The dual energy 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 (SET), specifically, the hypothetical ADP-producing unit, the SET of anaerobic glycolysis (SET-AG), and the SET of oxidative phosphorylation (SET-OP). SET-AG is responsible for the anaerobic fermentation, while SET-OP is for the aerobic oxidative phosphorylation. The importance of Hypoxia Inducible Factor (HIF)-1 α in tissue regeneration is also discussed.

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Introduction

Energy conversion

Gasoline or petrol, used as a fuel in spark-ignited internal petrol engines, must be made by fractional distillation of petroleum. Similarly, glucose must be transformed into Adenosine Triphosphates (ATP) to get a usable energy-carrier for living organisms.

The human body comprises eukaryotic cells, so it is essential to know the properties of their energy supply. This communication summarizes the evolution of eukaryote cells and their energy supply path — the dual energetic stock results in the possibility of the regeneration of tissue damage.

Energy and energy-carrier transformation, ATP synthesis

Glycolysis and oxidative phosphorylation are autonomous mechanisms. It is well known that the energy supply of cells is provided by glycolysis which occurs in the cytosol of cells. During glycolysis, glucose breaks down into pyruvate and energy; a total of 2 ATP is derived in the process: Glucose + 2 NAD^+ + 2 ADP + 2 Pi → 2 Pyruvate + 2 NADH + 2 H^+ + 2 ATP + 2 H_2O. The specific form of glucose used in glycolysis is glucose 6-phosphate. Under aerobic conditions, Pyruvate derived from glucose will enter the mitochondria to undergo oxidative phosphorylation. Anaerobic conditions result in Pyruvate staying in the cytoplasm and being converted to lactate by the enzyme lactate dehydrogenase. [1][2] Energy is liberated in the cells during energy transformation. At the same time, ATP, one new energy-carrier molecule, will be created.

We suppose that a hypothetical structure is responsible for ADP production. Based on this hypothesis, it is proposed that glucose, NH_3, uric acid, and $H_2PO_4^-$ will result in the formation of ATP. In addition, ribose, the part of the adenosine + CO_2, will be created from the D-Glucose during the process.

Energy and energy-carrier transformation is realized in unique permanent structures such as Structure for Energy Transformation (SET). Adenosine Diphosphate Producing Unit (ADP-PU) is the basic unit of SETs. The SET of anaerobic glycolysis (SET-AG) is responsible for the anaerobic fermentation, while the SET of oxidative phosphorylation (SET-OP) is for the aerobic oxidative phosphorylation.

The development of eukaryotic cells

There was no O_2 in Earth's atmosphere more than three billion years ago. At that time, the possibility of the formation of life was already ensured. The earliest cells to produce oxygen were the cyanobacteria (blue-green algae), which evolved oxygen via photosynthesis. The appearance of O_2 in the atmosphere caused the first environmental disaster, as the ancient fermenting microorganisms did not have sufficient defense capacity against the highly destructive O_2.

According to Lynn Margilus' hypothesis, an ancient cell entered into symbiosis with a cell that could 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 organelle is now known as a mitochondrion.[3]

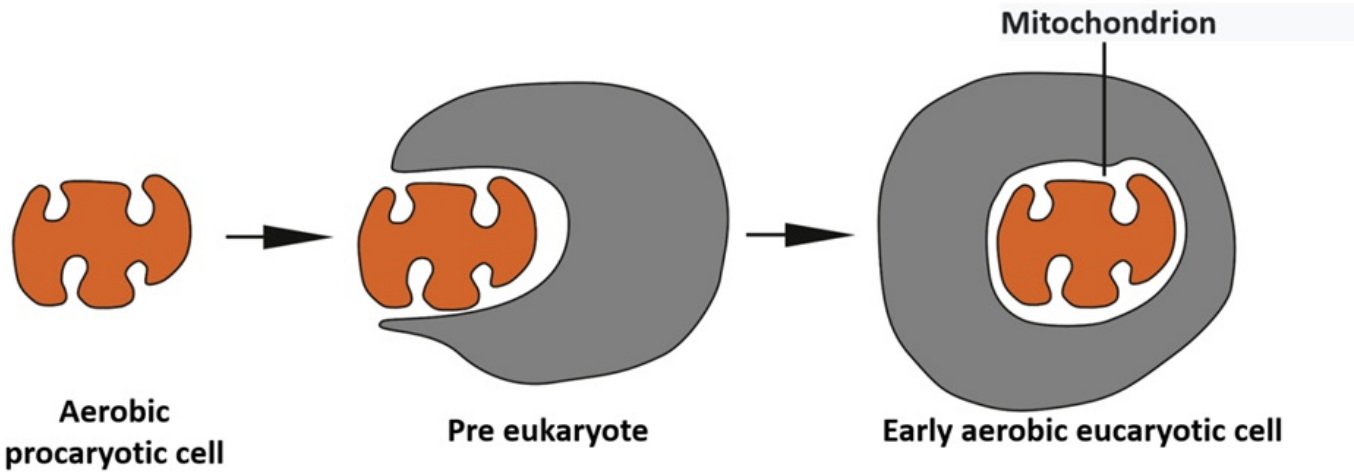


Illustration 1. The procaryotic cell, which developed features of an early mitochondrion (defense system against reactive oxidative species and aerobic energy production), fuses with pre-eukaryote to give rise to early aerobic eukaryotic cell. [3]

The Evidence Supporting the Endosymbiotic Conception: [3][4]

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.

