The dual energetic supply of eukaryotic cells

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Abstract

The regeneration of tissue damage is possible because our cells have a dual-energy supply system and can ensure tissue regeneration without O_2. The publication summarizes the defining elements of the structures responsible for energy transformation. It points out the importance of Hypoxia Inducible Factor (HIF)-1 alpha in tissue regeneration and details the way of renewal. Unfortunately, the same structures help the development of cancer and the increase of its malignancy.

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Introduction

The human body comprises eukaryotic cells, so it is essential to know their properties regarding the energy supply. This communication summarizes the evolution of eukaryote cells and their energy supply path. The dual energetic supply results in the possibility of the regeneration of tissue damage and the cause of cancer's progression process.

Energy transformation

It is well known that the energy supply of cells is provided by glycolysis ($C_6H_{12}O_6$ = 6 CO_2 + 6 H_2O + 2880 kJ/mol).

However, this is only partly true. In fact, ATP is also formed from sugar simultaneously when carbon dioxide is formed. Energy transformation is realized in unique structures such as Structure for Energy Transformation (SET). Adenosine Diphosphate Producing Unit (ADP-PU) is the basic unit of SET [1].

The development of eukaryotic cells

There was no O_2 in Earth's atmosphere more than three billion years ago. The possibility of the formation of life was ensured by the conditions for the creation of life. Among the many cells with different properties were blue algae, which continuously produced O_2 molecules. The appearance of O_2 in the atmosphere caused the first environmental disaster, as the cells were not prepared to protect against the highly destructive O_2. According to Lynn Margilus' hypothesis, an ancient cell entered into symbiosis with a cell that was able to defend itself against the dangerous effects of O_2 (Illustration 1). In addition, the modern cell produced an order of magnitude more energy with the help of O_2. The contemporary cell is now known as a mitochondrion [2]. The advantages of symbiosis are significantly more energy, protection against free radicals, and regeneration ability of organisms [3].

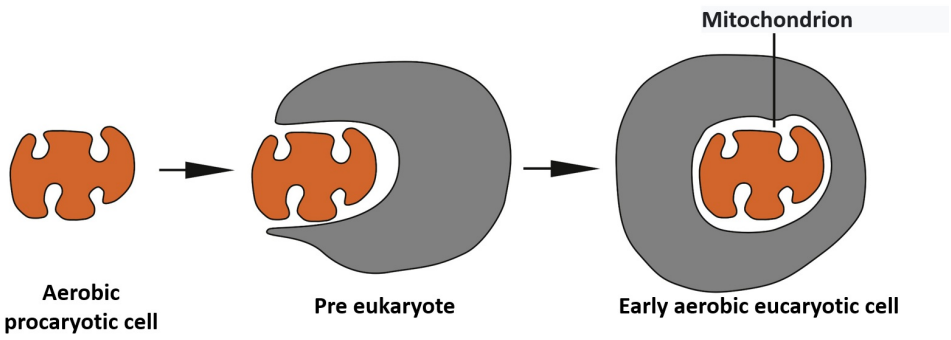


Illustration 1. The evolution of mitochondria according to the theory of endosymbiosis (2).

The Evidence Supporting the Endosymbiotic Conception:

a/ Mitochondria are capable of division, and their dimensions and form are like today's bacteria.
b/ They have their DNA, which is identical in structure to the DNA of prokaryotes.
c/ They have a protein-synthesizing system, similar to prokaryotes.

Mitochondria provide the cell with protection against free radicals and a significantly better energy supply. Eukaryotic cells formed by symbiosis can function in both anoxic and oxygenized environments [2].

In the body formed by eukaryotes, cells can adapt to the O_2 deficiency. Due to the lack of O_2 caused by injury or any cause, the hydrolysis of the Hypoxia-Induced Factor (HIF)-1α is cancelled. Subsequently, the HIF system influences about 200 genes, converting cells to ancient energetics. As a result, the circulation will be restored with the help of newly-formed

blood vessels. In addition, increasing tissue O_2 will hydrolyse the HIF-1α; thus, the cells will return to the mitochondrial oxidative phosphorylation [4][5][6][7][8].

