liver and enters a different pathway via 1,2-propanediol. Though the pathway follows a different series of steps requiring ATP, 1,2-propanediol can be turned into pyruvate.[27]

Production, anaerobic conditions

[edit]

Fermentation is the metabolism of organic compounds in the absence of air. It involves substrate-level phosphorylation in the absence of a respiratory electron transport chain. The equation for the reaction of glucose to form lactic acid is:

$$C_6H_{12}O_6 + 2\ ADP + 2\ P_i \rightarrow 2\ CH_3CH(OH)COOH + 2\ ATP + 2\ H_2O$$

Anaerobic respiration is respiration in the absence of O_2. Prokaryotes can utilize a variety of electron acceptors. These include nitrate, sulfate, and carbon dioxide.

ATP replenishment by nucleoside diphosphate kinases

[edit]

ATP can also be synthesized through several so-called "replenishment" reactions catalyzed by the enzyme families

of nucleoside diphosphate kinases (NDKs), which use other nucleoside triphosphates as a high-energy phosphate donor, and the ATP:guanido-phosphotransferase family.[citation needed]

ATP production during photosynthesis

[edit]

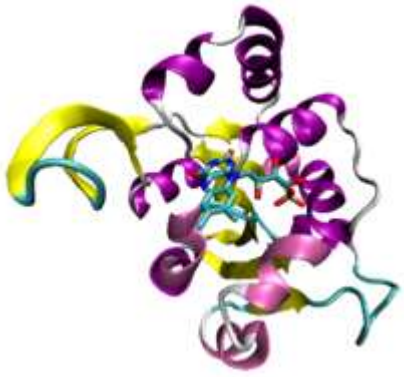
In plants, ATP is synthesized in the thylakoid membrane of the chloroplast. The process is called photophosphorylation. The "machinery" is similar to that in mitochondria except that light energy is used to pump protons across a membrane to produce a proton-motive force. ATP synthase then ensues exactly as in oxidative phosphorylation.[28] Some of the ATP produced in the chloroplasts is consumed in the Calvin cycle, which produces triose sugars.

ATP recycling

[edit]

The total quantity of ATP in the human body is about 0.1 mol/L.[29] The majority of ATP is recycled from ADP by the aforementioned processes. Thus, at any given time, the total amount of ATP + ADP remains fairly constant.

The energy used by human cells in an adult requires the hydrolysis of 100 to 150 mol/L of ATP daily, which means a human will typically use their body weight worth of ATP over the course of the day.[30] Each equivalent of ATP is recycled 1000–1500 times during a single day (150 / 0.1 = 1500),[29] at approximately 9×10^{20} molecules/s.[29]



An example of the Rossmann fold, a structural domain of a decarboxylase enzyme from the bacterium *Staphylococcus epidermidis* (PDB: 1G5Q) with a bound flavin mononucleotide cofactor

Biochemical functions

[edit]

Intracellular signaling

[edit]

ATP is involved in signal transduction by serving as substrate for kinases, enzymes that transfer phosphate groups. Kinases are the most common ATP-binding proteins. They share a small number of common folds.[31] Phosphorylation of a protein by a kinase can activate a cascade such as the mitogen-activated protein kinase cascade.[32]

ATP is also a substrate of adenylate cyclase, most commonly in G protein-coupled receptor signal transduction pathways and is transformed to second messenger, cyclic AMP, which is involved in triggering calcium signals by the release of calcium from intracellular stores.[33] This form of signal transduction is particularly important in brain function, although it is involved in the regulation of a multitude of other cellular processes.[34]

DNA and RNA synthesis

[edit]

ATP is one of four monomers required in the synthesis of RNA. The process is promoted by RNA polymerases.[35] A similar process occurs in the formation of DNA, except that ATP is first converted to the deoxyribonucleotide dATP. Like many condensation reactions in nature, DNA replication and DNA transcription also consume ATP.