The advantages of symbiosis are significantly more energy, protection against free radicals, and the regeneration ability of organisms. [3][4]

The peroxisome

Peroxisome is a membrane-bound oxidative organelle, a type of micro-body, found in the cytoplasm of virtually all eukaryotic cells. [5][6][7] They perform critical roles in lipid metabolism and the conversion of reactive oxygen species. They also contain approximately 10% of the total activity of two enzymes (Glucose-6-phosphate dehydrogenase and 6-Phosphogluconate dehydrogenase) in the pentose phosphate pathway, [8] which is essential for energy metabolism. [9] Key players in peroxisome division are conserved in animals, plants, and fungi, and key fission components are shared with mitochondria. [10]

Regulation by the HIF system

In the case of anoxia, the oxidative phosphorylation enzymes are inactive. In this situation, the HIF system helps realize regeneration after tissue damage.

The Hypoxia-Induced Factor (HIF)-1α subunit is continuously synthesized and degraded under normoxic conditions,

while it accumulates rapidly following exposure to low oxygen tensions. Thus due to the lack of O_2 caused by injury or any cause, the hydrolysis of the HIF-1α is annulled. [11][12] Subsequently, the HIF system influences about 200 genes, converting cells to ancient energetic. 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. [12][13]

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 and energy-carrier 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 α, which will result in the activation of the SET-AG.

The importance of Fe-S clusters

Several Fe-S clusters [e.g., Fe2S2, Fe4S4, P-cluster of nitrogenase Fe8S7 $(cys\text{-}S)_6$] are known [14]. They play an essential role in maintaining life by ensuring continuous electron transfer. In the central part of the Fe2S2 cluster, two irons are bonded to two sulphurs. The two irons in the Fe2S2 cluster can bind four more sulphurs. The iron of Fe-S clusters is Fe^{2+} (deoxy, Fe II) or Fe^{3+} (oxy, Fe III) forms. The iron's oxidation state influences the iron's binding affinity to oxygen and sulphur. In the case of Fe III, it binds the oxygen, while in the case of Fe II, the sulphur bind is preferred.

Fe II modification to Fe III results in the possibility of binding oxygen-containing molecules, such as H_2PO_4, NHO, uric acid (UA), or aminated UA. Then, in an additional step, Fe III returns to Fe II. In the Fe2S2 cluster, it results in four O^{2-} productions.

Other Fe-S clusters might have similar nature. Thus, the 8Fe7S P-cluster of nitrogenase has six Cys-S structures [14]. Thus it might produce six O^{2-} (illustration 2).

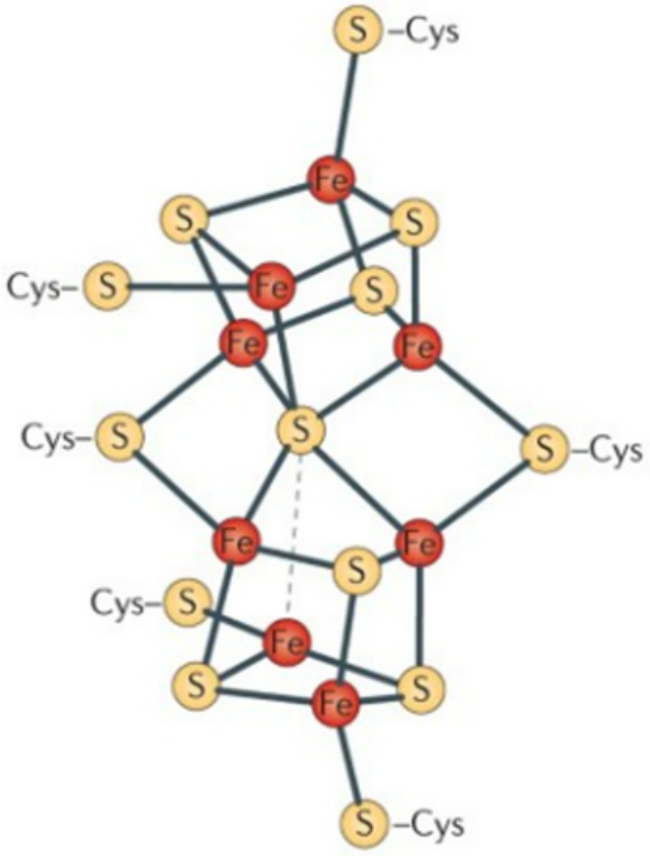


Illustration 2. Fe8S7 (cys-S)$_6$ P-cluster of nitrogenase [14].