The dual energy supply of eukaryotic cells

The mitochondria in eukaryotic cells have their genetic stock. Accordingly, our cells must have two structures to ensure energy transformation: SET-AG (belonging to the ancestral cell) and SET-OP (belonging to the mitochondria). The operational activity of these structures can be determined by the amount of ATP produced. In an oxygenated environment, SET-AG will not function, as the ATP produced by the mitochondria significantly exceeds the capacity of SET-AG, resulting in the shutdown of its activity.

In an anoxic or hypoxic environment, mitochondria stop working. At the same time, there is no hydrolysis of HIF-1 alpha, which will result in the activation of the SET-AG.

In the case of anoxia, ADP-PU produces ten CO_2, while in an oxygenated environment, SET-OP forms 9 X (ten + six CO_2). Accordingly, the energy production capacity of SET-AG is significantly lower than that of SET-OP.

The importance of Fe-S clusters

Several Fe-S clusters (e.g., 2Fe-2S, 4Fe-4S, 6Fe-6S, P-cluster of nitrogenase (8Fe-7+6S)) are known. They play an essential role in the development of life by ensuring continuous electron transfer. In the central part of the 2Fe-2S cluster, two irons are bonded to two sulphurs. The two irons in the 2Fe-2S cluster can bind four more sulphurs. The outermost electron shell of iron can contain two, three, or four electrons (Table 1). The binding affinity of iron to oxygen and sulphur is determined by the number of electrons in the outer electron shell of iron. In the case of two electrons, the iron binds the oxygen, while in the case of three, the sulphur bind is realized. The process produces four O^{e2-}, producing two CO_2 or four H_2O molecules. Other Fe-S clusters might have similar nature. Thus, the P-cluster of nitrogenase might make six O^{2e-} (illustration 2).

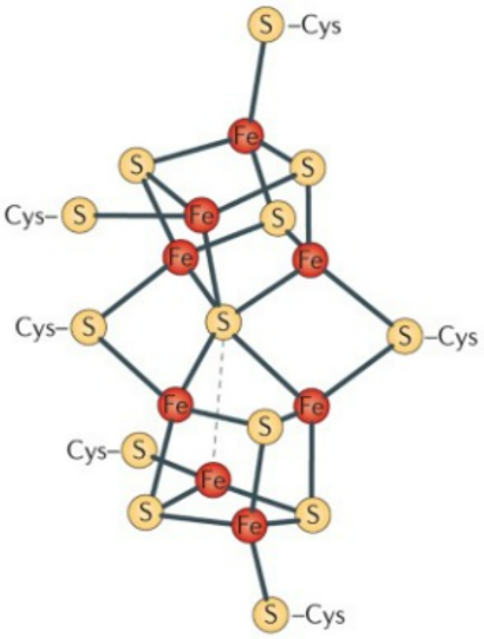


Illustration 2. *P-cluster of nitrogenase (8Fe-7+6S)*

Table 1. The structure of the electron shell of oxygen, sulphur, and iron.

	atomic Number	Number of electrons in the electron shell
Oxygen	**8**	**2, 6**
Sulphur	**16**	**2, 8, 6**
Iron	**26**	**2, 8, 14, 2 or 3 or 4**

Complex V

The binding change mechanism of Complex V involves the active site of a β subunit's cycling between three states.[9] In the "open" state, ADP and phosphate enter Complex V; in Illustration 8, this is shown in white. The enzyme then changes shape and forces these molecules together, with the active site in the resulting "tight" state (shown in yellow) binding the newly produced ATP molecule. Finally, the active site cycles to the loose state (red) and will be ready for the next cycle of ATP production [10].

