The dual energy supply of eukaryotic cells

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

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 and energy-carrier 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 Hypoxia Inducible Factor (HIF)-1 α in tissue regeneration is also discussed.

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Keywords: eukaryotic cell; HIF; cell energetic; tissue regeneration; Fe-S cluster.

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) for living organisms to get a usable energy carrier.

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.

The hypothetical way of the 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; 2 ATP is derived: 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, Pyruvate and acetic acid will be created from the D-Glucose during the process.

Energy and energy-carrier transformation are realized in unique permanent structures such as Structure for Energy Transformation (SET). The Starter Unit (SU), Adenosine Diphosphate Producing Unit (ADP-PU), D-glucose-6phosphate Producing Unit (G6p-PU), and Pi- Producing Unit (Pi-PU) are the basic units 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 defence 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]

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]

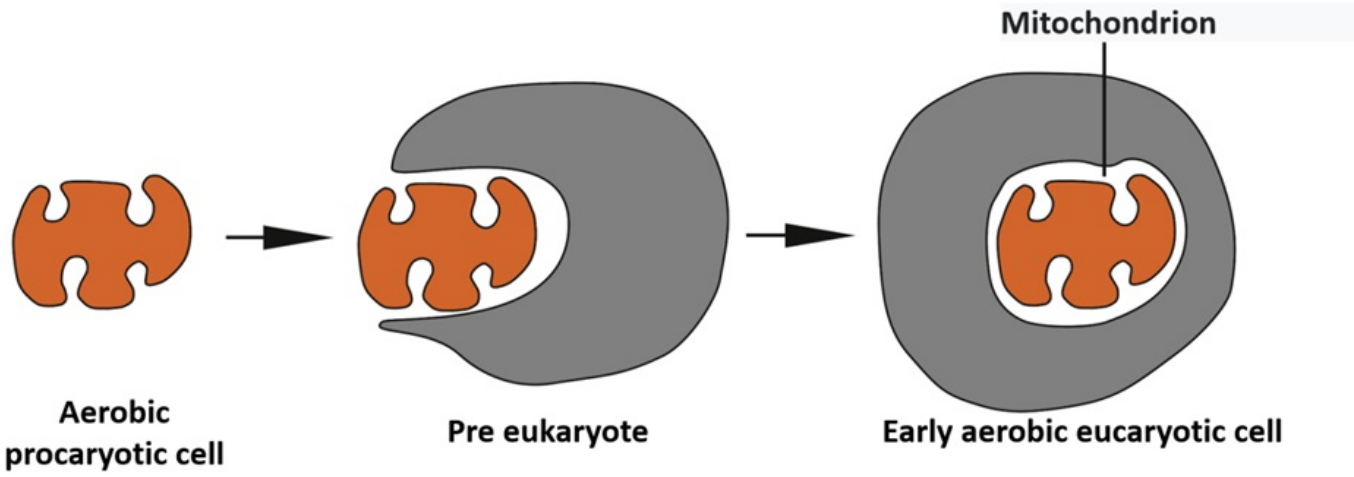


Illustration 1. The procaryotic cell, which developed features of an early mitochondrion (defense system against reactive oxidative species and aerobic energy production), fuses with pre-eukaryote to give rise to an early aerobic eukaryotic cell. [3]

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]

The electron transport chain

An electron transport chain (ETC) is a series of protein complexes and other molecules that transfer electrons from electron donors to electron acceptors via redox reactions (both reduction and oxidation co-occurring) and couples this electron transfer with the transfer of protons (H^+ ions) across a membrane. The electrons transferred to the ETC involve four multi-subunit large enzyme complexes and two mobile electron carriers. Many of the enzymes in the electron transport chain are membrane-bound. [11][12]

Regulation by the HIF system, the control of tissue regeneration

Cells will become viable in a hypoxic environment with the help of the HIF system, which ensures adaptation to a hypoxic environment. The Hypoxia-Induced Factor (HIF)-1α subunits are 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 reason, the hydrolysis of the HIF-1α is annulled. [13][14]

HIF-1 α combines with HIF-1 beta to modify the activity of about 200 genes. As a result, the circulation will be restored with the help of newly formed blood vessels. After that, increasing tissue O_2 will hydrolyse the HIF-1α; thus, the cells will return to the mitochondrial oxidative phosphorylation. [14][15]

The most significant changes are: [6][7][16][17]

1. 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.
2. The sensitivity to apoptosis decreases.
3. Induction of neovascularization.
4. 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 (Illustration 2). [6][7][16][17]

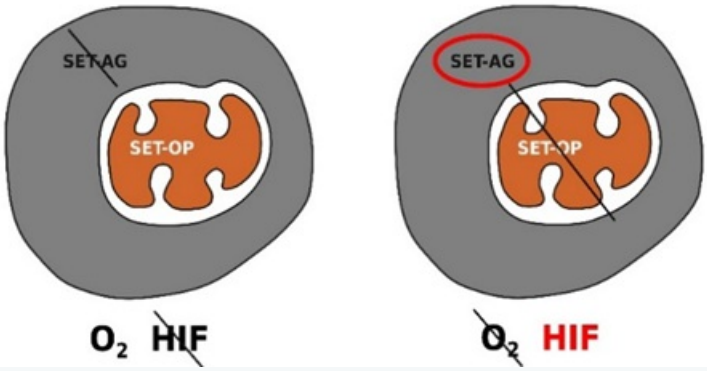


Illustration 2. The HIF system is the detector and organizer of the oxygenated and O_2-free environment.

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

SET-AG is always present in the cell but does not function in normoxic conditions. The permanent structures of SET-AG may be in their determined place.

The dual energy supply of eukaryotic cells

Eukaryotic cells have two genetic stocks, as mitochondria contain their own. 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 activate the SET-AG.

The importance of Fe-S clusters

Several Fe-S clusters [e.g.,2Fe-2S $(cys\text{-}S)_4$, 3Fe-4S $(cys\text{-}S)_3$, 4Fe-4S $(cys\text{-}S)_4$, P-cluster of nitrogenase 8Fe-7S $(cys\text{-}S)_6$] are known. They play an essential role in maintaining 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 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.

Other Fe-S clusters might have similar nature. Thus, the 8Fe-7S P-cluster of nitrogenase has six Cys-S structures[18] and might produce six O^{2-}(illustration 3).

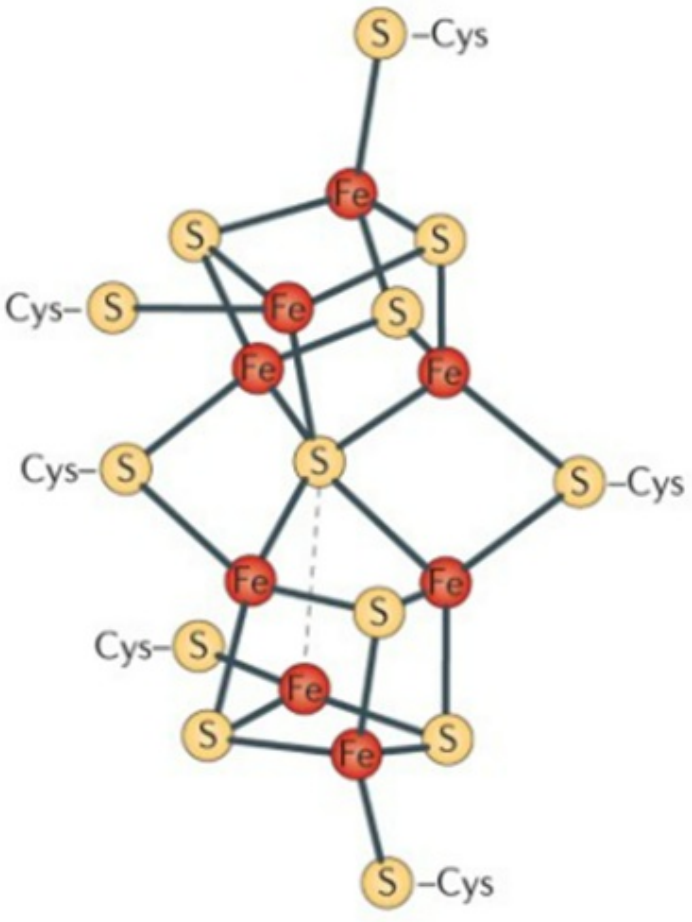


Illustration 3. 8Fe-7S $(cys\text{-}S)_6$P-cluster of nitrogenase[18].