Adenosine diphosphate-producing unit

The basic unit of both SETs is the ADP-PU. In addition,ATP synthase is also required to generate ATP. ADP-PUs are permanent structures. Four Fe8S7 (cys-S)$_6$ (P-cluster of nitrogenase), one Flavin, and one nicotinamide molecule are the determining structures of the unit. Four UA, four NH_2-UA, four D-glucose, four D-glucose 6-phosphate, four NHO, and eight $H_2PO_4^-$ are the transient molecules of the unit (Illustration 3). The unit's proper function depends on determined structure proteins and specific enzymes.

The four NH_2-UA and eight $H_2PO_4^-$ molecules create the tetra adenine octo phosphate ring, where four Fe8-S7 P-cluster of nitrogenase clusters connect the molecules. The mechanism of S – O exchange might be similar to the processes of Fe2S2 as described above.

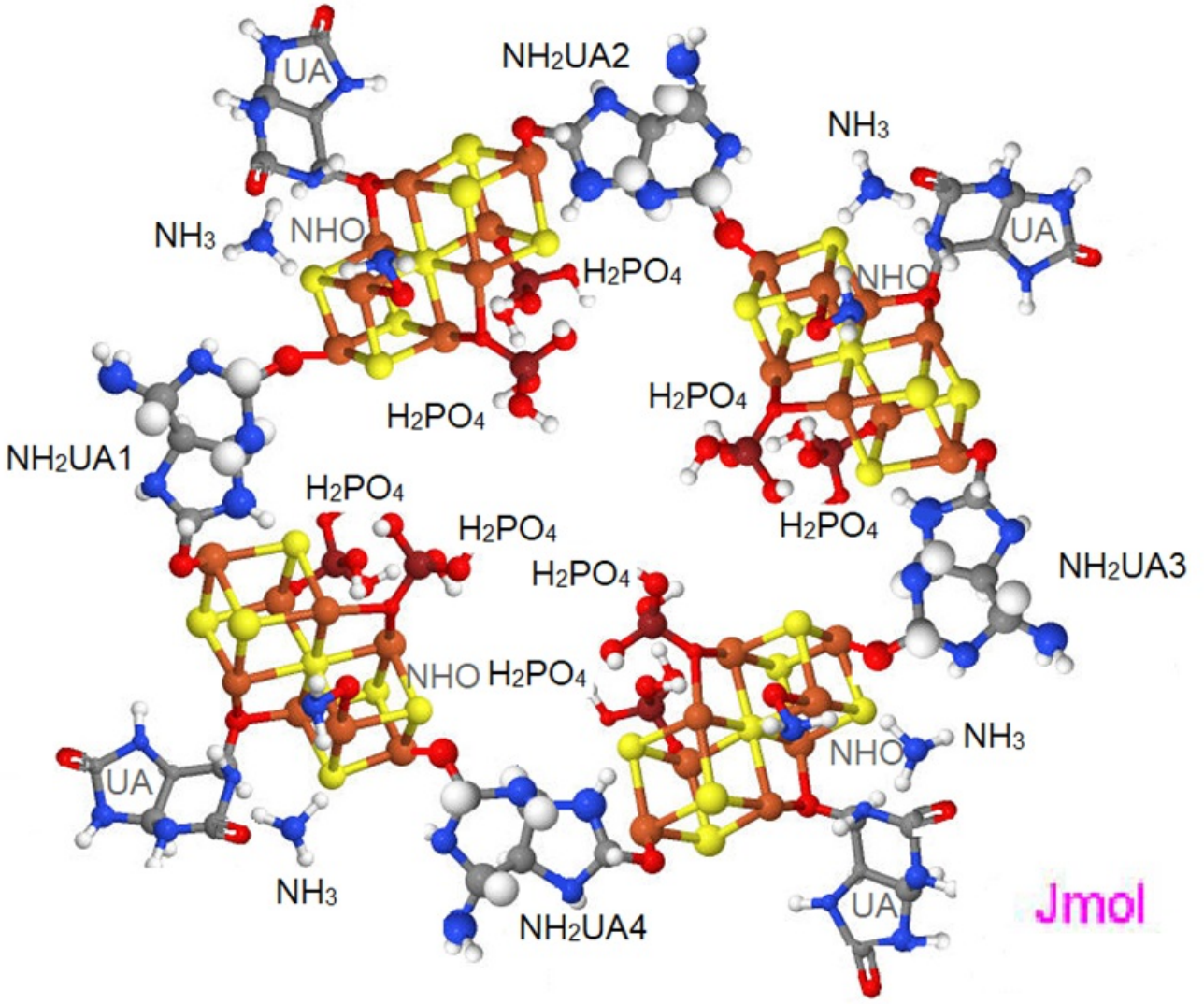


Illustration 3. Adenosine diphosphate producing unit. Four Fe8S7 (cys-S) $_6$, four UA, four NH_2-UA, four D-glucose, four D-glucose 6 phosphate, four NHO, and eight $H_2PO_4^-$ are the determining parts of the unit producing four ADP.

Glucose molecules are not presented.

Energy investment:the initiation of the four Fe8S7 $(cys\text{-}S)_6$ P-clusters is realized by 4 x 3 ATP and four AA molecules.