Vitamin C and ATP are the initiators of energy transformation

Grano et al. stated that AA is an oxidative stress sensor and a gene expression regulator. In addition, they pointed out that the change of AA to DHA regulates the modulation of the electron shell of Fe. [11][12]

The way of action, assumed by me: the two OH on the lactone ring of vitamin C are exchanged with the two central sulphur atoms of the 2Fe-2S sulphur-iron cluster, forming two Fe^{2+} from the two Fe^{3+}, while it turns into Dehydro Ascorbate (DHA), and two H^{+} are formed. As a result of the change in the properties of iron, the four other sulphur atoms are replaced by molecules containing oxygen atoms. Oxygen atoms of two uric acids (UAs) (or two NH_2-UAs) and two $H_2PO_4^{e-}$ will occupy the place of the four sulphur atoms. After that, two hydrogen atoms of the two $H_2PO_4^{e-}$ molecules transform DHA into AA, while the iron atoms become three-electronic again (Illustration 3). This change results in a sulphur-oxygen exchange, creating four O^{e2-}, which leads to CO_2 or H_2O molecules forming. A similar reaction might run on regarding the two OH of the ribose part of the ATP when initiating one Fe-S cluster.

two Fe^{3+} + AA = two Fe^{2+} + DHA + 2 protons

two Fe^{2+} + DHA + two $H_2PO_4^{e-}$ = two Fe^{3+} + AA + two HPO_3^{2e-} + four O^{2e-}

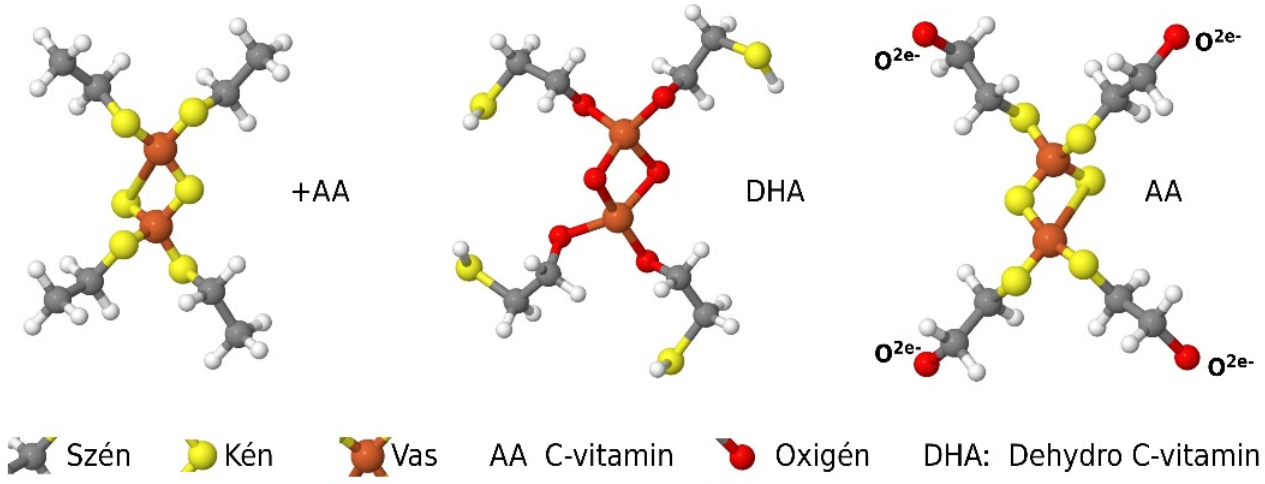
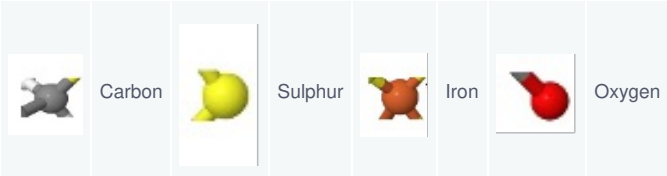


Illustration 3. Vitamin C initiates the flow of electrons in the sulphur-iron cluster.



AA: Ascorbic acid; DHA: Dehydroascorbic acid

The change of the Fe-S cluster's nature might also be initiated by the two OH of the ATP molecule.

