Bioenergetics of the Normal and Malignant Cell

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PREFACE

This book *Bioenergetics of the Normal and Malignant Cell* is based on solid scientific information, gained through basic research in the country and abroad. The wealth of modern data, and the systems which we use to record this data, were especially useful in the drafting this book. I'm especially thankful for the information regarding practical in care physicians of all specialties, medical students, and staff working in clinical laboratories.

All of the theoretical and practical work within this publication are original content. This publication aims to show the great need for biological sciences, in general, and medicine (in particular considering progress in pathophysiology). Appropriate authority, and the novelty aspects treated, makes this volume constitute an important reference point for those studying and deepening problems of hematologic and metabolic aspects of the pathological body. The chapters convince the readers that these issues are addressed to medical personnel for all specialties, which can find the ideas on physiology and pathophysiology in the light of current concepts and modern principles.

In one chapter of the book, Bioenergetics of the malignant cell, is emphasized the energy levels of the metabolic pathways in malignant B and T lymphocytes and is presented the latest evidence from the literature, on cellular metabolites that may be oncogenic by modifying cell signals and blocking cellular differentiation. Advances in cancer metabolism research in the last decade have increased our understanding of aerobic glycolysis, anaerobic and other metabolic changes that are associated with cell growth and proliferation.

Blocking apoptosis in malignant diseases may be due to the high concentration of ATP from anaerobic metabolism. The energy difference between anaerobic ATP B and T lymphocytes in peripheral blood samples from hematopoietic malignancies measured by bioluminescence was 2.68 μM ATP, a value that appears as an energy transfer between normal B cells and T cells. The energy level can initiate the process of carcinogenesis by suppressing the activity of anti-oncogene proteins such as p-53 protein which is inhibited in its function of apoptosis and autophagy in the cellular

anaerobic metabolism. It is concluded that anabolic metabolism in B and T cells in hematological malignancies are under complex regulatory control, directed by receptors on the cell membrane, CD-5, CD-19, CD-20, CD-28, CD-38 and Zap protein Z, associated with an increase in signal transduction in cells transformed into malignancy.

The interests of doctors in all specialties, medical students, and staff working in clinical laboratories, from different countries on five continents, are based on the fact that this work is a large volume of data, experiences, and clinical and laboratory research. in a systematic and logical display. Due to the wealth of modern data and because the system adopted in drafting the Book is very useful, especially practical in care physicians of all specialties, medical students, and staff working in clinical laboratories.

Prof. Univ. Dr Viliam Lustig, MD, PhD, FCACB

CHAPTER I

INTRODUCTION TO CELLULAR BIOENERGETICS

The major energy source of the cell is the oxidation of the substrates of food principles in O2 from the air, transported by the blood to the tissues. The living cell obtains its energy by oxidizing the hydrogen released from the organic substrate processed by the body, the formation of CO2 appears as a secondary phenomenon, often dependent only indirectly on oxidation reactions, which ultimately lead to decarboxylation.

Numerous unknowns and many uncertainties over the years of medical research have made it almost impossible to delineate the preclinical phase of chronic disease from the initial state of health. The detection of biochemical changes in the body's apparatus and systems before their clinical expression has been quite uncertain through investigations conducted with the usual paraclinical means.

Modern methods of clinical and paraclinical investigation, by introducing new means of exploration, biological reagents, enzymes, coenzymes, antibodies, and antigens, try to solve the problems involved in basic research, with the following aspects: - the existence of persistent or transient disturbances in the molecular plane of the biological phenomenon that inevitably leads to the pathological alteration of the relationship between cellular structures and functions; - the precession of the biochemical and enzymatic phenomenon compared to the morphological one, such as the differentiation of the epiphenomena induced by the damaged structural support - oscillating states of cellular bioenergy in healthy and diseased cells. In the following, we will try to analyze these problems, while highlighting the bioenergetic complexity of metabolic processes in normal and malignant cells.

Most often, the energy is released in the form of heat released by the human body. In non-biological systems, caloric energy can be converted into mechanical or electrical energy. How biological systems are essentially isothermal, it is not possible to use directly the heat released in biological reactions to carry out vital processes. Such processes as synthetic reactions,

muscle contraction, and active transport, procure their energy by coupling with exergonic oxidative reactions. Processes that take place with energy release are called exergonic processes, and those that take place with energy consumption are called endergonic.

In living cells, the main macro-energic compound formed during exergonic reactions, which is used as an energy source in endergonic processes, is **ATP (or AMP-P-P).** Of great importance for specifying the direction of metabolic reactions and the energy exchange that accompanies them are the functions of the thermodynamic state: **- enthalpy (H)** or the total energy content of the system; free energy (G), which represents that part of the total energy of the system that can be completely converted into mechanical work in isothermal conditions and is the driving force of spontaneous reactions; - **entropy (S),** which is related to intrinsic characteristics (vibration, rotation, molecular translation) and which increases in all spontaneous processes, **[Figure 1].**

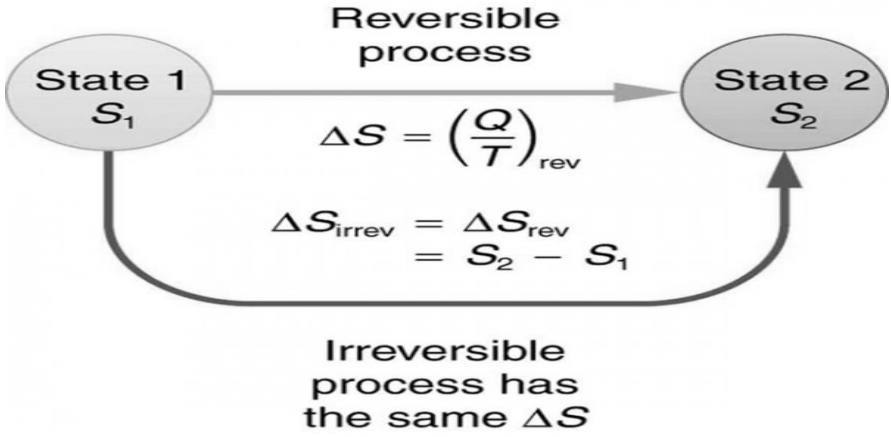


Figure 1. *There is an inverse relationship between free energy and entropy: when the entropy of the system increases, the free energy decreases.*

In the steady state, the entropy reaches its maximum value and the free energy the minimum value. free energy (G) is the part of the "usable" energy of a system and the entropy is the unusable (unavailable) energy, between these quantities there is the relation: **ΔG = ΔH - TΔS** where T is the absolute temperature K ° (273 ° C). ΔG will be higher the difference ΔH - TΔS if is the smaller ΔS and vice versa.