The functional importance of Fe-S clusters' s cys-S components

The cys-S components of the Fe-S clusters (R-SCH2CH(NH_2)CO2H) contain one sulfur atom, one carboxamide, and

one OH (Illustration 4)

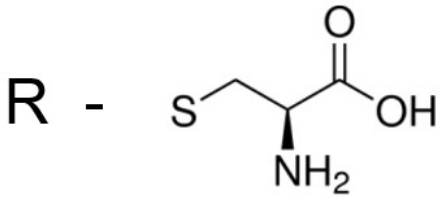


Illustration 4. The structure of cys-S.

Sulfur – Oxygen change

The four Fe8S7 $(cys\text{-}S)_6$ clusters of the ADP-PU have 4 x 6 cys-S parts. Thus they offer places for 24 oxygen-containing molecules as eight $H_2PO_4^-$, four NHO, four UA, and eight oxygen of four NH-UA molecules (Illustrations 3 and 5).

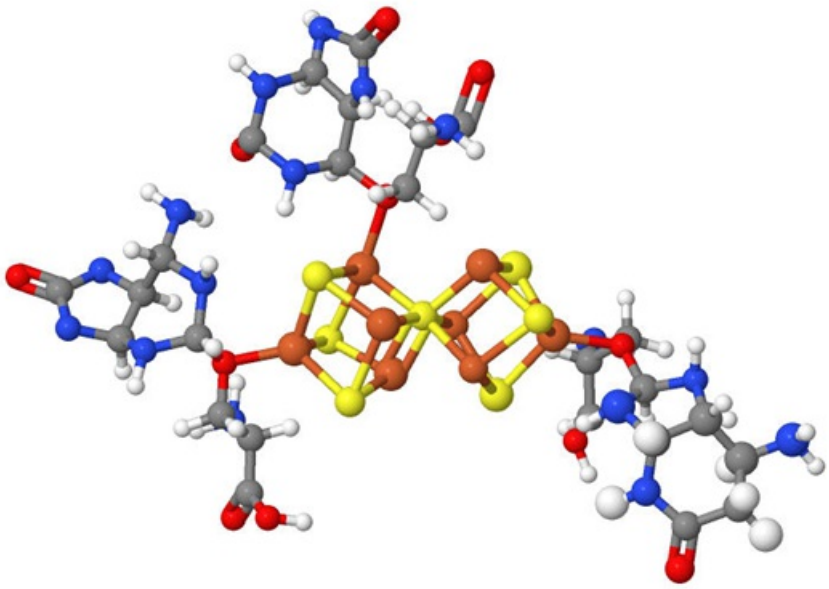


Illustration 5. Fe8S7$(cys\text{-}S)_6$, uric acid, and two NH_2uric acids (only three cys-S are illustrated).

NH_2 part of the carboxamide

The NH_2 part of the structure might bind D glucose (Illustration 6) or L ascorbic acid molecules. Circle 1 indicates the binding of NH_2 to the oxygen. Circle 2 demonstrates the change of sulfur atoms to oxygen by the two OH of the AA (Illustration 7).

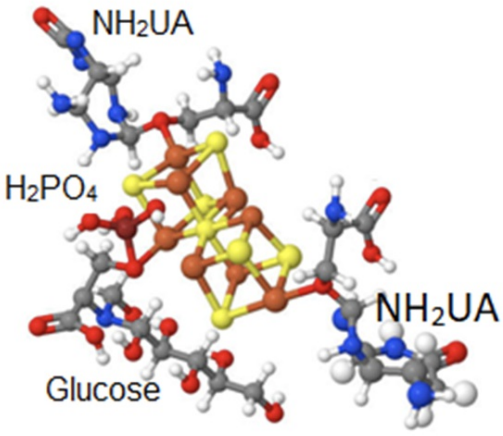


Illustration 6. Fe8S7(cys-S)$_6$, glucose, H_2PO_4, two NH_2uric acids.(only three cys-S are illustrated).