Fe^{2+} modification to Fe^{3+} 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^{3+} returns to Fe^{2+}. The change results in three O^{2-} production in the 3Fe-4S cluster, four in the 2Fe-2S and 4Fe-4S clusters, and six O^2 in the 8Fe-7S cluster.

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

The cys-S components of the Fe-S clusters (R-SCH_2CH (NH_2) CO_2H) contain one sulfur atom, one carboxamide, one carboxyl part, and one OH (Illustration 4)

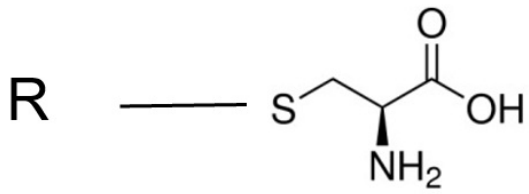


Illustration 4. The structure of cys-S.

NH_2 part of the cys-S

The NH_2 part of the structure might bind D glucose (Illustration 5) or L ascorbic acid molecules. Circle 1 indicates the binding of NH_2 to oxygen. Circle 2 demonstrates the change of sulfur atoms to oxygen by the two OH of the AA (Illustration 6).

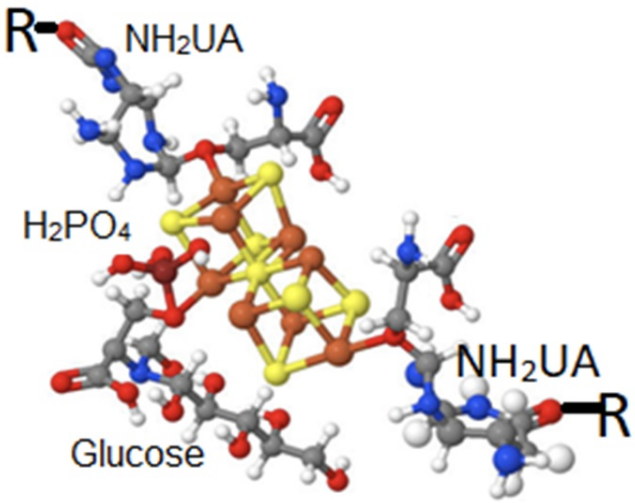


Illustration 5. *8*Fe-7S (cys-S)$_6$, glucose, $H_2PO_4^-$, two NH_2uric acids (NH_2UA).(Only three cys-S are illustrated).

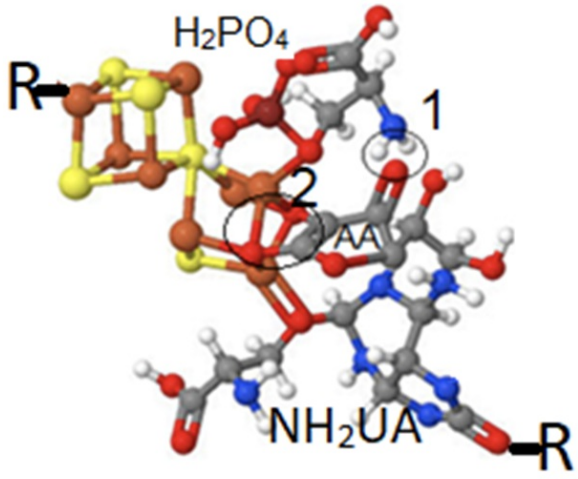


Illustration 6. 8Fe-7S (cys-S)$_6$, $H_2PO_4^-$, Ascorbic acid (AA), NH_2 uric acid. (Only three cys-S are illustrated).

Carboxyl part of the cys-S

The C=O part might bind the adenine of ATP (Illustration 7). 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.

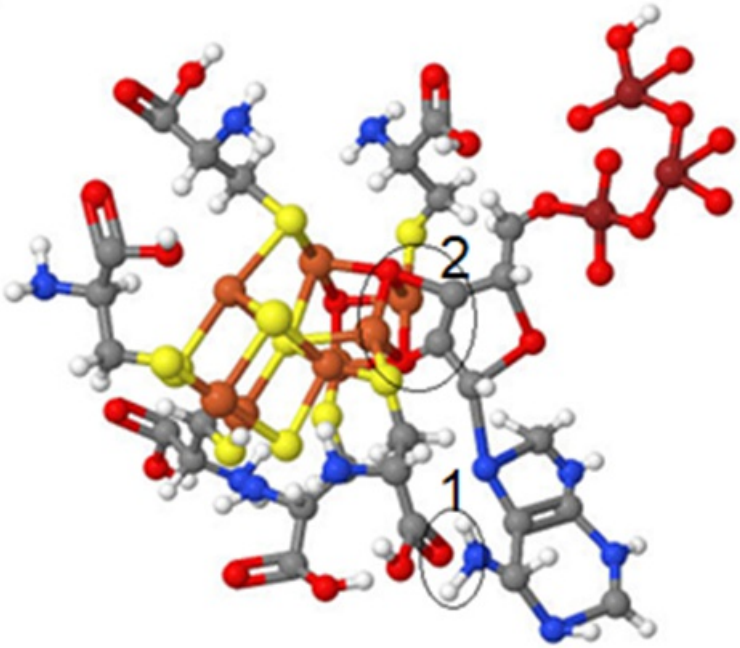
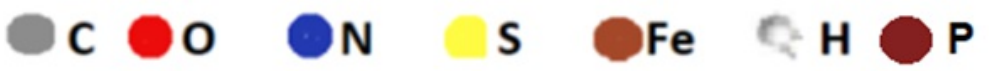


Illustration 7. One ATP binds to 8Fe-7S (cys-S) $_6$ cluster.



Carbamide – carboxyl connection between two cys-S chains

Fe-S clusters might create one Multipart ETC (METC) realized by the cys-S parts of the clusters. The NH_2 and the Carboxyl parts of the cys-S offer the possibility of continuous chain creation, as demonstrated in Illustration 8.

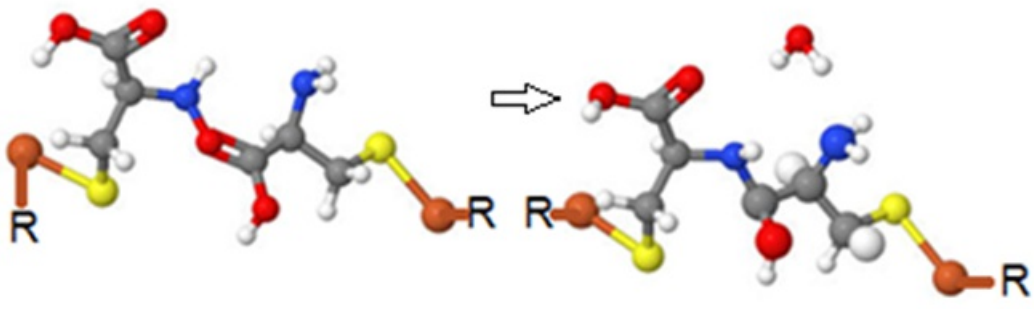


Illustration 8. Two cys-S chains are connected with the help of the carbamide and carboxyl parts of the structures while liberating one H_2O.

Transformation of the source molecules

NH_3 – NHO, Uric Acid – NHUA transformation

Two O^{2-}transforms NH_3 to NHO + H_2O while one uric acid (UA) will be aminated in the 8Fe-7S cluster of nitrogenase.

$NH_3 + 2\ O^{2-} = NHO + H_2O$

$UA + NHO = NHUA + O^{2-}$

D-glucose

Phosphorylation

Phosphorylation of the D-glucose is created in the D-glucose 6-phosphate Producing Unit (G6P-PU).

Glucose – ribose – Pyruvate - acetic acid transformation

Ribose + CO_2 is created from D-glucose during the transformation in the ADP-PU.

D glucose + two O^{2-} = D-ribose + CO_2 + energy

Ribose + adenine = adenosine

Ribose is transformed into Pyruvate and acetic acid.

Acetic acid + four O^{2-}= two CO_2+ two H_2O + energy

Pyruvate + six O^{2-} = three CO_2 + three H_2O + energy

$H_2PO_4^-$

Dihydrogen phosphate will be transformed into PO_3^{3-} (Pi) + two H^+ + O^{2-} in the Pi-PU, the ADP-PU, and the SU.