If the variation of the free energy of reaction A -> B has a negative sign (ΔG < 0), meaning that the compound B has a lower free energy than A, the reaction is exergonic and therefore can take place spontaneously.

When ΔG = 0 the system is in equilibrium, and the reaction proceeds without the release or consumption of energy.

The variation of free energy is influenced by the concentration of the components and therefore, in the case of equilibrium reactions it is a function of an equilibrium constant.

Consider the reaction A + B C + D; energy variation of the reaction will be: **ΔG = ΔGo + RT** log K where R is the general gas constant (1.987 kcal/mol/fence), and T is the absolute temperature. Going from the natural logarithms to the decimal ones we obtain: **ΔGo = - 2,303 RT log K.**

If more C and D are formed during the equilibrium reaction than A and B the equilibrium constant has a value and ΔGo is negative. In a reversible reaction, the compounds formed by the exergonic reaction are more than those resulting from the endergonic reaction. In a reversible reaction, compounds that are formed by the exergonic reaction generate energy that can be used to form energy-rich chemical bonds, which is the conservation of biological energy. Biosynthetic reactions are endogenous; for them to have, they must be coupled with exergonic reactions.

This coupling is most often performed by the synthesis during the exergonic reaction of a macro-ergic compound of the ATP type, which will take part in the endergonic reaction that provides the necessary energy. The energy contained in a chemical bond is equal to the energy released by the hydrolysis of that bond. According to the amount of energy released by hydrolysis, the chemical bonds can be divided into two groups: • energy-poor bonds, which release by hydrolysis below 5,000 horsepower; • energy-rich bonds highlighted by the Lipmann sign (~) which releases by hydrolysis over 5000 cal.

They play a key role in transforming energy by transferring it from one exergonic to an endergonic process. Among the macro-energic bonds, a privileged is occupied by the phosphate bond. This link is found in the nucleoside diphosphate and triphosphate through which ATP plays a central role (AMP ~ P ~ P). At the hydrolysis of a macro-energic phosphate bond from ATP or ADP the standard free energy variation is ΔGo = -7.3 kcal/mol. The mixed anhydrous bond between phosphoric acid and an organic acid is also rich in energy. A standard free energy variation will be obtained by

hydrolysis of the macro-energic bond. The phospho-enol bond is also very rich in energy.

For example, phospho-enol-pyruvic acid resulting from glycolysis releases a large amount of energy by hydrolysis (ΔGo = -14.8 kcal). The thioester bond, such as acyl-S ~ CoA, is another type of macro-energic bond. The guanidine-phosphate bond found in phosphocreatine is an important energy reserve in muscle. By its hydrolysis, ΔGo = -10.3 kcal is released. All these macro-energic bonds are of great importance, on the one hand, because they constitute a reserve of energy immediately usable by the cell, and on the other hand they make it possible to transform a radical together with the binding energy on another molecule. For example: ADP + P – enol-pyruvate ATP + pyruvate.

The frequency of this reaction increases in cellular neoplastic states when there is an intense degradation of nucleotides in the body with increased synthesis of IMP --> AMP --> ADP --> ATP in the coupling, on the one hand, and on the other hand an intensification of anaerobic glycolysis with increased phospho-enol-pyruvic acid production. These metabolic pathways may explain the increased levels of ATP in the cancer cell, which is measured experimentally. In this way, the binding energy was conserved by transfer.

The continuous use of macro-energic bonds necessitates a mechanism for their permanent regeneration. This is achieved by coupling exergonic reactions in the cell, especially those in oxidative catabolism, with the endergonic synthesis of ATP in ADP + H3PO4. ATP in turn is used to provide the energy needed for endergonic biosynthetic reactions as well as to obtain the energy needed for any manifestation of cell life. Excess phosphate binding will regenerate ATP from ADP. When an organic substance burns "in vitro" the temperature reached is that at which C and H in the molecule combine directly with O2 in the air, according to the reaction:

CnH2m + O2 ----------> nCO2 + mH2O

The major energy source of the cell is the oxidation of the substrates of food principles in O2 from the air, transported by the blood to the tissues. The living cell obtains its energy by oxidizing Major energy source of the cell is the oxidation of the substrates of food principles in O2 from the air, transported by the blood to the tissues. The living cell obtains its energy by oxidizing the hydrogen released from the organic substrate processed by the

body, the formation of CO2 appears as a secondary phenomenon, often dependent only indirectly on oxidation reactions, which ultimately lead to decarboxylation.

Oxidation can be expressed in three different ways: O2 fixation, dehydrogenation, and electron loss. In the final analysis, oxidation is a loss of electrons and a reduction of an electron gain. Any oxidation reaction (loss of electrons) simultaneously involves a reduction reaction (electron fixation).

Biological oxidations are always redox reactions in which H * or e- are transferred from one molecule (H + or e- donors) to another (H or e- acceptors). In redox reactions, the variation of free energy is proportional to the tendency of the reactants to donate or accept electrons. This is expressed numerically by the redox potential (or redox potential). A compound can only give up electrons to a compound that has a higher redox potential. This means that a compound can only be oxidized by a system with a higher redox potential.

The unevenness of the standard redox potential (ΔEo) is related to the variation of the standard free energy (ΔGo) by the reaction ΔGo = - nFΔEo, where n is the number of electrons exchanged in the redox reaction by a molecule, and F is the Faraday constant (96.399 kg or 23.06 kcal/volt). Because the value of the normal potential Eo varies with the concentration of H + ions and with the temperature.

In biochemistry, the Eo potential determined at Ph - 7.0 and T = 30 ° C is preferred. Cellular respiration is based on a remarkable enzymatic mechanism that allows the cell not to lose the resulting energy during respiration but to preserve it in a usable form stored in the phosphate-macro-energic bonds in ATP from where it can be easily transferred or released. The mitochondrial respiratory chain is a linear redox reaction sequence catalyzed by oxidoreductases in the inner membrane of the mitochondria.