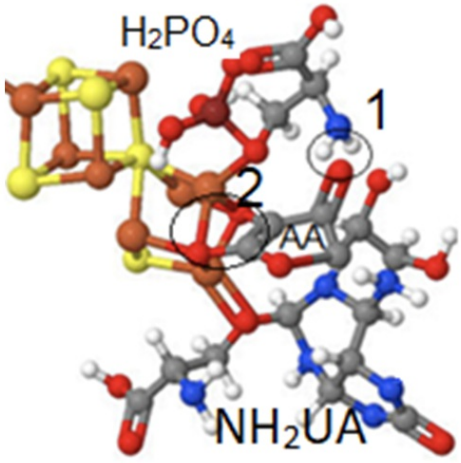


Illustration 7. Fe8S7(cys-S)$_6$, H_2PO_4, Ascorbic acid(AA), NH_2 uric acid. (only three cys-S are illustrated).

: C : O :N :S :Fe :H

Carboxyl part of the carboxamide

The C=O part might bind the adenine of ATP (Illustration 8). Circle 1 indicates the binding of NH_2 to the oxygen, while circle 2 demonstrates the change of sulfur atoms to oxygen by the two OH of the ribose belonging to ATP.

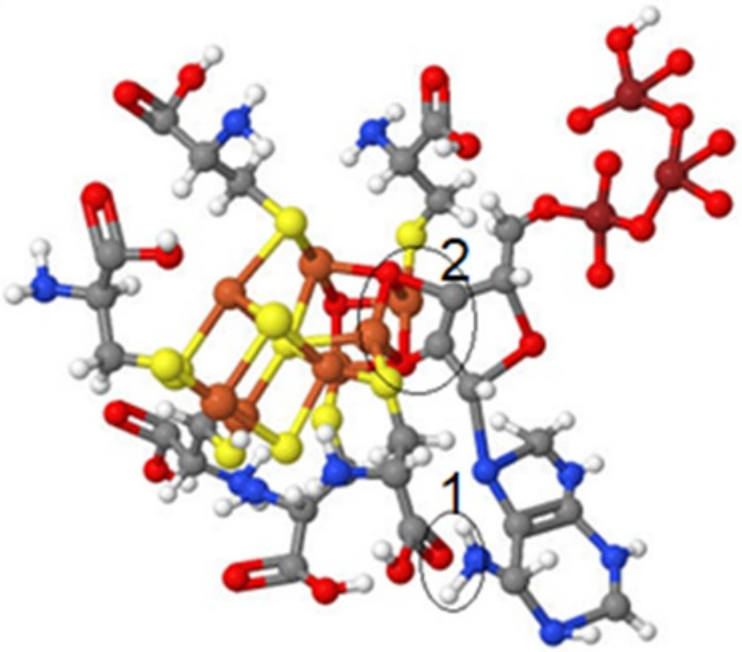


Illustration 8. Fe8S7 $(cys\text{-}S)_6$, ATP

: C : O :N :S :Fe :P :H

Fe8S7 $(cys\text{-}S)_6$

In each of the six cys-S 3 ATP, two D-glucose and one L-AA molecule are situated. The remaining three NH_2 and

three C=O structures offer connecting points for the stabilization of the complex structure of the ADP-PU. Illustration 9a demonstrates two Fe8S7 clusters bounded by two cys-S. Illustration 9b shows one NH2UA molecule attached to the structure.

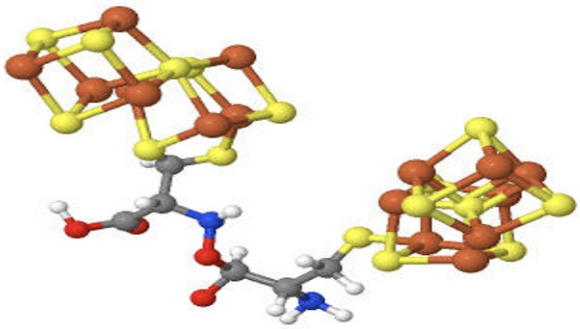


Illustration 9a Two Fe8S7 clusters bounded by two cys-S waiting for the NH_2UA.

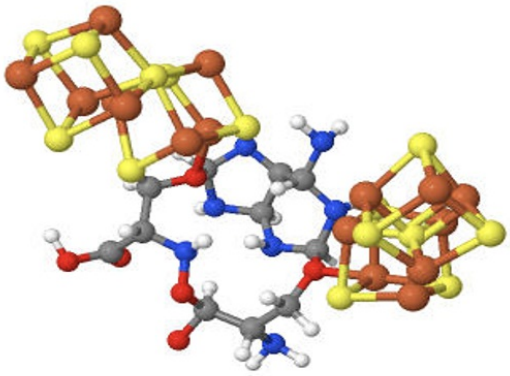


Illustration 9b NH_2UA molecule attached to the structure.