Vitamin C and ATP are the activators and 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 dehydro ascorbic acid (DHA) regulates the modulation of the iron's electron state in Fe^{2+} -dependent dioxygenases (Illustration 9). [19] Two H^+ are liberated during the AA – DHA transformation.

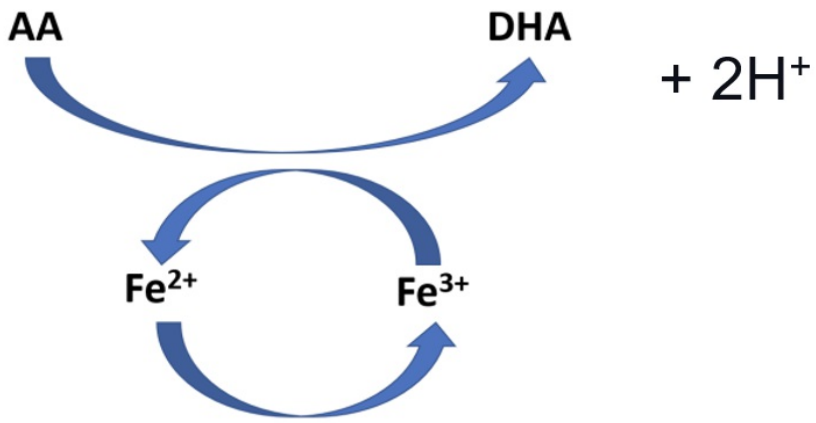


Illustration 9. Vitamin C's role in Fe^{2+} - Fe^{3+} transformation. Abbreviations: AA: ascorbic acid; DHA: dehydroascorbic acid

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

A similar reaction might occur by the two OH of the ribose part of the ATP activating the Fe-S cluster.

Illustration 10. presents the bound of two 8Fe-7S clusters by vitamin C (circle).

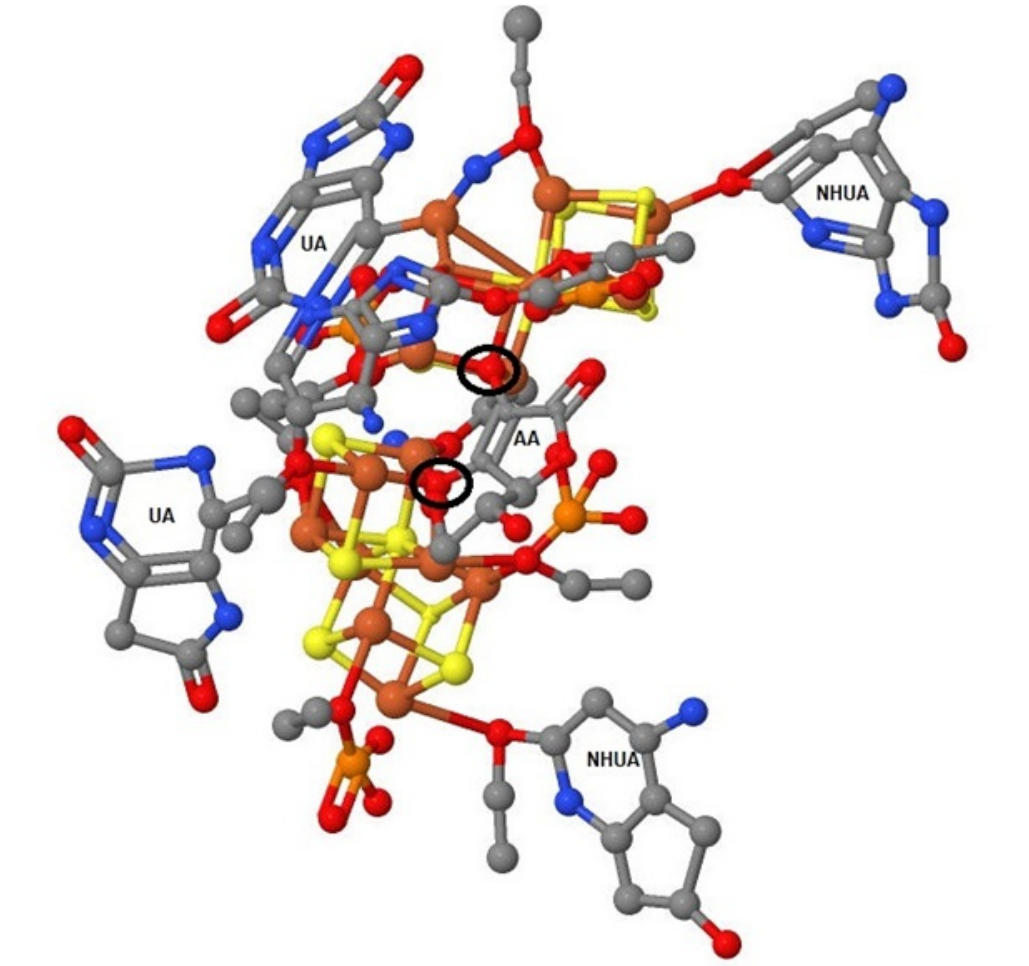


Illustration 10. One Ascorbic Acid bounds two 8Fe-7S clusters by its OH of the lactone ring.

Abbreviations: UA: Uric Acid, NHUA: Aminated Uric Acid AA: Ascorbic Acid

ATP synthase

The binding change mechanism of ATP synthase involves the active site of a β subunit's cycling between three states. [20] In the "open" state, ADP and Pi enter ATP synthase. The enzyme then changes shape and forces these molecules together, with the active site in the resulting "tight" state binding the newly produced ATP molecule. Finally, the active site cycles to the loose state and will be ready for the next cycle of ATP production. [20]

Structures for energy and energy-carrier transformation

SETs are places of energy and energy-carrier transformation. They contain permanent structures where the arriving

molecules are converted to energy, new energy-carrier molecules (ATP), and CO_2.

All SETs are built up by Starting Unit (SU), D-glucose 6 Phosphate Producing Unit (G6P-PU), PO_3^{3-} (Pi)-Producing Unit (Pi-PU), ADP-PU, and ATP-synthase. Primary molecules that arrive at the structure will be transformed into new energy-carrier molecules, CO_2 and energy, while the membrane potential is also realized.

The transformation is completed in an electron transfer structure.

Four 2Fe-2S, one 3Fe-4S, and seven 4Fe-4S clusters offer the proper function of the complex, as described by Austin et al. [21] (Illustration 11).

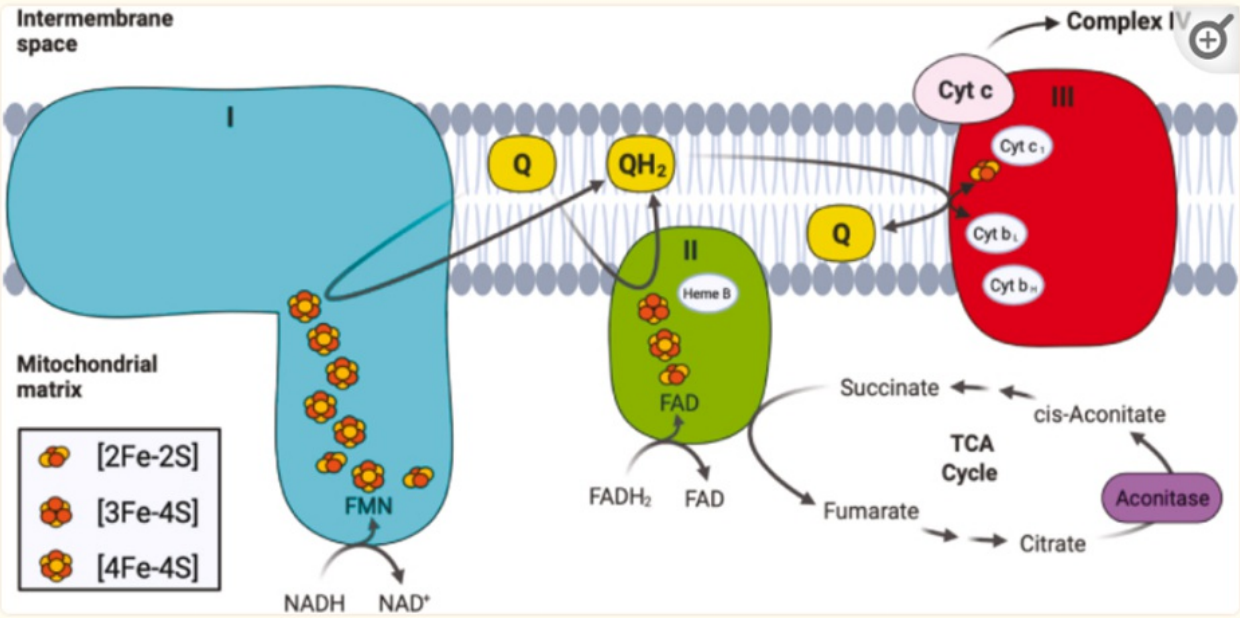


Illustration 11. A simplified version of the mitochondrial ETC, showing Complexes I (blue), II (green), and III (red).