Because cytochrome-oxidase located in the mitochondria is practically the only enzymatic system of cellular respiration in animals that reduces molecular oxygen, it turns out that mitochondria represent the energy center of the cell. In aerobiosis, mitochondria generate almost all of the ATP used by the cell to meet energy requirements based on phosphorylating redox processes. The force generated by this gradient is used to form ATP from ADP and Pi through a dehydration reaction involving Racker Coupling Factor (ATPase).

During cellular respiration, the passage of electrons through the respiratory chain determines the coupling of H + protons and their expulsion. In the contracted state of the mitochondria, the transporters in the respiratory chain are widely oxidized, the rate of ATP activation is high (ATP --> cAMP), the cation content is low and the protons are highly concentrated internally. In the swelling state, these parameters are reversed, the cations being accumulated inside and the protons being released outside.

Ballooning can be prevented and contraction can be induced by the addition of electron transport inhibitors (oligomycin) or by oxidative phosphorylation decouplers. Oxidative phosphorylation in the respiratory chain is determined by the electrochemical potential created between the outer and inner faces of the mitochondrial membrane as a result of electronic transport in the respiratory chain. The process of decoupling oxidative phosphorylation isolates the production of energy from its preservation by preventing the formation of ATP from ADP + Pi.

Most decoupled agents have some common physicochemical properties: they are fat-soluble substances that contain an acid group and an aromatic ring, and which seem to act by dissolving or discharging the macro-ergic intermediate or annihilating the cellular energy state by inhibiting electron transport (2, 4 dinitrophenols, cyanides, CO).

Inner membrane: NADH + H -> Fe S -> FMN -> b -> e -> a—> a3 -> 02: e-> 2H *> e-> 2H *> e

Mitochondrial membrane transport systems for ATP and ADP are inhibited by aromatic compounds (a cyclic aromatic compound with a free radical - O3SO) in position 4 as well as by other antibiotics (free radical acid - $OCH3^{+}$).

In transport through the inner mitochondrial membrane, 6 C2% ions accumulate for the three phosphorylation sites along the respiratory chain, but the C2 + accumulation processes are not simultaneous but alternative. The development of the electronic transport process from NADH to O2 is carried out with maximum speed only when phosphate and ADP are present in the system in large quantities. By adding ADP, the 3rd state or active respiration, characterized by an increase in O2 consumption at the same time as the formation of ATP and ADP, is installed.

After the complete transformation of ADP into ATP, the speed of O2 consumption suddenly decreases, and the system returns to the 4th state. Stimulating O2 consumption is inhibited anaerobic glycolysis. The

explanation for the phenomenon is as follows: Phosphofructokinase, an allosteric enzyme that catalyzes the regulatory reaction of fructose-6-phosphate to fructose-1-6-diphosphate, is inhibited by excess ATP as a final product of aerobic glycolysis and oxidative phosphorylation.

Decreased activity of this enzyme slows down the rate of the whole glycolytic process. In the increased production phase, ATP and other mitochondrial respiration products may function as inhibitors of anaerobic glycolysis. The main compounds, citrate and isocitrate, leave the mitochondria through transport mechanisms immediately through the tricarboxylic ring pathway (**Krebs**) and which, when they reach the cytoplasm, inhibit phosphofructokinase. In isolated mitochondria, volume oscillations, ionic motions, and oxidation-reduction states of hydrogen transporters can occur.

At the cellular level, we discover the chemical language of mutual information with important implications for fundamental biological processes such as multiplication, those based on excitability and contractility as well as heredity, mutagenesis, carcinogenesis or normal cell division. The energy stored in ATP is used in the biosynthesis processes of biomolecules with high specificity and a high level of organization. Their biosynthetic process takes place based on simple small molecule compounds, which come as such from the environment or catabolic processes. Of the four nucleic acid bases, adenine (A) has the highest resonance energy on the Π electron, followed by guanine. The basic nucleus of ATP is adenine, a nitrogenous base bound to a tri-phosphorylated ribose.

The important theoretical conclusion deduced from this situation is that the base resonance is higher for purine than for pyrimidine and that the highest value of the respective index has adenine. The π electrons appear to be responsible for the aromaticity of the ring hydrocarbon system. The double bonds of adenine correspond to the mobile electrons Π, delocalized, with orbitals asymmetric concerning the molecular plane.

The free energy of ATP is considerably higher than that released by the hydrolysis of low-energy phosphoric compounds such as glycerophosphates. The peculiarity of the macro-energic connection is explained by two essential factors: • the anhydrous character of the two macro-energic terminal links (pyrophosphates) of ATP and the properties of the products that these bonds generate when hydrolyzed; in the anhydrous form, intramolecular electrostatic stresses are created which are released by hydrolysis.

The main factor that gives anhydrous bonds the macro-energic character is the resonant stabilization of acids resulting from hydrolysis. The multiplicity of resonant structures is an energetic stabilizing factor of the form. There are fewer resonant forms in pyrophosphate than in phosphate:

Resonance forms in pyrophosphate

Another structural feature that gives pyrophosphate its energetic character is the distribution of negative electronic charges (Π electrons in the pyro-phosphor axis) which is such that it generates electrostatic repulsions that are annihilated as a result of hydrolysis. Because both H3PO4 'and ADP3 anions resulting from the ATP + Pi ATP hydrolysis are negatively charged, they will be rejected so that they can no longer recombine to form ATP in the absence of an exergonic energy supplement.

The second category of macro-energic compounds of paramount importance for cellular bioenergy is, after ATP, phosphocreatine in muscle:

CPK PC + ADP C + ATP ΔGo = (-13 kcal / mol)

Other classes of macro-energic compounds with ΔGo of negative hydrolysis are phosphoenolpyruvate, thioesters (acetyl COA) etc. In all cases, the special electronic configuration in the macro-energic connection (or close to it), which will undergo hydrolysis is responsible for the strong negative value of the thermodynamic factor ΔGo.