The change of Fe II to Fe III

The two OH of AA on the lactone rings (Illustration 7) and the two OH of the ATP's ribose (Illustration 8) change the nature of the Fe atoms from Fe II to Fe III.

SET is initiated by AA, and ATP. Their ratio determines the activation. A high intracellular AA level increases the activity of SET, and a high ATP level decreases it.

The production activity and sensitivity threshold of SET-AG and SET-OP are different. The ATP level reached by SET-OP inhibits the activity of SET-AG.

AA given intravenously initiates SET-AG. During this, ADP-PU produces 24 O^{2-}.

- 8 O^{2-} mediates the NH_3 – NHO transformation
  4 NH_3 + 8 O^{2-} = 4 NHO + 4 H_2O
- 16 O^{2-} produces 8 CO_2 by oxidizing the eight carbon atoms of 8 D-glucose 6-phosphate.

Suppose the activity has started, but there is no glucose in the cell. In that case, O^{2-} destroys the cell after the exhaustion of the caspase protection system since tumor cells consume 200 times more sugar than normal cells and their ROS activity is low. [15]

Vitamin C and ATP are the initiators of energy transformation

Kinga Linowiecka et al. stated that ascorbic acid (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 iron's electron state in Fe^{2+} dependent dioxygenases (Illustration 10). [16]

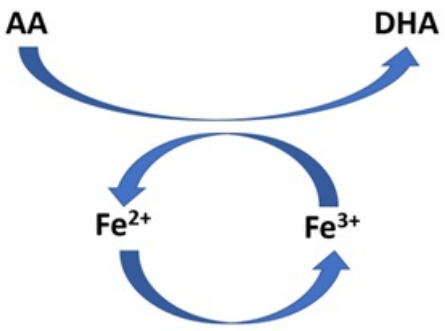


Illustration 10. Vitamin C's role in Fe^{2+} - Fe^{3+} transformation. Legend abbreviations: AA: ascorbic acid; DHA: dehydroascorbic acid

This change might be valid for the Fe atoms of the Fe-S clusters. The reaction results in a sulphur-oxygen exchange, creating four O^{2-} in the Fe2S2 cluster.

A similar reaction might occur by the two OH of the ribose part of the ATP when initiating the Fe-S cluster,

ATP synthase

The binding change mechanism of ATP synthase involves the active site of a β subunit's cycling between three states. [9] In the "open" state, ADP and phosphate enter ATP synthase; in Illustration 10, 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. [17]

Structure of SET-AG and SET-OP

Structure for anaerobe glycolysis

SET-AG consists of three ADP-Pus (ADP-PU-A, ADP-PU-B, and ADP-PU-C) and three ATP synthase. These structures work together in a synchronized way. When ADP-PU releases the ADP, the ATP synthase is in the open phase, ready to accept it. 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 11).

The four UAs with four NHO molecules forms four aminated UAs + four H_2O, while the four aminated UAs produce four adenine molecules.
In the transformation process, eight ribose molecules are created from eight D-glucose molecules.

Four ribose with four UA-originated adenine molecules forms four adenosines. In an O_2 -free environment, four lactates are formed from the four Pyruvates, while in an oxygenated environment, 4x3 CO_2 + twelve H_2O molecules + energy are realized through oxidative phosphorylation. During the energy transformation, the carbon atoms of the four citric acids are converted into eight CO_2. We suppose that SET-AG has three, and SET-OP has nine ADP-PUs.[15][18]