Structure of SET-AG and SET-OP

The basic unit of both SETs is the ADP-PU. In addition, complex Vs are also required to generate ATP. The participating molecules are four UA, four NH_2-UA (four UA + four NH_3), six D-glucose, two L-ascorbic acids, and twelve $H_2PO_4^{e-}$. The four NH_2-UA and eight $H_2PO_4^{e-}$ molecules create the tetra adenine octo phosphate ring (ADP-PUa), where four P-cluster of nitrogenase Fe-S clusters connect the molecules (Illustration 4a, 4b).

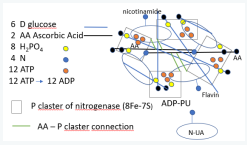


Illustration 4a ADP-PUa

Products

4 ADP
2 Pyruvate
10 CO_2
2 citrates +
2 lactone rings = 2 new L-AA

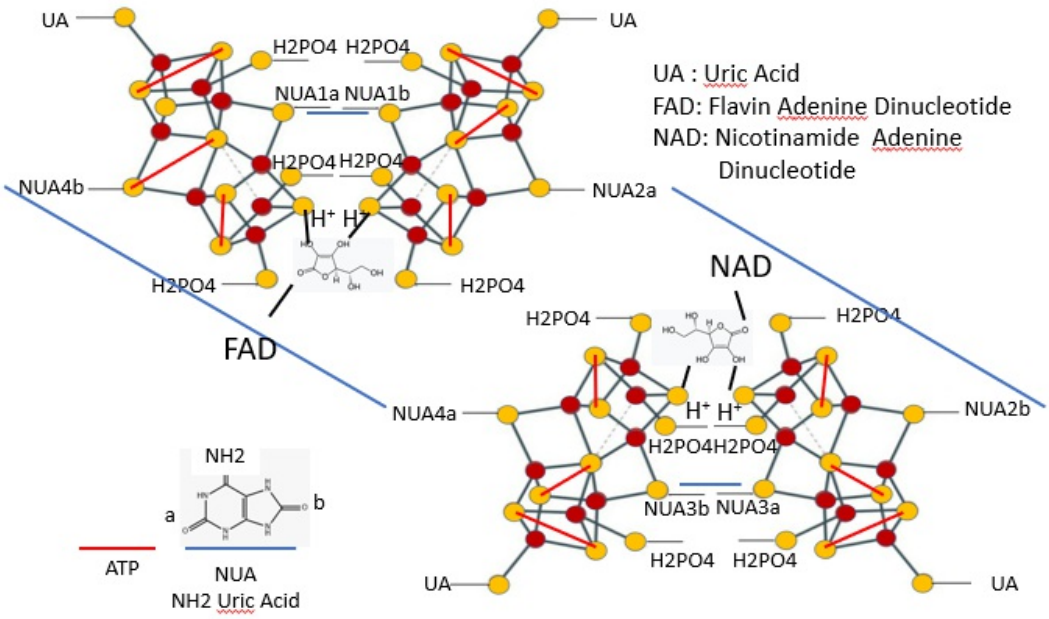


Illustration 4b ADP-PUa

The other part of ADP-PU (ADP-PUb) is responsible for the amination of UA and the production of HPO_3^{2e-} (Illustration 5).

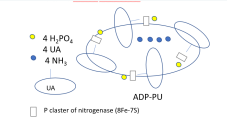


Illustration 5. ADP-PUb

Products

4 NH_2-UA
4 HPO_3
4 H_2O
4 O^{2e-} *

** These oxygens are responsible for the oxidation of the 5th carbon atoms of two vitamin C.*

The structural elements of ADP-PU are four sulphur-iron clusters, one flavin, and one nicotinamide molecule. Four P-cluster of nitrogenase (Illustration 2) might mediate the electron flow. The mechanism of S – O exchange might be similar to the processes of 2Fe-2S as presented above. Energy investment: the initiation of the four P-clusters (8Fe-7+6S) is realized by two AA and 4 x 3 ATP molecules. They result in the phosphorylation of six glucose and two AA and nitrification of four uric acids.