Hormones are also factors in the mechanism of control and regulation of life cells, factors that belong to the extracellular coordinating systems superimposed on the primary intracellular ones. The binding of the hormone to the specific cellular receptor triggers the formation of an intracellular messenger molecule that triggers or depresses the biochemical activities characteristic of the target tissue:

Hormones known to work with cAMP in the two-messenger system are the anterior pituitary hormones: ACTH, LH, FSH, TSH, hypo-parathyroid hormone, and calcitonin. CAMP is a specific mediator in other types of

cellular regulatory systems: - acts as a mediator in immune and inflammatory reactions; - stimulates the synthesis of antibodies, the phenomenon being proven in the regulation of the anamnestic response in vitro; - intervenes in the differentiation of B and T lymphocytes by cooperating with thymepectin and allergic hormones; - it also seems to participate in cell-mediated phenomena through sensitized T lymphocytes; - also participates in synaptic transmission in the nervous system.

In the regulation of cell division along with cAMP, cGMP also intervenes, both being involved in the regulation of gene expression during the cell cycle. They appear to act as inhibitors of the cell cycle phase by lowering the mitotic rate. In vitro, it has been shown that cAMP bacteria directly or indirectly intervene specifically on the operative site by removing the suppression of β-galactosidase synthesis.

The action of cAMP on nuclear transcription was shown to be mediated by a specific protein that can bind the nucleotide. This protein is called CRP (cAMP - receptor - protein). Models of the place-operon transcript have been released, involving cAMP, CRP protein and RNA polymerase. The functions of cAMP are influenced by calcium, which in some cases may increase the activity of the nucleotide and in other cases inhibit it. Very important for the regulation of cell life is the interaction between cAMP and other intermediate messengers of which prostaglandins have been recognized as first-rate regulatory agents. Prostaglandins, especially PGE1, serve as intermediate messengers between the surface hormone receptor and membrane-bound adenyl cyclase.

A general property of living matter is its ability to transfer energy to the needs of vital functions. In the phenomena of intracellular metabolic cooperation, it has been shown that a cellular biosynthesizing capacity can be transmitted by contact with a cell that does not possess this capacity. The hypothesis of free energy transfer without material carriers has also been issued within molecular structures.

All essential biomolecules that perform fundamental functions in living matter, proteins, nucleic acids, and macro-energic compounds, are composed of fully or partially conjugated (resonant) clinical systems, rich in delocalized π electrons (Pullman B, 1967).

One of the major features that electronic relocation imposes on compounds in which it exists is the increase of their stability, a state that defines the amount of resonant energy. These resonant molecules would produce, under

the influence of radiation, stable states of excitation of relatively long duration. This reactive capacity was advantageous in the primordial conditions of life on earth by using solar energy with ionic discharges as the primary source for the synthesis of molecules, which led to biological molecules.

A free radical lipid peroxidation reaction (chemical species that have an unpaired electron in the outer orbital) can be propagated by phosphatide fatty acids in the mitochondrial membrane. Both the electronic transport in the mitochondrial respiratory chain (the phenomenon of ballooning - swelling) and the electronic transport through the OFMN system by the cytochrome P456 in the micro can be altered.

In membranes, however, the process of peroxidation can be stopped by vitamin E. Radical damage to the purine and pyrimidine bases can cause mutations and thus carcinogenesis. In the field of carcinogenesis, it has been observed that to be carcinogenic, a molecule must possess a K-reactive region (reactive aromatic bond) but be devoid of the L-para-reactive position region. These reactivities are expressed quantitatively in terms of the localization energy of the K and L regions, and some quantitative regions are established that allow the prediction of the carcinogenic properties of the substance.

Heidelberger (1973) indicated the formation of a strong chemical bond between proteins and carcinogens. Carcinogens are electrophilic reagents that establish covalent bonds with important biological macromolecules such as proteins and nucleic acids. Epoxides, which are highly reactive binding intermediates, are produced by microsomal hydroxylation of aromatic rings, which react as carcinogens.

Malignantly transformed cells continue to divide after confluence and reach a high saturation density. Malignant cell colonies then transfer the malignancy. In malignant metabolic pathways, pyrimidine, DNA, purine, hexose-monophosphate shunt, ribose-5-P generator, and key anabolic enzymes have increased activity, while catabolizing enzymes have increased low activity. In the anaerobic glycolysis sphere, the variation occurs inversely: the key anabolic enzymes have low activity while the activity of the catabolizing enzymes increases, thus ensuring a large amount of energy necessary for cell growth and division. In the normal cell it is admitted that under various boundary conditions, the various parts of the glycolytic system are in a state of self-oscillation, which in turn can be a source of self-oscillation.

The focus of our study will be on the biosynthesis of ADP-ATP and its bioenergetic role. In all cells of the organism, the biosynthesis of ADP begins with the molecule ribose-5-phosphate, on which the skeleton of inosine acid (I.M.P.) will be built. In the first stage, R-5-P reacts with reserve ATP to form phospho-ribosyl / pyrophosphate (PRPP). The second participation of exogenous or endogenous reserve ATP occurs in the reaction between glycochol and PRA (B-5-ribosyl-1-adenine), forming GAR (glycyl amide nucleotide). The third participation of ATP takes place in the reaction:

FGAR (formyl – glycylamide - diribonucleotide) + glutamine + ATP --> FGAM + glutamic acid + ADP + H3PO4.

FGM + ATP -> AIR + ADP + H3PO4 FGAM contains in an open chain all 5 atoms of the purine imidazole ring. The next reaction has a cyclization reaction which will require the participation of an ATP molecule to form AUR (5 - amino-imidazole - ribose). In 4 carboxy - AIR the introduction of a nitrogen atom will also be done with ATP, consumption:

4 carboxyl AIR + aspartic acid + ATP ---> ISCAR + ADP + H3PO4

ISCAR - amino-imidazole-N-succinct-carboxy-amide-ribosyl. After the introduction of a CO2-containing formyl group from the purine nucleus, the FAIR product is cyclized by removing a water molecule, resulting in the inosinic acid, the purine ribonucleotide, the primary product of intracellular biosynthesis. FAIR -> IMP + H2O.

The biosynthesis of IMP and purine nucleotides is an initial endergonic process. 6 ATP were required for IMP biosynthesis if the process was initially started from rebozo-5-phosphate. Inosinic acid (IMP) is readily converted to adenyl acid AMP (by replacing the 6-position hydroxyl group of inosinic acid with an amino group derived from aspartic acid: IMP + aspartic acid + GTP -> adenyl-succinic acid, cleaved into fumaric acid and AMP. GMP is formed by the oxidation of IMP with the formation of xanthic acid and the consumption of 8 molecules of ATP.