The hypothetical way of the energy transformation

The hypothesis of Multipart Electron Transfer Chain

The Multipart ETC might contain one 4Fe-4S cluster and four 8Fe-7S clusters of nitrogenase instead of the seven 4Fe-4S clusters, suggested by Austin et al. [21]. The four 8Fe-7S clusters of nitrogenase are the determining part of the ADP-PU. The remaining 4Fe-4S cluster, the D-Glucose 6-phosphate Producing Unit (G6P-PU), might be responsible for the production of D-Glucose 6-phosphate, while the four 2Fe-2S might create the Pi-producing Unit (Pi-PU).

The change of Fe^{2+} to Fe^{3+}

The two OH of AA on the lactone rings (Illustration 6) and the two OH of the ATP's ribose (Illustration 7) change the

nature of the Fe atoms from Fe^{2+} to Fe^{3+}.

SET is activated by ATP and initiated by AA. Their ratio determines the initiation. A high intracellular AA level increases the activity of SET, and a high ATP level decreases it, as it occupies the place of AA.

The 3Fe-4S cluster starts the reaction and connects the three specialized units, resulting in a functioning Multipart Electron Transfer Chain (METC) (Illustration 12).

The unit's proper function depends on determined structure proteins and specific enzymes.

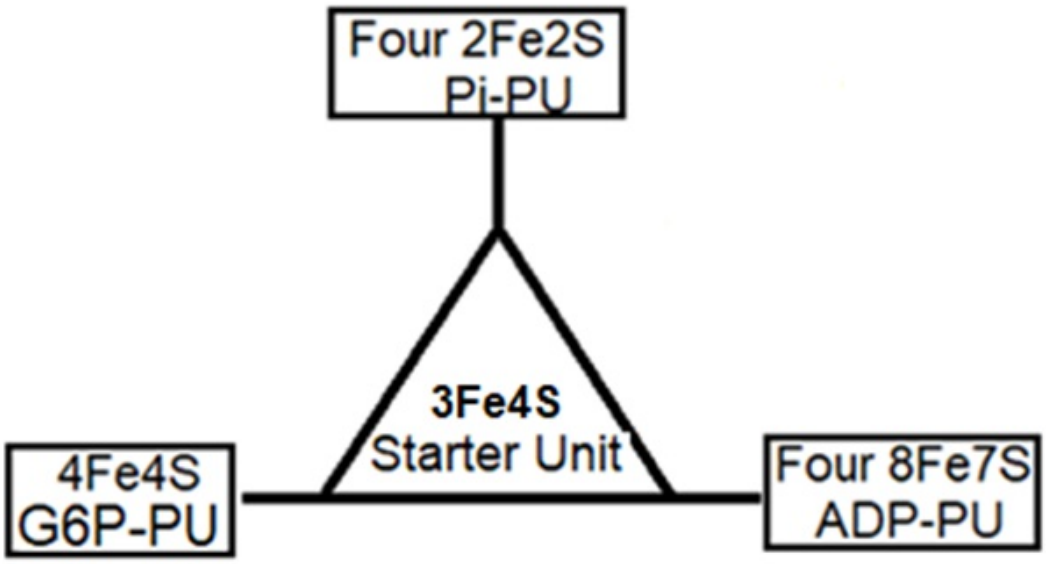


Illustration 12. The 3Fe-4S (Starter Unit) connects the three specialized units: the Pi-producing Unit (Pi-PU), the D-glucose-6phosphate Producing Unit (G6p-PU), and the ADP Producing Unit (ADP-PU).

Starter Unit (SU)

Molecule of the permanent structure:

One 3Fe-4S $(cys\text{-}S)_3$ cluster (Illustration 13).

SUs of two METCs, are responsible for the oxidation of one Pyruvate molecule.

Source molecules of two SU:

2 X Three $H_2PO_4^-$ + one Pyruvate

Products of two SU:

2 X Three PO_3^{3-} (Pi) + 3 CO_2

Activation and initiation of the Starter Unit and the METC

Two ATP activates two SU, while two AAs will initiate the function of two METCs.

PO_3^{3-} (Pi) Producing Unit (Pi-PU)

Molecules of the permanent structure:

Four 2Fe-2S $(cys\text{-}S)_4$ clusters.

Source molecules:

4 x [acetic acid+ four $H_2PO_4^-$]

Products:

4 x [four Pi + 8 H^+ + two CO_2 + energy].

Activation of the unit

Four ATP are responsible for the activation of the structure.

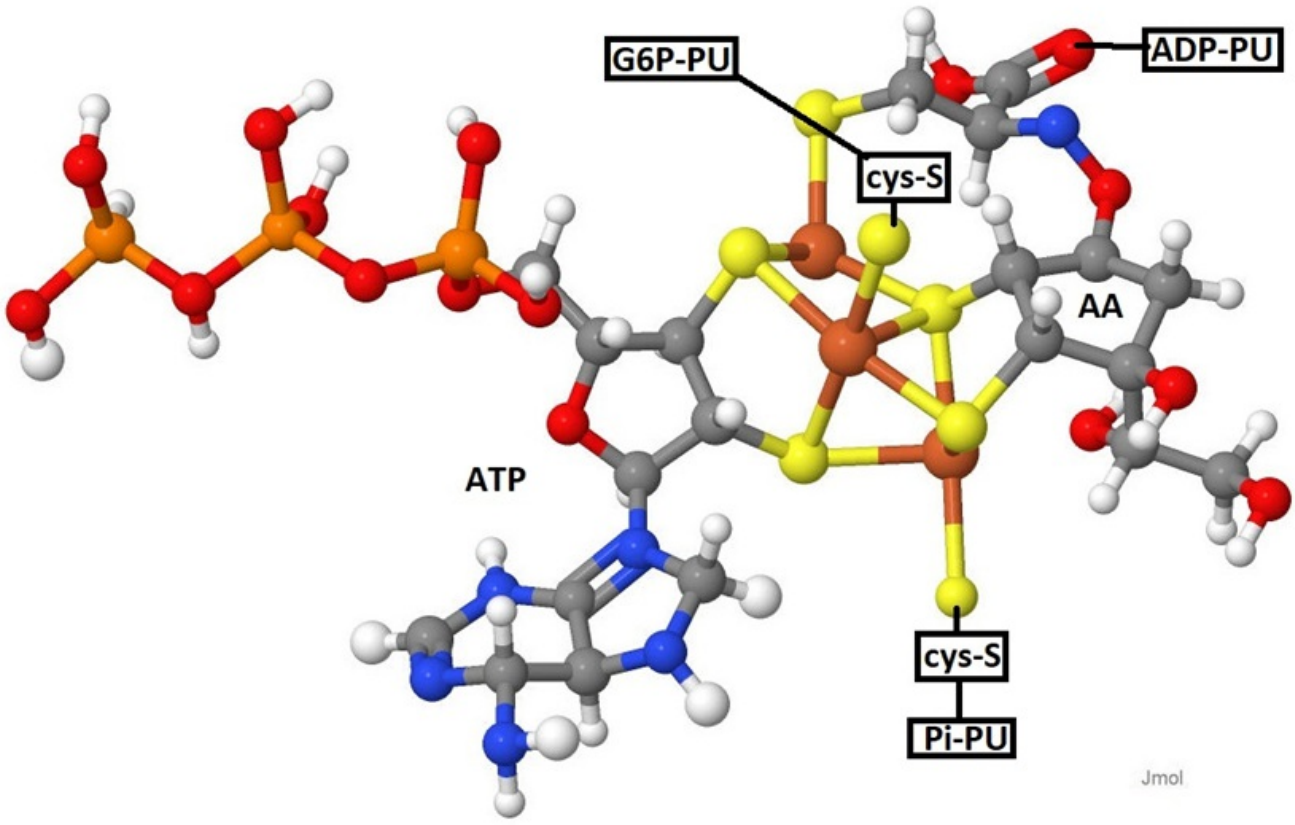
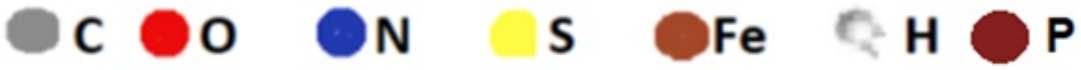


Illustration 13. Starter Unit. Two OH of ATP activating and two OH of vitamin C initiate the transformation process.