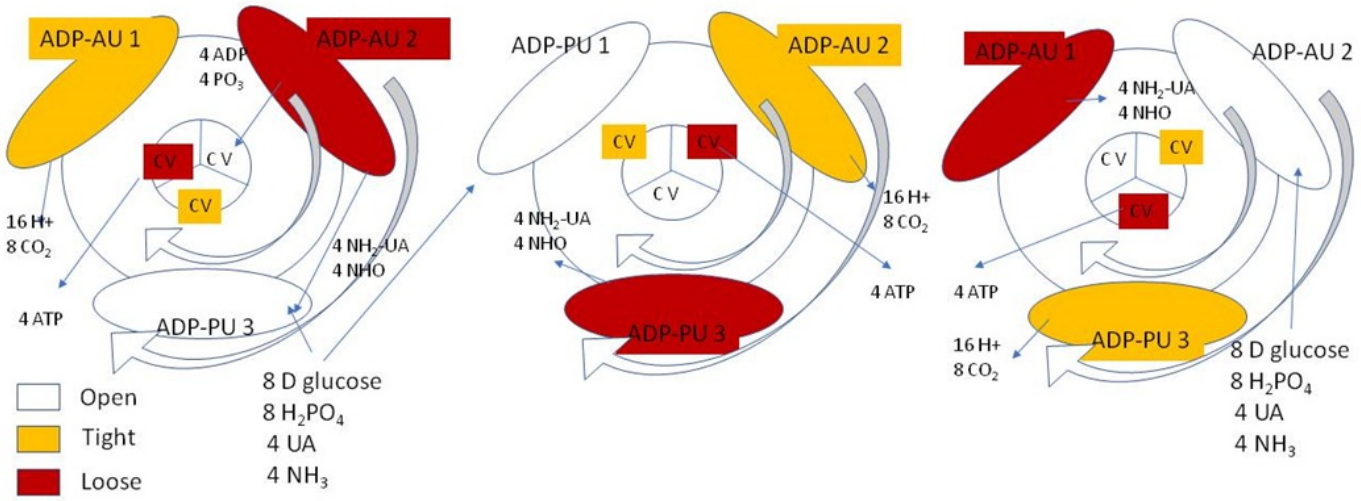


Illustration 11. The synchronised function of three ADP-Pus (I, II, III) and three ATP synthase

Structure for oxidative phosphorylation

The SET-OP consists of three SET-AG - (3x3) ADP-PUs. It also contains one Pyruvate dehydrogenase complex (PDC) and three high molecular weight cytochromes (Hmc) [15][18].

Location of the SET-AG and SET-OP in the cells

Austin et al. suggest that Complex 1 is in the mitochondrial membrane hanging in the mitochondrial matrix[19]. In our hypothesis, ADP-PU is built up by four Fe8S7 $(cys\text{-}S)_6$ (P-cluster of nitrogenase) instead of the six Fe4S4 clusters suggested by Austin et al. The unit's proper function needs two Fe2S2 clusters, complex II, III, and IV (Illustration 12).

We assume that SET-AG is located in the peroxisomes or near the cytoplasmic membrane, while SET-OP is in the intermembrane space hanging in the mitochondrial matrix.

The role of HIF in the control of regeneration

The HIF system

The HIF system is the detector and controller of the oxygenated and O_2 -free environment. It facilitates the cell back to ancient times. The HIF system ensures adaptation to a hypoxic environment. [13][20][21][22][23][24][25]

In an anoxic or hypoxic environment there is no hydrolysis of HIF-1 α, which will result in the activation of the SET-

AG. In the existence of O_2, the SET of Oxidative Phosphorylation (SET-OP) presents the oxidative phosphorylation. In contrast, cells use aerobic glycolysis offered by the SET-AG in a hypoxic environment (Illustration 13). [15][18]