The accumulation of purine nucleotides in the cell has the effect of inhibiting the biosynthesis process by a feedback mechanism. Aminotransferase is a multivalent regulatory enzyme and can be inhibited by ATP, ADP and AMP by controlling the transfer of the amino group from glutamine to phospho-ribosyl-pyrophosphate. The biosynthesis of IMP and purine nucleotides is an initial endergonic process.

IMP biosynthesis required 6 ATP if the process was initially started from ribose - 5 - P. Ionic acid (IMP) is readily converted to adenyl acid AKP (by replacing the 6th position hydroxyl group of inosinic acid with an amino group derived from aspartic acid). IMP + aspartic acid -> adenyl-succinic acid -> cleavage -> = fumaric acid + AMP The accumulation of purine nucleotides in the cell has the effect of inhibiting, through a feedback mechanism, the process of biosynthesis. Aminotransferase is a multivalent regulatory enzyme and can be inhibited by ATP, ADP and AMP, controlling the transfer of the amino group from glutamine to phospho-ribosyl-pyrophosphate.

The phosphorylation in the above reactions occurs with the partitioning of ATP, which in most cases is the direct product of oxidative tissue phosphorylation. Thus, phosphorylation reactions are catalyzed in the first stage by nucleoside monophosphokinase and in the second stage by nucleoside di-phospho-kinase.

In living organisms, there are sometimes free purine and pyrimidine bases, most often from the total hydrolysis of the corresponding mononucleotides. These bases can be catalyzed by the formation of appropriate excretion products, but they are often preserved in the body and transformed into nucleotides that enter the metabolic circuit. This preservation process is very high in malignant cells.

Summarizing the above, we conclude that the biosynthesis of nucleotides from endogenous or exogenous nitrogenous bases can be done directly or after their conversion to the corresponding nucleosides. Direct biosynthesis involves the condensation of nitrogenous bases assimilated or resulting from endogenous catabolism, with 5 - PRPP - 1 under the action of nucleoside synthetase. Nucleoside - synthetases that catalyze the condensation of adenine, guanine, hypoxanthine, nitric acid, and uracil have been identified:

Riboză - 5 - P ATP —> APP 5' - P - Ribozil 1 - Pi + adenină —> AMP

exogenous or endogenous reserve. Indirect biosynthesis of nucleotides from nitrogenous bases after conversion to nucleosides is as follows: nucleoside:

1) Nitrogen base (adenine + R - 1 - P nucleoside - 1 - P phosphorylase nucleoside

2) Nucleoside + ATP nucleoside - 5 - P + ADP kinase. The nucleoside-5-P thus obtained can be converted to bisphosphate nucleosides by monophosphate and di-phosphate-kinase in the presence of ATP. The nucleoside

triphosphates thus obtained are the immediate precursors in the synthesis of nucleic acids.

3) Nucleoside - 5 - P + ATP Nucleoside diphosphate + ADP

4) Nucleoside diphosphate + ATP Nucleoside triphosphates + AD In the phosphokinase 2 reaction the equilibrium is strongly shifted in the direction of phosphoric ester formation. Reactions 3 and 4, representing a transformation process, are reversible under the influence of phosphokinases. ADP is also formed from the phosphorylation of GMP, UDP, UMP, and IDP, with the help of reserve ATP or of exogenous direct origin:

GMP + ATP; GDP + ADP; UDP + ATP; UTP + ADP; UMP + ATP; UDP + ADP; IDP + ATP; ITP + ADP

Nucleic acids from food suffer degradation through a series of reactions such as those in tissues, in this way, the body, along with the formation of syntheses for nucleotide reserves, retains considerable energy reserves.

In cancer biochemistry, research on chemical carcinogenesis, enzymes of fundamental metabolic pathways, in all cells and their regulatory mechanisms predominates today, pathogenic chemotherapy aimed at inhibiting key enzymes and fundamental metabolic pathways for the transformation of neoplasia into normal states (DNA synthesis and degradation, synthesis and degradation of purines and pyrimidines, anaerobic glycolysis, hexose-monophosphate shunt). We can also talk today about the pathology of free radicals involved in carcinogens, [1].

CHAPTER II

ATP, THE UNIVERSAL ENERGY RESERVOIR

The vegetation of the planet we live on does not create energy but only one transforms the one received from the Sun. Our lives depend on this property of the green planets. Thus, the energy consumed by humans and mammals during life comes from solar radiation. The process of photosynthesis that takes place in green living matter is a large-scale example of the transformation of energy into nature.

The general equation of photosynthesis has been written as a reaction between carbon dioxide and water. light energy **CO2 + H2O --> O2 +** organic matter green plants. Solar energy comes from the fusion of four hydrogen nuclei with the formation of two helium nuclei**. - H - He + 2e- + hv (energy**) Since the frequency of the radiation υ is inversely proportional to the wavelength, it means that the photons in the light with the short wavelength it is much richer in energy than long-wavelength light photons.

The photons in blue light are richer in energy than photons in red light. Pigments, present in plant tissues, must absorb the energy of a photon at the characteristic wavelength and then use this energy in photochemical reactions. A pigment after absorbing a convenient amount of energy (light) immediately releases an electron. By releasing the electron, the pigment molecule enters a state of excitation and at a later stage, there is a possibility that the energy absorbed in the system (the pigment molecule) can perform a photochemical reaction. Photon energy can be expressed in volts (eV). The energy of one mole of orange light (650nm) carries 1.9 eV. j / mol, **eV =9,65 x 104.**

White light energy contains 11.33 eV. Ultraviolet radiation contains 3,100 eV. In the process of photosynthesis, plants use the energy of sunlight to transform two inorganic molecules, extremely stable and poor in energy, CO2 and H2O, into unstable organic molecules but rich in energy and molecular oxygen.

Most of the organic molecules formed in photosynthesis are carbohydrates, which will polymerize to form polysaccharides. Thus, the formation of

glucose from photosynthesis can be represented by the equation: enzymatic system:

6CO2 + 6H2O 6 (CH2O) + 6CO2 with accumulated energy being 626 Kcal / mol.

The incorporation of CO2 with the formation of phospho-glyceric acid (PGI) initially as a product of photosynthesis is independent of light. Glucose will be formed from two molecules of phospho-glyceric acid, following reactions whose chaining is opposite to glycolysis. The process is carried out with the help of NADPH2 and ATP, formed during the light phase. In this case, oxidation of NADPH2 and hydrolysis of ATP to ADP + Pi take place.