Abbreviations: G6P-PU: D-Glucose 6-phosphate Producing Unit; Pi-PU: PO_3^{3-} (PI) Producing Unit; ADP-PU: ADP Producing Unit.

D-glucose-6-phosphate Producing Unit

Molecule of the permanent structure:

One 4Fe-4S $(cys\text{-}S)_4$ cluster.

three G6P-PUs of three METCs, are responsible for the oxidation of two Pyruvate molecule.

Source molecules of three G6P-PUs:

3 X [Four $H_2PO_4^-$ + four D-Glucose] + two Pyruvate

Products of three G6P-PUs:

3 X Four D-Glucose 6-phosphate + six co_2

Activation of the unit

Two ATP are responsible for the activation of the structure.

Adenosine diphosphate and NHO-producing unit

The basic unit of SET-AG and SET-OP is the ADP-PU. In addition, ATP synthase is also required to generate ATP.

Molecules of the permanent structure:

Four 8Fe-7S $(cys\text{-}S)_6$ clusters of nitrogenase, one Flavin, and one nicotinamide molecule.

Source molecules:

Four UA, four NH_2-UA, four NH_3, four NHO, eight $H_2PO_4^-$, four D-glucose, and four D-glucose 6-phosphate.

The four NH_2-UA and eight $H_2PO_4^-$ molecules create the tetra adenine octo phosphate ring, where four 8Fe-7S P-clusters of nitrogenase connect the molecules (Illustration 14).

Products:

4 ADP + 8 CO_2 + 16 H^+ + 4 ribose + 4 Pi + energy. Four Pyruvate and four acetic acids will be created from the four persisted ribose.

Activation of the unit:

Energy investment: the activation of the four Fe8-S7 $(cys\text{-}S)_6$ P-clusters is realized by 12 ATP and two AA molecules resulting in 12 ADP.

The structural elements of ADP-PU are four sulphur-iron clusters, one Flavin, and one nicotinamide molecule. In addition, four P-cluster of nitrogenase (Illustration 3) might mediate the electron flow. The mechanism of S – O exchange might be similar to the processes of 2Fe-2S as presented above. The size of the ADP-PU is about 2.5 - 3.5 nm.

Energy investment: the initiation of the four P-clusters (8Fe-7S+6S) is realized by two AA + 4 x 3 =12 ATP molecules. One AA molecule bounds two 8Fe-7S clusters by the seventhes sulphur atoms of the two clusters (Illustration 15). The UA molecule will be aminated by one NHO molecule.

The transformation results in four ATP, the nitrification of four uric acids and four NHO.

SET-AG consists of two x three ADP-Pus (ADP-PU-A, ADP-PU-B, and ADP-PU-C), and six ATP synthase. These structures work together in a synchronized way. Wen ADP-PU releases the ADP and HPO_3, the ATP synthase 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 16).

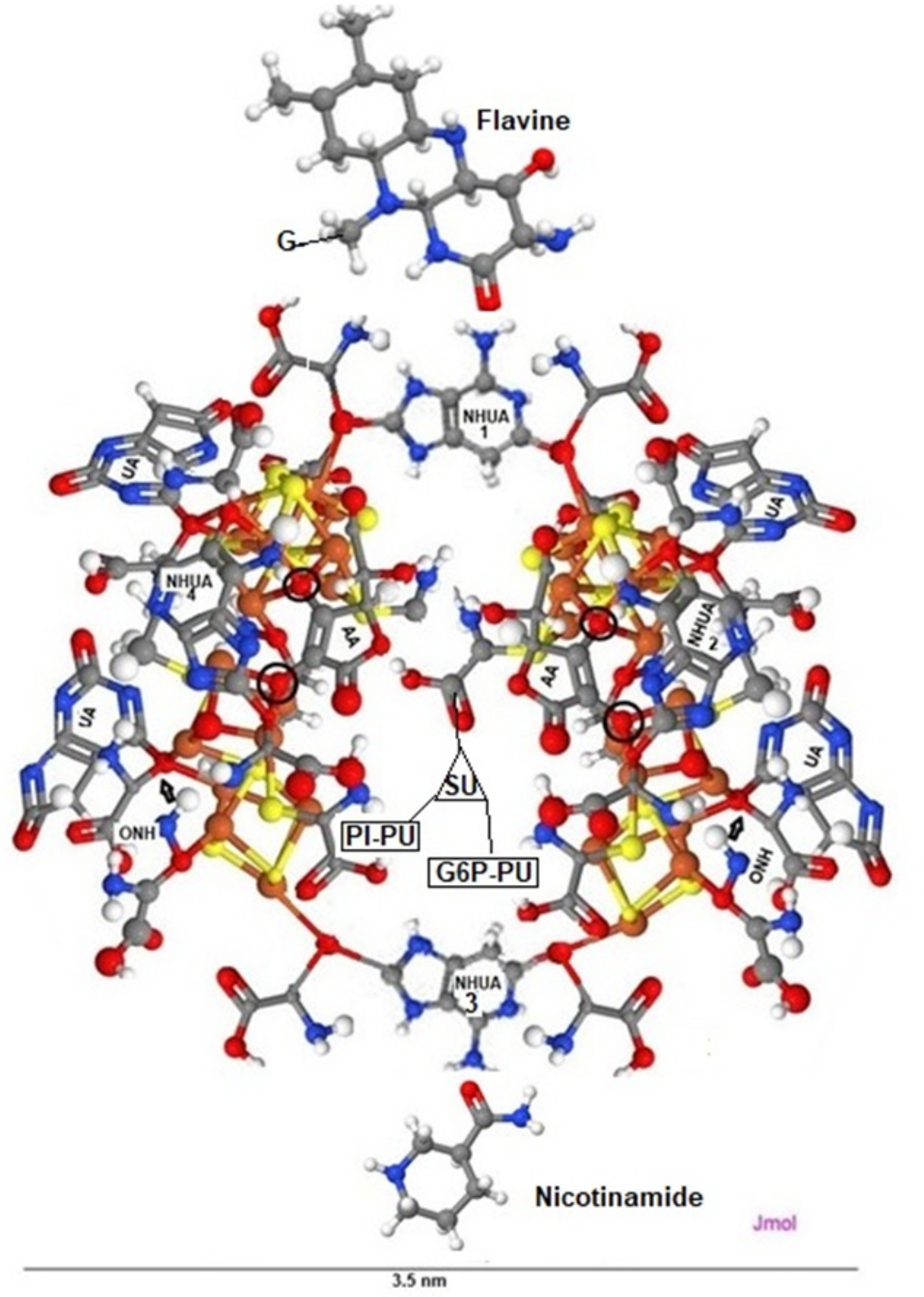


Illustration 14. Adenosine diphosphate producing unit. Four Fe8-S7 (cys-S) $_6$ clusters of nitrogenase, four UA, four NH_2-UA, four NHO, four NH_3, and eight $H_2PO_4^-$ in the ADP-PU.

The structure's four D-glucose and four D-glucose 6-phosphate and the eight H_2PO_4 molecules are not presented.

Abbreviations: UA: Uric Acid, SU: Starting Unit, Pi-PU: Pi Producing Unit, G6P-PU: Glucose 6-Phosphate Producing

Unit.