SET-AG consists of three ADP-Pus (ADP-PU-A, ADP-PU-B, and ADP-PU-C) and three Complex V. These structures work together in a synchronized way. Wen ADP-PU releases the ADP and HPO_3, the complex V is in the open phase, ready to accept them. Furthermore, when ADP-PU-A is in the open state, ADP-PU-B is in the tight, and ADP-PU-C is in the loose state. This synchronization ensures continuous membrane potential and ATP formation (Illustration 6).

The four UAs with four NH_3 molecules form four aminated UAs + four H_2O, while the four aminated UAs produce four adenine molecules.

In the transformation process, four ribose, two Pyruvate, two citrates, and six CO_2 are created from six D-glucose molecules.

Four ribose with four UA-originated adenine molecules forms four adenosines. In an O_2 -free environment, two lactates are formed from the two Pyruvates, while in an oxygenated environment, six CO_2 molecules + energy are realized through oxidative phosphorylation. During the energy transformation, the two AAs' 5th and 6th carbon atoms are converted into four CO_2. Then the remaining two lactone rings are supplemented with the two citrates to form two new AAs.

SET-AG has three, and SET-OP has nine ADP-PUs.[1]

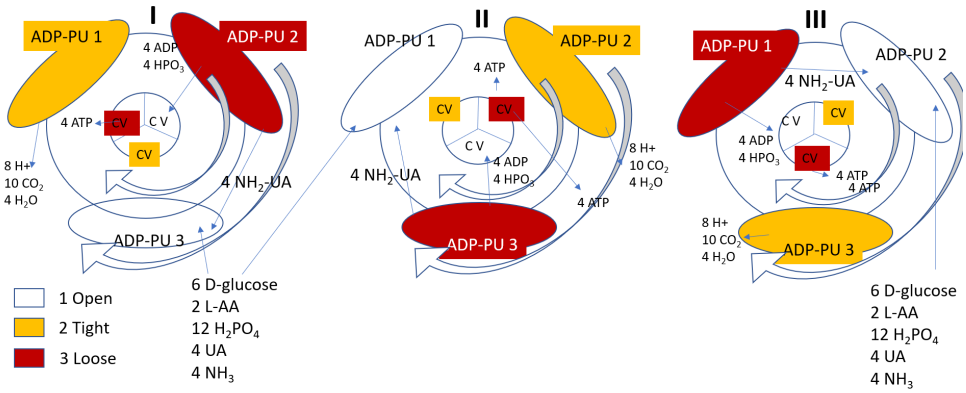


Illustration 6. The synchronised function of three ADP-Pus (I, II, III) and three Complex Vs

The role of HIF in the control of regeneration

The HIF system

The HIF system is the detector and conductor of the oxygenated and oxygen-free environment. It facilitates the cell back to ancient times. The HIF system ensures adaptation to an environment without O_2. [6][7][8][9][13][14][15]

In the existence of O_2, the SET of Oxidative Phosphorylation (SET-OP) presents oxidative phosphorylation. In contrast, cells use aerobic glycolysis offered by the Structure for Energy Transformation (SET)-Aerobic Glycolysis (SET-AG) in an anoxic environment (Illustration 7). [1]

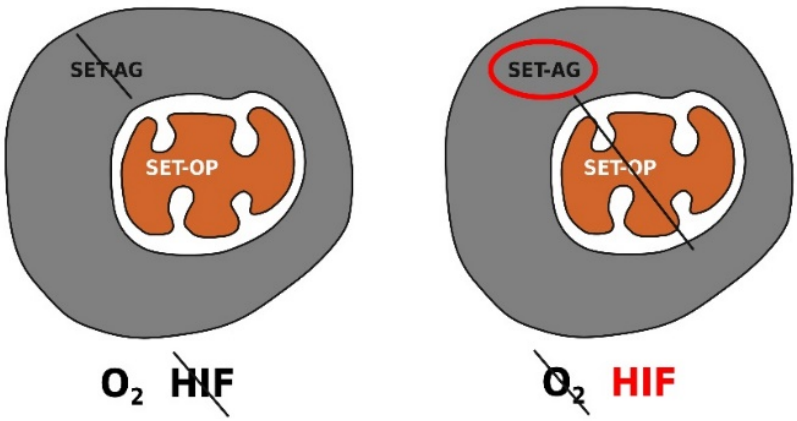


Illustration 7. The HIF system is the detector and conductor of the oxygenated and oxygen-free environment.