But not only carbohydrates are formed from AGP but also amino acids, organic acids, fatty acids and glycols. AGP also serves to regenerate ribulose-diphosphate (which has been used in the formation of AGP). Trioses (glycerol phosphorylated aldehyde and its phosphorylated de-hydroxy-acetone isomer) by condensation can give rise to various phosphorylated carbohydrates with C6 (fructose, glucose), C7 atoms and finally with C5 (ribose).

There are many analogies between chloroplast phosphorylation and oxidative phosphorylation observed in mitochondria where ATP synthesis is associated with electron transfer. The energy required for the flow of electrons from chloroplasts is ensured by the absorption of light radiation energy by assimilating pigments, concentrated in the two points of the electron transport chain P650 and P700 (P comes from the pigment and its number from the light wavelength which the molecule absorbs). Each absorbed photon will conduct one electron through the inner membrane of the chloroplast. The main result that leads to the flow of electrons is the phosphorylation of ADP with the formation of ATR.

A. Phosphorylation of ADP in the plant cells

Following various research (Mitchell P., 1967) phosphorylation reactions in the plant cell are performed using enzymes (ATPases) implanted in the cell membrane. It is now accepted that the synthesis of several ATP molecules is associated with three protons in ATPases. ATP can therefore use two forms of energy, one from the proton gradient and the other from differences in membrane potential. The enzymes involved in ATP synthesis are similar for mitochondria, chloroplasts and bacteria. These enzymes, in electron

microscopy, look like globular bodies like protuberances on the surface of membranes. In plant cell chloroplasts these enzyme systems have been termed CFi1 • CF2 complexes oriented in the opposite direction to similar formations of mitochondria, bacteria, namely protuberances on the outer surface of membranes.

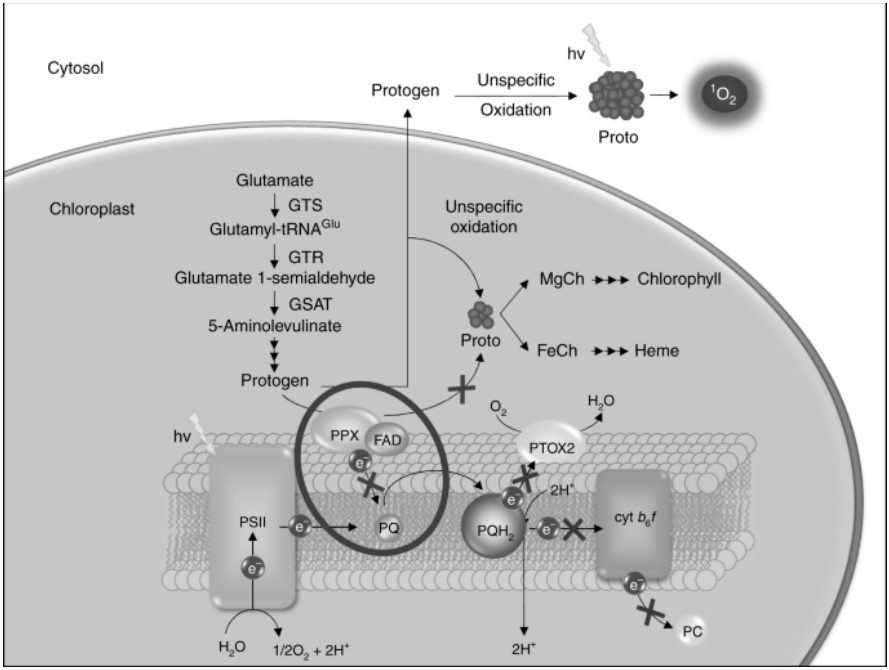
Electron flux is directed through the CFj • CF2 complex, and ATP is formed in the space between the inner and outer membrane of the chloroplast. In chloroplast, the CF] - CF2 complex requires the presence of three protons for each molecule of ATP synthesized, as opposed to mitochondria, in which the enzyme complex uses only two protons. Being an electron current, the phosphorylation that takes place from CF1 to F2 is called cyclic phosphorylation, as opposed to the phosphorylation that occurs in the transport of electrons from CF2 to CF1, which is linear.

All the transformations that take place after the carbon chain is charged with energy and H + from ATP and NADPH2, formed during the light reactions, no longer require a significant effort of energy and continue in the dark. Since these transformations in the reductive cycles of photosynthesis can also occur in the absence of light, the anabolic phase is also known as the dark phase of photosynthesis.

In the primary stages of photosynthesis, electron transfer, NADP production and ATP synthesis, O2 release occurs at the level of chloroplast thylakoids and is based on the accumulated bioenergetic background. The most important components of thylakoids are assimilation pigments, chlorophylls, carotenoids and phycobilin. Chlorophyll is a proto-porphyrin that contains a tetrapyrrole ring that has a cyclic system of 9 conjugated double bonds. These together with the 4 nitrogen atoms bound to the Mg atom correspond to the approximately flat part of the chlorophyll molecule (form a - form c). The main carotenoids, yellow or orange, are present in all photosynthesizing cells. In the leaves, their color is normally masked by chlorophyll, but in autumn, when the chlorophyll disintegrates, becomes visible**, [Scheme 1].**

The main carotenoids are p-carotene and xanthophylls. Carotene (C40 H56) is a hydrocarbon whose chain is cycled at the ends. Xanthophylls are oxygenated derivatives of carotene (C40H56O2). Carotenoids are located in the lamellae of chloroplasts in the vicinity of chlorophylls. In the process of photosynthesis, the energy absorbed by the carotenoids can be transferred to chlorophyll "a", which thus passes into an excited state (b, c), the carotin returning to their unexcited ground state. The resulting phycobilin has a structure close to that of pigments that come from light degradation.

The energy absorbed by phycobilin is transferred to chlorophylls to stabilize photochemical processes, **[Scheme 1].**



Scheme 1. *The scheme represents not only the natural balance of the process but also the energy balance. The atmosphere of the Sun is mainly made up of hydrogen.*

Photorespiration the process by which CO2 is released into the atmosphere has been considered a respiratory process of energy, however, it is suggested that this feature is not so pronounced because for every molecule of CO2 released into light 3 molecules of ATP-rich in energy are synthesized. Only 40% of the received energy is used in photosynthesis, 50% is the infrared region of the spectrum that cannot be absorbed by assimilating pigments, and the remaining 10% is lost through reflection, transmission and absorption.