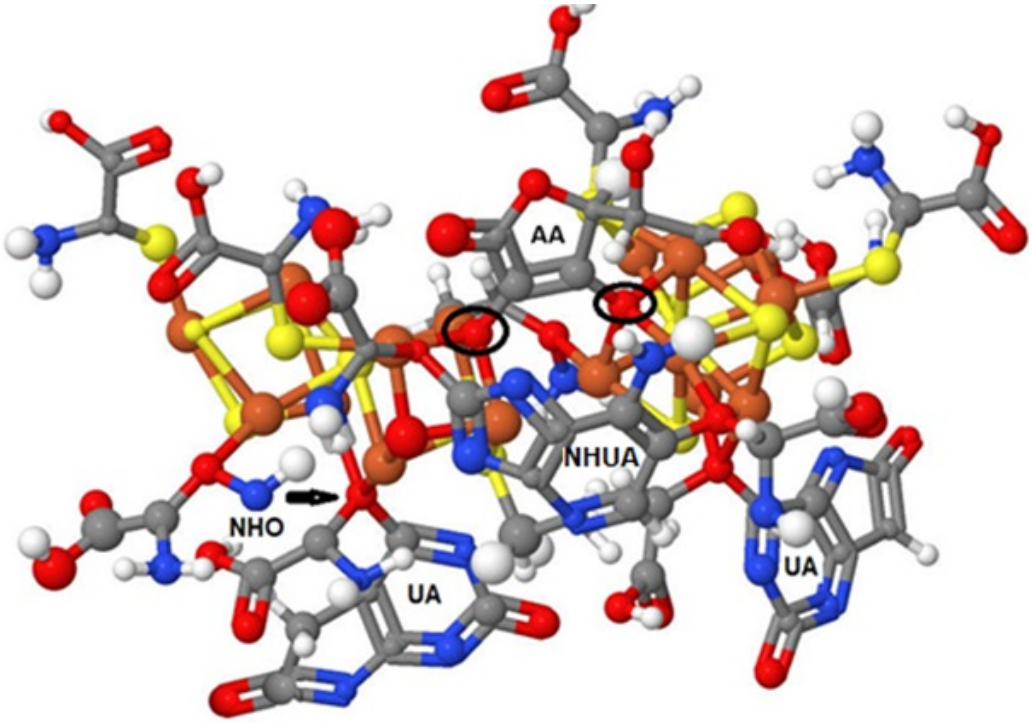


Illustration 15. One ascorbic acid connects two 8Fe7S clusters initiating the electron transfer.

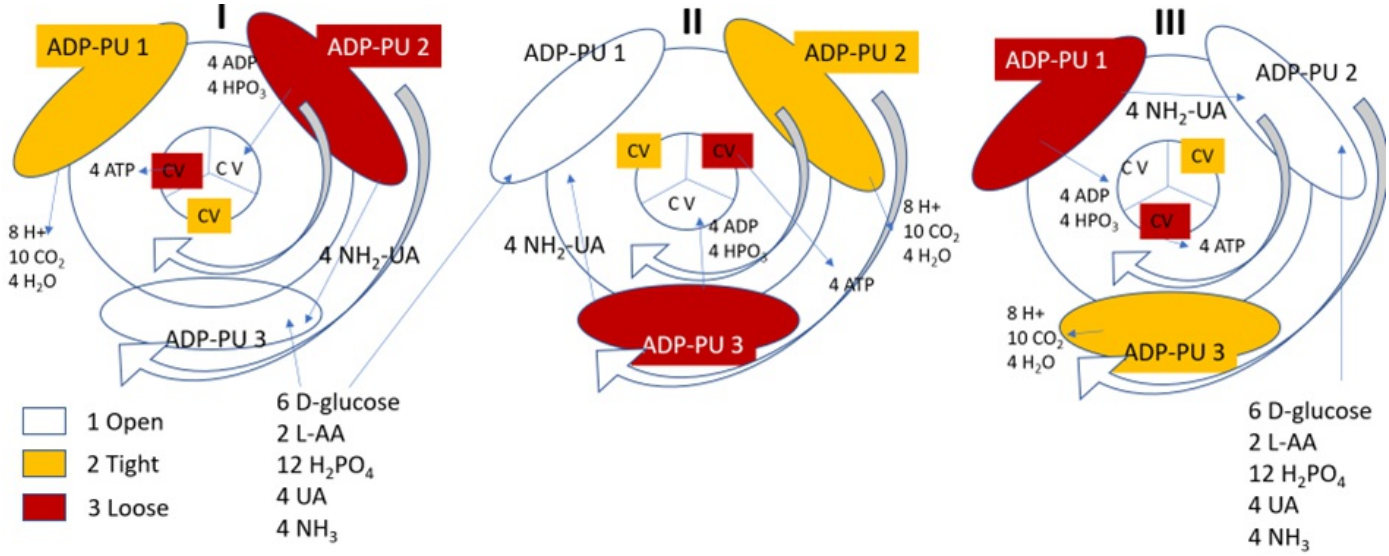


Illustration 16. The synchronised function of three ADP-PUs and three ATP synthases (CV)

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 ADP, four ribose, four Pyruvate, four citrates, and eight CO_2 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 molecules + energy are realized through oxidative phosphorylation.

SET-AG has 2 x 3, and SET-OP has 2 x 6 ADP-Pus + eight HMCs.

Sulfur – Oxygen change

The affinity of Fe^{2+} to OH is more extensive than to S.

Binding OH by Fe^{2+} results in three electrons.

Fe III will become Fe II after the liberation of the hydrogen (Table I).

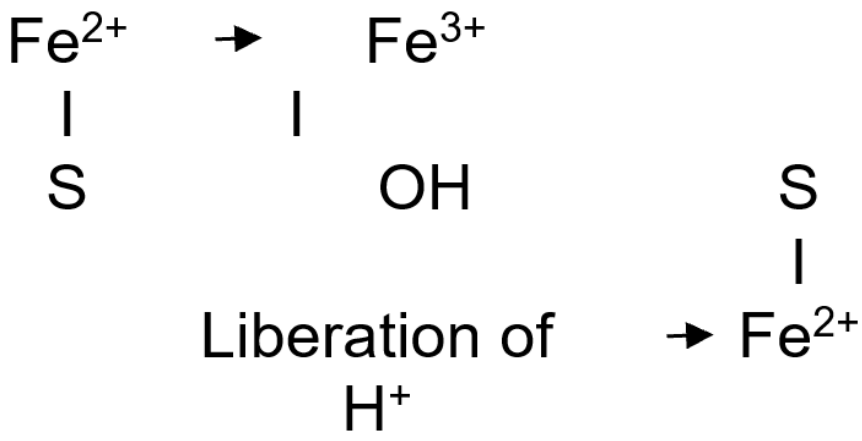


Table I. Electron transfer in Fe-S clusters

Both AA and ATP can change the S to OH in the Fe-S clusters. First, ATP activates the Fe-S clusters. After this, the cluster is ready for function. AA is needed for the initiation, realized by the double bound of the lactone ring of AA.

The four Fe8-S7$(cys\text{-}S)_6$ 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. (One UA offers one the NH_2UA two Oxygens, Illustrations 17).

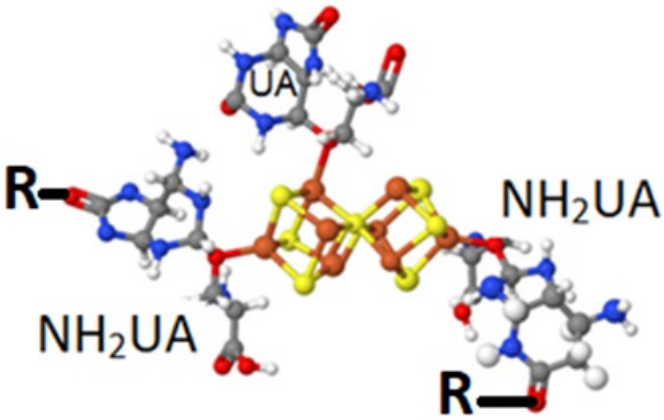


Illustration 17. 8Fe-7S (cys-S)$_6$, uric acid (UA), and two NH $_2$uric acids (NH_2UA) (only three cys-S are illustrated).

8Fe-7S (cys-S)$_6$

The NH_2 and C=O structures of the cys-S offer connecting points for the stabilization of the complex structure of the METSs. Illustration 18a demonstrates two 8Fe-7S clusters bounded by two cys-S. Illustration 18b shows one NH_2UA molecule attached to the structure.

The four UAs with four NHO molecules form four aminated UAs, while the four aminated UAs produce four adenine molecules.