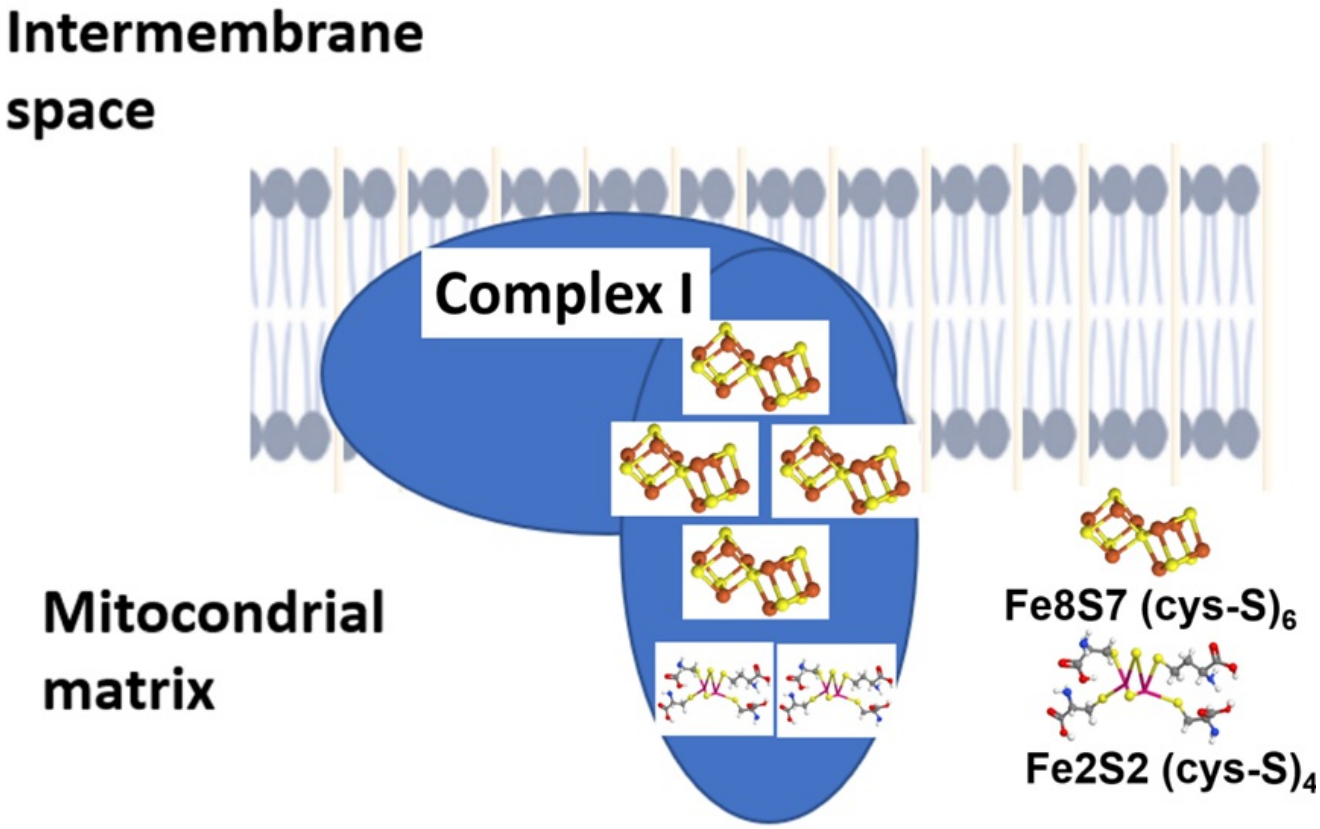


Illustration12. Four Fe8S7 $(cys\text{-}S)_6$ clusters form the ADP-PU of the SET-OP, in the intermembrane space hanging in the mitochondrial matrix.

The hypothetical way of the energy transformation is summarised in Table I.

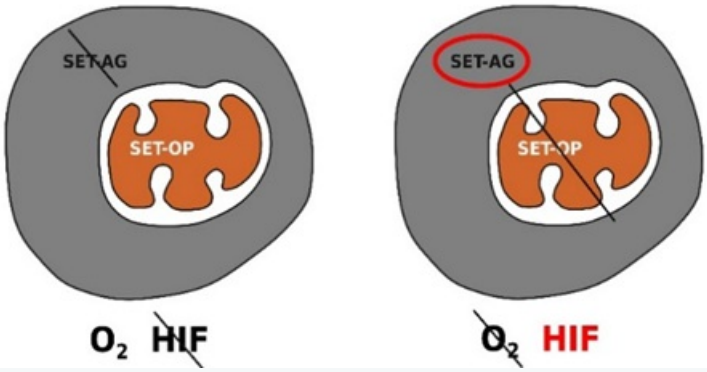
Table I. The hypothetical way of the energy transformation.

	Transient molecules	Product				
		O^{2-}	CO_2 + energy	H_2O	H^+	
I **2 Fe2S2 (cys-S_4)**		8				
8 H_2PO_4 + 2 CH_3COOH + 4 D-glucose = 4 CO_2 + 4 H_2O + 4 D-glucose 6-phosphate	8 H_2PO_4 2 CH_3COOH 4 D-glucose	8	4	4	16	4 D-glucose 6-phosphate 4 PO_4^{3-}
II **4 Fe8S7 (cys-S_3)**		24				
1. A. 4UA + 4 NHO = 4 NHUA + 4 O^{2-} 4 NH_3 + 8 O^{2-} = 4 NHO + 4 H_2O 1. B. 4 NHUA + 8 H_2PO_4 + 4 D-glucose + 4 D-glucose 6-phosphate = 4 ADP + 4 PO_4 + 4 ribose + 8 CO_2 + 8 H_2O + 16 H^+	4 NH_3 4 UA 4NHUA 8 H_2PO_4 8 D-glucose	8 16	8	4 4 8	8	4 NHO 4 NHUA 4 ribose 6-phosphate 4 ADP
III **ATP synthase**						
4 ADP + 4 PO_4^{3-} = 4 ATP						4 ATP
			12	22	24	4 ATP 4 ribose 6-phosphate 4 PO_4^{3-}

Cells will become viable in a hypoxic environment with the help of the HIF system, which ensures adaptation to a hypoxic environment. HIF-1 α combines with HIF-1 beta to modify the activity of about 200 genes. The most significant changes are: [6][7]

1. Genetic changes results 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. [6][7]



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

Illustration 13. The HIF system is the detector and organizer of the oxygenated and O_2-free environment.

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.

The efficiency of ADP-producing unit

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.

The hypothetical structures responsible for the energy and energy-carrier transformation must be much more complicated than described here. Their proper functions must depend on the transport and stabilizing-proteins and of many enzymes and enzyme cofactors.

Conflicting Interests

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

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