Man depends solely on solar energy, used or current, to meet his growing energy and food needs. Solar energy is abundant, continuous, clean and free. That is why it is important to learn to use it most cost-effectively and effectively, imitating as much as possible the process of photosynthesis, which is carried out with extraordinary efficiency by plants, perfectly

adapted for photoconversion. As in animal cells, mitochondria in plant cells, due to the enzymatic equipment located in both membranes and matrices, play the following roles in cell biology: • partially ensures the degradation of synthetic cell glucose; • represents the headquarters of the Krebs cycle and of the respiratory chain that derives from this cycle; • are the site of syntheses and accumulations of substance.

There are two categories of ATPs in the plant cell: a) ATP of mitochondrial origin arising from oxidative phosphorylation; b) ATP of cytoplasmic origin that arises during anaerobic and partly aerobic glycolysis. Research (Niculescu et al., 1971) has shown that the mitochondrial membrane, which does not show a change in its intra-structural integrity, is much more permeable to bivalent ions (Ca2 +, St2 +, Mn2 +, Mg2 +) and less permeable to monovalent ions (K +, Na +). This permeability to cation anions leads to their accumulation in the matrix as well as on the inner mitochondrial membrane, a process materialized by a swelling of the mitochondria.

The movements performed by mitochondria by ballooning and contraction, depending on the nature of the ions in the environment and intramitochondrial, atmosphere, pH, changes in the cytoplasmic environment, etc. are in reality only movements related to the active transport of ions through the mitochondrial membrane. Studies have shown that the passage of mitochondrial membrane by cations and anions requires energy from either ATP in the extra-cyto-cytoplasmic environment or intermediate precursors of ATP synthesis, ex, DP + P2. One thing is certain: in the absence of light radiation, ATP is not initially produced from light:

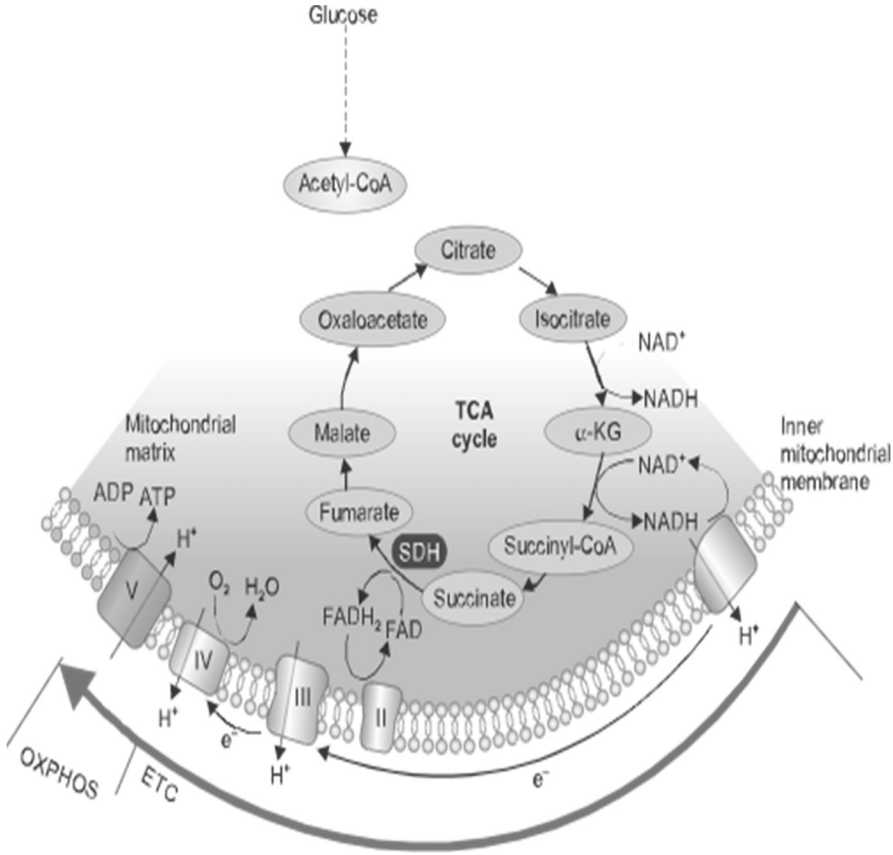
LIGHT -> CHLOROPLASTS -> ADP + Pi -> ATP

Glucose biosynthesis also takes place with the help of light energy in the process of photosynthesis with the help of ADP synthesized from the three elements: adenine, ribose and phosphoric acid.

B. Biosynthesis of ATP in the human cells

From the histo-chemical point of view, the mitochondrial energy apparatus is represented by a set of intracellular formations of different shapes and sizes, with a double membrane (external and internal). The inner membrane is 1μ thick and has more intra-cytosolic septa, which increases their surface area, favoring surface catalysis. The essential function of mitochondria is related to the transport of hydrogen and electrons, oxidative phosphorylation and the Krebs cycle. In the mitochondria, there is an enzymatic assembly

called the respiratory chain that makes it possible to oxidize organic substances into the substrate, with the formation of water molecules. The substrate entering the respiratory chain undergoes the action of dehydrogenases, enzymes that carry hydrogen and trans-electron transporting enzymes. In the mitochondria, 300 enzymes have been isolated with a role in energy metabolism, among which are the enzymes of the aerobic catabolism cycle of energy principles (**Krebs)** as well as oxidative phosphorylation, **[Scheme 2].**



Scheme 2. *The oxidative process of water formation together with that of ATP formation is called oxidative phosphorylation.*

The reaction cycles release an energy of 52,000 cal/mol, of which almost 40% is used by the cell to synthesize ATP from ADP and inorganic

phosphate. ADP > ATP <. The highest amount of ATP is formed during carbohydrate metabolism coupled with oxidative phosphorylation.