Eight ribose molecules are created from eight D-glucose molecules in the transformation process.

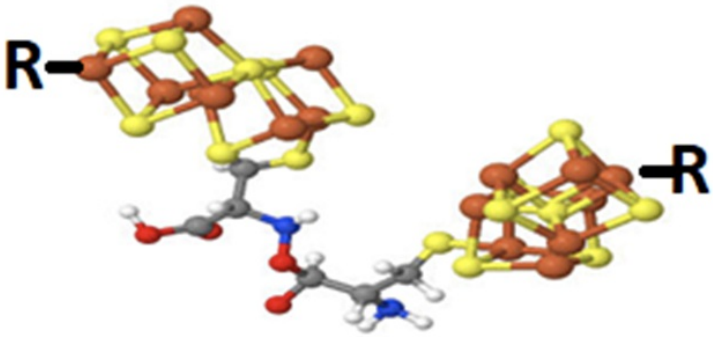


Illustration 18a. Two Fe8-S7 clusters bounded by two cys-S waiting for the NH_2UA.

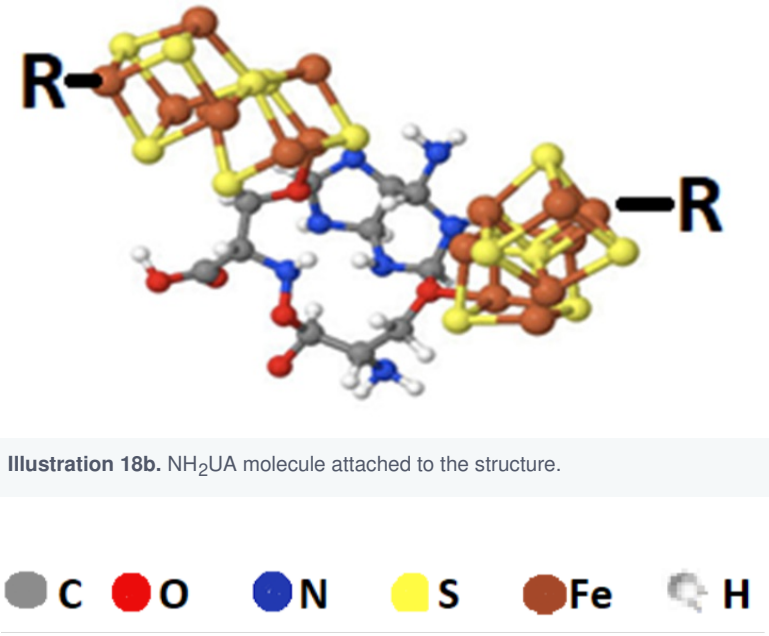


Illustration 18b. NH_2UA molecule attached to the structure.

Four ribose with four UA-originated adenine molecules forms four adenosines. In an O_2-free environment, from the remained four ribose, 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 acetic acids are converted into eight CO_2 in the Pi PU.

Structure for anaerobe glycolysis

SET-AG contains six METCs. They produce 6x4 Pyruvate. The 24 Pyruvate is converted to lactate by the enzyme lactate dehydrogenase. [1][2] Three of the Pyruvate molecules are converted to nine CO_2 in the six SUs, while four other Pyruvate is oxidised in the six G6P-Pus, resulting in 12 CO_2 molecules. The remaining seventeen Pyruvate will be converted to lactate by the enzyme lactate dehydrogenase.

Structure for oxidative phosphorylation

The high molecular weight cytochrome C (HMC) is able to oxidise three Pyruvate (Illustration 19).

The SET-OP consists of three SET-AG. The 3 X 17 Pyruvate molecules are oxidized by night teen MHC.

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[21] (Illustration 11). In our hypothesis, ADP-PU is built up by four Fe8-S7 $(cys\text{-}S)_6$ (P-cluster of nitrogenase) instead of the six 4Fe-4S clusters suggested by Austin et al. The unit's proper function needs one 4Fe-4S (G6P-PU), four2Fe-2S (Pi-PU), and one 3Fe-4S (SU-PU) cluster as well (Illustration 20).

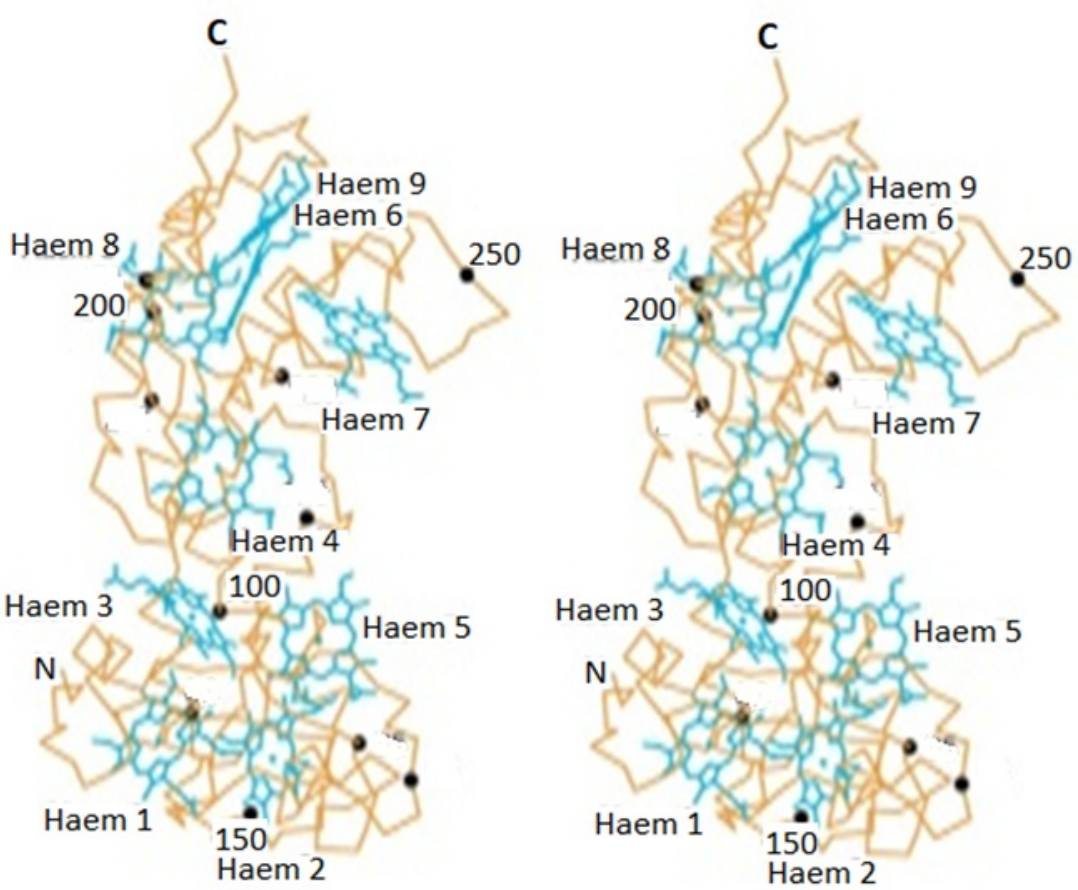


Illustration 19. High-molecular weight cytochrome C

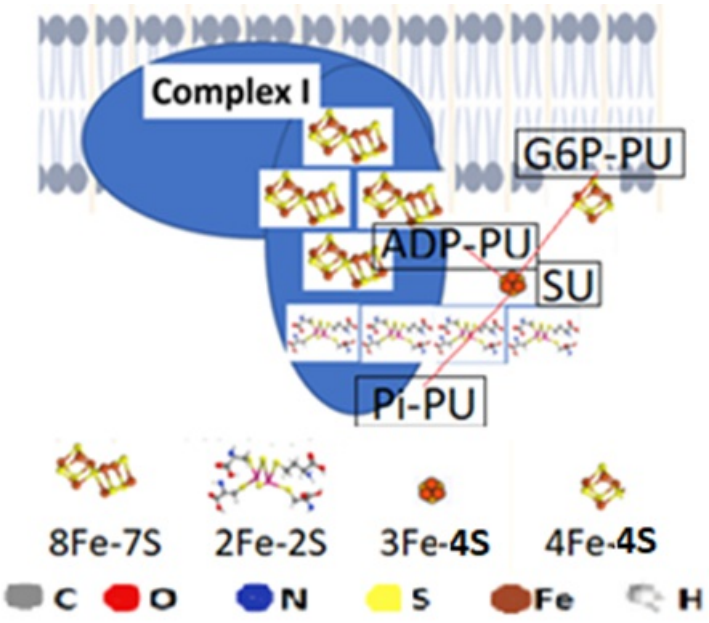


Illustration 20. Four 8Fe-7S $(cys\text{-}S)_6$ clusters form the ADP-PU of the SET-OP in the intermembrane space.