Amino acid activation in protein synthesis

[edit]

Main article: Amino acid activation

Aminoacyl-tRNA synthetase enzymes consume ATP in the attachment tRNA to amino acids, forming aminoacyl-tRNA complexes. Aminoacyl transferase binds AMP-amino acid to tRNA. The coupling reaction proceeds in two steps:

1. aa + ATP ⟶ aa-AMP + PP_i
2. aa-AMP + tRNA ⟶ aa-tRNA + AMP

The amino acid is coupled to the penultimate nucleotide at the 3′-end of the tRNA (the A in the sequence CCA) via an ester bond (roll over in illustration).

ATP binding cassette transporter

[edit]

Transporting chemicals out of a cell against a gradient is often associated with ATP hydrolysis. Transport is mediated by ATP

binding cassette transporters. The human genome encodes 48 ABC transporters, that are used for exporting drugs, lipids, and other compounds.[36]

Extracellular signalling and neurotransmission

[edit]

Cells secrete ATP to communicate with other cells in a process called purinergic signalling. ATP serves as a neurotransmitter in many parts of the nervous system, modulates ciliary beating, affects vascular oxygen supply etc. ATP is either secreted directly across the cell membrane through channel proteins[37][38] or is pumped into vesicles[39] which then fuse with the membrane. Cells detect ATP using the purinergic receptor proteins P2X and P2Y.[40] ATP has been shown to be a critically important signalling molecule for microglia - neuron interactions in the adult brain,[41] as well as during brain development.[42] Furthermore, tissue-injury induced ATP-signalling is a major factor in rapid microglial phenotype changes.[43]

Muscle contraction

[edit]

ATP fuels muscle contractions.[44] Muscle contractions are regulated by signaling pathways, although different muscle types being regulated by specific pathways and stimuli based on their particular function. However, in all muscle types, contraction is performed by the proteins actin and myosin.[45]

ATP is initially bound to myosin. When ATPase hydrolyzes the bound ATP into ADP and inorganic phosphate, myosin is positioned in a way that it can bind to actin. Myosin bound by ADP and P_i forms cross-bridges with actin and the subsequent release of ADP and P_i releases energy as the power stroke. The power stroke causes actin filament to slide past the myosin filament, shortening the muscle and causing a contraction. Another ATP molecule can then bind to myosin, releasing it from actin and allowing this process to repeat.[45][46]

Protein solubility

[edit]

ATP has recently been proposed to act as a biological hydrotrope[47] and has been shown to affect proteome-wide solubility.[48]

Abiogenic origins

[edit]

Acetyl phosphate (AcP), a precursor to ATP, can readily be synthesized at modest yields from thioacetate in pH 7 and 20 °C and pH 8 and 50 °C, although acetyl phosphate is less stable in warmer temperatures and alkaline conditions than in cooler and acidic to neutral conditions. It is unable to promote polymerization of ribonucleotides and amino acids and was only capable of phosphorylation of organic compounds. It was shown that it can promote aggregation and stabilization of AMP in the presence of Na^+, aggregation of nucleotides could promote polymerization above 75 °C in the absence of Na^+. It is possible that polymerization promoted by AcP could occur at mineral surfaces.[49] It was shown that ADP can only be phosphorylated to ATP by AcP and other nucleoside triphosphates were not phosphorylated by AcP. This might explain why all lifeforms use ATP to drive biochemical reactions.[50]

ATP analogues

[edit]

Biochemistry laboratories often use *in vitro* studies to explore ATP-dependent molecular processes. ATP analogs are also used in X-ray crystallography to determine a protein structure in complex with ATP, often together with other substrates.[*citation needed*]

Enzyme inhibitors of ATP-dependent enzymes such as kinases are needed to examine the binding sites and transition states involved in ATP-dependent reactions.[*citation needed*]

Most useful ATP analogs cannot be hydrolyzed as ATP would be; instead, they trap the enzyme in a structure closely related to the ATP-bound state. Adenosine 5′-(γ-thiotriphosphate) is an extremely common ATP analog in which one of the gamma-phosphate oxygens is replaced by a sulfur atom; this anion is hydrolyzed at a dramatically slower rate than ATP itself and functions as an inhibitor of ATP-dependent processes. In crystallographic studies, hydrolysis transition states are modeled by the bound vanadate ion.

Caution is warranted in interpreting the results of experiments using ATP analogs, since some enzymes can hydrolyze them at appreciable rates at high concentration