The biochemical components of ADP are adenine, ribose, and orthophosphoric acid. a) Adenine is a 6-aminopurine formed on a purine nucleus. Adenine biosynthesis is performed either "de novo" from single metabolic fragments:

- CO2, aspartic acid, glycochol;

- NH3, glutamine; -formic acid, glycine, either from nitrogenous bases or nucleotides (ribose-coupled nitrogenous bases) from plant and animal nutrition as well as from nitrogenous bases resulting from the cellular catabolism of nucleic acids and nucleotides. Ribose is found in all cells with a nucleic acid composition and in the nucleotides of the animal and plant cytoplasm.

An important biological role is played by ribosomes as a component of nucleotides as enzymes. In these compounds, it is found in the form of furanone, glycosidic bound to apyrimidinic purine derivatives and phosphoric acid. Ribose, from a biochemical point of view, is a Penta-carbohydrate that can be absorbed from the diet at the intestinal level by simple fusion, an absorption process that does not involve an active energy-consuming mechanism. Ribose synthesis takes place in the human body via pentose-phosphates as well as in most green plants during the process of photosynthesis.

The pentose-phosphate pathway is the third major pathway for glucose degradation in the cells of the human body. The process begins with the oxidation of glucose-6-phosphate. Under the action of glucose-6-phosphate dehydrogenase (GPDH), 6 phospho-gluco-lactone is formed and then 6-phosphoglucose acid. In the next step, 6-phosphoglucose acid under the action of the enzyme 6-phosphogluconate dehydrogenase (PGDH) oxidizes and forms as final products CO2, ribulose-5-phosphate and NAPDH> Ribulose-5-phosphate isomerase isomerized to ribose-5-phosphate

In some cases, the process can be stopped here from the oxidation of glucose-6-phosphate resulting in CO2 and NAPDH2, which enter the biosynthetic reactions that take place in the extramitochondrial cytoplasm and D-ribose-phosphate which is a precursor in mitochondrial synthesis. The global equation is as follows: G-6-P + NAPDBT ribose-5-phosphate + CO2 + NADPH + 2H + In other cases, however, the resulting pentoses can be converted from hexoses into an independent sequence of reactions. The

pentose-phosphate pathway is not coupled to the respiratory chain and does not form ATP but is even consumed to activate glucose to glucose-6-phosphate. The different stages of this metabolic sequence have a role in the soluble phase of the cytoplasm and the products of the stages are implications in the biosynthesis of mononucleotides and nucleic acids, respectively. NADPH2 is the supplier of H2 and electrons in the biosynthesis of fatty acids, sterol compounds, etc. The penta-phosphate pathway is a strategic pathway used by the malignant cell for multiple, fast, energy-efficient cellular biosynthesis.

Ortofosphoric acid, H3PO

Phosphorus is the main biochemical element in its composition. In adults, the amount of phosphorus (P) required daily is 1.5 g and is provided by a normal diet. Phosphorus in the body is found in the form of various chemical combinations: -H3PO4 in the form of salts: Na, Ca, Mg; -compositions with pseudo-aldehyde function-monoesters of pentoses and hexoses; -organic esters and acids; -phospho-amino-lipid-type digesters; -pyrophosphoric acid derivatives:

Phosphorus absorption is in the form of soluble inorganic phosphate and occurs in the upper part of the small intestine. Phosphorus plays multiple roles in the body: - structural role in bone tissue, in the form of phospholipids that enter the structure of cell membranes; - functional role through its participation in the intermediate metabolisms of carbohydrates, lipids, and proteins; - energetic role through its participation in strong energetic bonds from macro-energetic compounds such as ATP, AMP, ADP phosphocreatine; - role of an enzymatic component of some enzymes NAD +, TPP, COA, pyridoxal phosphate. ATP formation occurs in the presence of specific enzyme systems, found in all living cells.

Given that many metabolic processes are not possible without the intervention of ADP and especially ATP, research has focused primarily on specifying the biochemical mechanisms that lead to the synthesis of these two groups of nucleotides. Thus, it has been established that in most cases ADP arises through a process of phosphorylation of AMP by ATP, a reaction catalyzed by AMP kinase:

AMP + ATP……. ADP + ADP
AMP-kinase

Regarding the biosynthesis of ATP, it was found that it requires precursors of ADP + Pi and can be achieved in aerobic as well as anaerobic cells. It has also been observed that to the same extent that ATP biosynthesis is performed, to the same extent there is a cleavage of ATP resulting from ATP + Pi with the activation of other intracellular chemical constituents as phosphate group acceptors. Living plant cells can synthesize ribose existing in the constitution of nucleic acids even in the absence of chlorophyll. Research on the biosynthesis of the purine and pyrimidine bases that make up the nucleic acids has shown that these bases are not found in the living cell as such, but only in the form of nucleotides (nitrogen base + ribose-phosphorylated).

In the "in vivo" synthesis of the purine nucleus it was stated that the carbon and nitrogen atoms of the nucleus have various origins: - N3 and Mg nitrogen atones from the glutamine amide group; - N1 nitrogen atom from aspartic acid; - N7 nitrogen atom from glycol; - C4 and C5 carbon atom resulting from glycol; - C2 and C8 carbon atom in formyl-tetra-hydrophobic (THFA); - C6 carbon atom from CO2. Finally, the purine nucleus appears as a purine nucleotide, called inosinic acid or inosine-mono-phosphate (IMP). The starting point in this biosynthesis is the ribose-5-P, the support on which the basic components of the purine structure are fixed fragment by fragment. Throughout the reactions involved in this biological synthesis which suppresses 11 reactions, ribose-5-phosphate remains fixed on the final molecule which arises, i.e. on the inosinic acid. From inosinic acid (IMP), as a result of transmission reactions catalyzed by specific enzyme systems, AMP is born.

The synthesis of AMP requires GMP and GMP requires AMP, the excess of one component stimulates the formation of the other. AMP can also be formed during the synthesis of pyrimidine nucleotides, under the influence of the ATP synthesized from the components described above.

ATP+ Ribose-5-phosphate -> P-RPP + AMP

Also, starting from nucleoside-into-phosphate (DNMP), where d = deoxyribose, with ATP, AMP is formed. Transferases, d-NMP + ATP --> dNTP + AMP/. Biosynthesis of triphosphate d-nucleotides in eukaryotes occurs at the interphase, in the pre-syntactic period and the S-period, but before the depilation of the DNA molecule. Condensation of nucleotides into nucleic acids is not done from monophosphate molecules but from triphosphate nucleotides, an easy process in the cell because all monophosphate nucleotides, regardless of the nature of the nitrogenous