Abbreviations: ADP-PU: ADP Producing Unit, G6P-PU: Glucose 6-Phosphate Producing Unit, SU: Starting Unit, Pi-PU: Pi

Producing Unit.

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

The efficiency of the Multipart Electron Transfer Chain

After energy investment, energy is produced in the SET. In addition, new ATP molecules are created, and the membrane potential will be realized. At the end of the process, in addition of the newly synthetized four ATP, the ADP molecules formed during the energy investment are transformed back into ATP, using the energy and Pi, produced by the transformation. The hypothetical yield of the energy transformation is summarised in Table II.

Nigh-teen ATP is responsible for the activation of the METC, resulting in 19 ADP. At the end of the reaction, these ADPs will be converted to ATP, using up the produced energy. Therefore, twelve Pi are needed for the 4 ATP, while the remaining 19 Pi reconstitute the 19 ADP.

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 further factors as the transport and stabilizing-proteins, enzymes and enzyme cofactors.

The relation of our hypothesis to the vitamin C-based cancer therapy

In vitro obtained results and murine experiments consequently prove the cytotoxic effect of AA on cancer cells. However, current clinical evidence for the therapeutic effect of high-dose intravenous vitamin C therapy (HAAT) is ambiguous. The difference might be caused by the missing knowledge of AA's actions. The hypothesis described above helps to understand the mechanism of the iv vitamin C's way of action.

In the literature, there are many publications regarding vitamin C and cancer. Based on four review articles and the Cancer Information Summary of the National Cancer Institute's results, we analysed 20 publications related to HAAT. The results indicate that HAAT might be a useful cancer-treating tool in certain circumstances [22].

Because aerobic glycolysis produces significantly less energy, cancer cells can only be viable using more sugar. Thus, tumor cells use 200 times more glucose than healthy cells [23]. In addition, malignant tumor cells perform glycolysis ten times faster than their healthy tissue counterparts [24]. While rapidly growing tumor cells do not have adequate vessels during their genesis, the limited capillary support often results in hypoxia within the tumor. In addition, some tumor cells overexpress specific glycolytic enzymes, resulting in higher glycolysis rates, referred to as the Warburg effect [25]. The most common cellular metabolism changes involve intracellular glucose utilization and regulation loss between glycolytic metabolism and respiration [26]. Thus, tumor cells adapted to the hypoxic environment by the HIF-1α have unique energy production, realized by the low-efficiency aerobic glycolysis.

Korth et al. supposed that two L-vitamin C (ascorbic acid, L-AA) molecules are in the NADPH pocket, presumably near the adenine binding site in the inner membrane of the mitochondria [27]. Their conclusion is based on molecular mechanistic docking computations.

Our concept regarding energy transformation describes the strong relationship between vitamin C and energy transformation. We suppose that Vitamin C molecules are needed to initiate METCs. Furthermore, suppose the energy transformation process starts, and the glucose for the reaction is unavailable there. In that case, the produced O^{2-} radicals will kill the cells after the exhaustion of the caspase defence mechanism. A successful Vitamin C cancer therapy might be developed based on this knowledge.

Connection of the hypothesis with known facts.

The hypothesis was created based on scientific publications (Table III).

Facts, published background	Hypothesis
An ancient cell formed symbiosis with another cell, now known as the mitochondrion, and formed the eukaryotic cell. [3]	Thus, eukaryotes must have two energy-transformation structures (SET-AG and SET-OP).
Knowledge regarding Fe-S clusters, iron, sulphur, and oxygen.	$Fe^{2+} \rightarrow Fe^{3+}$ I I S OH S I Liberation of H^+ $\rightarrow$ Fe^{2+}
The possibility of carbamide–carboxy bound	carbamide and carboxyl Illustration 8. $R\text{-}C\text{-}NH_2 + O{=}C\text{-}R = R\text{-}C\text{-}N\text{-}C\text{-}R + H_2O$
mitochondrial ETC, Illustration 11	METC; Illustration 20; SU, ADP-PU, Pí-PU, G6P-PU
Korth et al. supposed that two L-vitamin C molecules are in the NADPH pocket, of the mitochondria[27].	ATP activates, while AA initiates the Fe-S clusters. Illustrations 13 and 15.
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 [19]	

Conflicting Interests

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

Table II The hypothetical yield of energy transformation

	ATP [a]	AA [b]	Source molecules	Product							
				O^{2-}	CO_2 + energy	H^+		Pi	H_2O[c]	Pyru-vate [c]	Pyru-vate[d]
	1	1	3 H_2PO_4 1 Pyruvate[e]	3	1,5	6		3	1		3[f]
	4		16 H_2PO_4 4 aceticacid	16	8	32		16			
	2		4 H_2PO_4 4 D-glucose	4			4 glucose 6 phosphate		4		4[g]
	16			24							
			4 NH_3 4 UA 4 NHUA 4 NHO 8 H_2PO_4 4 Glucose 4 glucose 6-phosphate	← 8 16 →	8	16	4 NHO 4 NHUA 4 ribose = 4 Pyruvate + 4 acetic acid 4 ADP	4		6x4=24	
	23			47	17.5	54		23		24-7=18	
							4 ATP				

ecule: ATP; b Initiating molecule: Ascorbic Acid, AA; c Used Pyruvate in six Multipart Electron Transfer

wo METC oxidizes one Pyruvate; f six METCs result nine CO_2 from three Pyruvate g six METCs result twelve

ruvate in the Glucose 6 phosphate producing units (G6P-PU);

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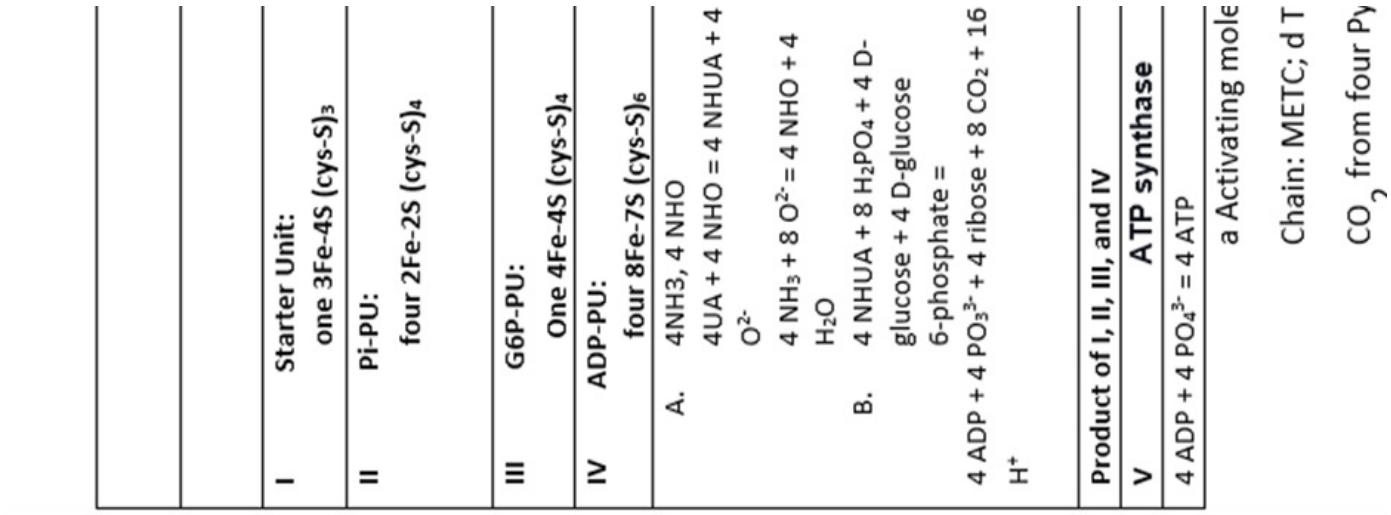

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