Abbreviations: Structure for Energy Transformation of Aerobic Glycolysis: SET-AG;

Structure for Energy Transformation of Oxidative Phosphorylation: SET-OP; HIF: Hypoxia-Inducible Factor.

Cells will become viable in an environment without O_2 with the help of the HIF system, which ensures adaptation to an environment without O_2. HIF-1 alpha combines with HIF-1 beta to modify the activity of about 200 genes. The most significant changes are:

1. Genetic changes result in the reactivation of SET-AG.
2. Due to the low energetic efficiency of SET-AG, the appropriate energy supply of the cell can be realized only by about two hundred times more glucose. Therefore, the number of glucose transporters in the cells increases.
3. The sensitivity to apoptosis decreases.
4. Induction of neovascularization.
5. Induction of the formation of pluripotent cells.

As a result of these changes, the cells survive in the hypoxic environment and ensure the realization of tissue regeneration and neovascularisation. SET-AG is always present in the cell but does not function in normoxic conditions. The Fe-S clusters of SET-AG may be in their determined place.

In the serum of intravenous AA-treated patients with cancer, the level of ADP increases. At the same time, the uric acid decreases, which may be because the high serum AA level activates the ADP-PU units of SET-AG of all cells, without ADP-ATP transformation.

Ribose

Numerous clinical studies and animal experiments have investigated ribose's physiological properties and effects on carbohydrate metabolism. [16] Oral and intravenous ribose has been shown to reduce serum glucose levels. The degree of reduction correlates with the amount of ribose administered. Twelve grams of ribose assisted 136 mg/minute infusion led to a decrease in blood glucose that was 48% of fasting value following 60- to 65-minutes. [17] It is known that phosphoglucomutase, the rate-limiting enzyme in the formation of glucose from glycogen in the liver, is inhibited by ribose. [18] Gross and Zollner administered ribose orally and/or intravenously to nine healthy subjects in doses of 83.3- to 222.2 mg/kg/hr for at least four hours. [19] In these subjects, serum ribose increased in a dose-dependent manner to a maximum of 75- to 85 mg%, and serum glucose levels decreased after beginning continuous ribose administration and remained reduced as long as ribose was administered. Both oral and intravenous administration of 166.7 mg/kg/hr resulted in an average 25% decrease in serum glucose. Still, higher doses did not elicit a more significant glucose-lowering response, suggesting a saturation of the glucose-lowering mechanism at serum ribose concentrations higher than approximately 30- to 40 mg%. [19]

The efficiency of SET-AG and SET-OP

After energy investment, energy is produced in the SET. In addition, new ATP molecules are created, and the realization of the membrane potential becomes possible. At the end of the process, the ADP molecules formed during the energy investment are transformed back into ATP using the energy produced.

In an environment without O_2, cells can produce significantly less energy than in an oxygenated environment. Table 2 summarizes eukaryotic cells' assumed energy production capacity in oxygenated and anoxic environments.

Anoxia	3 x (4 ATP +10 CO_2) = approx. 5700 kJ/mol
SET-AG	12 ATP + 30 CO_2 = approx. **17 100 kJ/mol**
Normoxia	3 x (12 ATP + 48 CO_2) = approx. 27 700 KJ/mol
SET-OP	36 ATP + 144 CO_2 = **83 100 kJ/mol**

Conflicting Interests

The author declared no potential conflicts of interest concerning the publication of this article.

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