Research Article

The Energetic System of Eukaryotic Cells

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Background: Adenosine Triphosphate (ATP) is pivotal in cellular energetics. It is traditionally understood to be synthesised from Adenosine Diphosphate (ADP) and inorganic phosphate (Pi) by ATP synthase. Recently, we introduced a novel hypothesis suggesting an alternative synthesis mechanism involving specific cellular structures: Structure for Energy Transformation (SET).

Hypothesis: The SET, consisting of a multiplex electron transfer chain, potentially facilitates a chemical process involving D-glucose, uric acid (UA), NO, and H_2PO_4 molecules. This leads to energy production and the synthesis of ATP, CO_2, and H^+, among other products. The SETs of aerobic glycolysis (SET-AGs) are located in the peroxisomes, while the SETs of oxidative phosphorylation (SET-OPs) are in the mitochondria of the eukaryotes.

Objective: To outline and explore the new hypothesis that ATP synthesis occurs through a complex process within the SET, implicating multiple chemical constituents in a distinct stoichiometry, producing ATP, PO_3^{3-}, (Pi), CO_2 and energy.

Conclusion: The hypothesis postulates a new way of ATP synthesis. The ATP synthase forms ATP from Adenosine Diphosphate (ADP) and inorganic phosphate (Pi). The hypothesis answers the origin of ADP, Pi and energy needed for ATP production. Furthermore, the hypothesis points out the mechanism of action regarding cancer treatment with intravenous high-dose vitamin C therapy.

Introduction

Properties of the atoms of the protonated adenine molecule

Turecek and Chen investigated the features of the atoms of the protonated adenine molecule in the gas phase, water clusters, and bulk aqueous solution. They calculated that proton in the adenine ion 1^+ undergoes fast migrations among positions N1, C2, N3, N10, N7, C8, and N9, which results in an exchange of hydrogen atoms before the loss of a hydrogen atom forming adenine cation radical at a 415 kJ mol^{-1} dissociation threshold energy[1]. The proton displacement signals the electrons' migrating path in the adenine molecule. Thus, according to the results of Turecek and Chen, the adenine molecule has two entering points for electrons (N1 and N7), while electrons might leave the molecule through the N10 atom[1] (Illustration 1).

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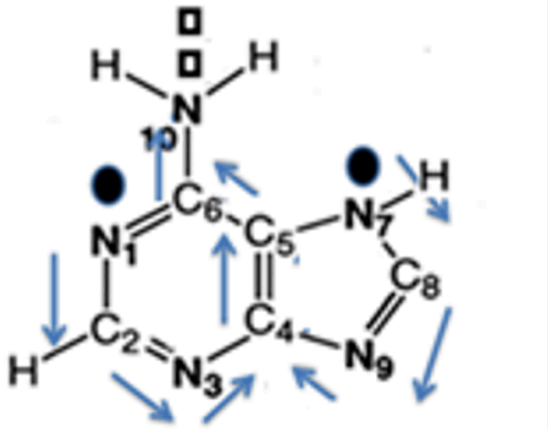

Illustration 1. Two entering points (N1 and N7) and one leaving point (N10) of the adenine molecule's electrons.

Fe-S clusters

Many Fe-S clusters are known in organometallic chemistry as precursors to synthetic analogues of the biological clusters.

The simplest polymetallic system, the [Fe_2S_2] cluster (Illustration 2), is constituted by two iron ions bridged by two sulfide ions and coordinated by four cysteine ligands (in Fe_2S_2 ferredoxins).

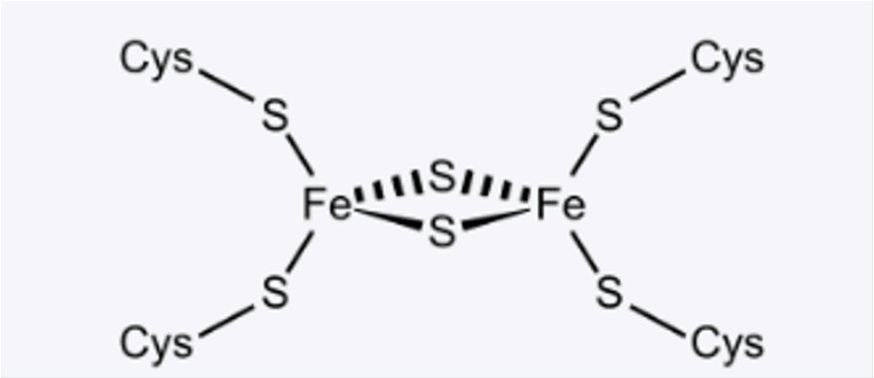

Illustration 2. Structural representation of a Fe_2S_2 ferredoxin.

The most abundant Fe-S clusters are of the rhombic [Fe_2-S_2] and cubic [Fe_4-S_4] types, but [Fe_3–S_4] [Fe_4–S_3] and [Fe_8-S_7] clusters of nitrogenase have also been described.

Cysteine

Cysteine (Cys) is a semi-essential proteinogenic amino acid with the formula HOOC-CH(-NH_2)-CH_2-SH (Illustration 3). Cys is a deterministic part of all Fe-S clusters, as it provides the continuity of the electron transfer in the Multiplex Electron Transfer

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Chain (METC) (Illustration 3). We suppose the Fe-S clusters create a continuous electron chain by connecting through their cys part. Two cys of two Fe-S clusters can create continuity between clusters as presented in Illustration 3. The Nitrogen-Oxygen connection results in N-C bound + H_2O while one C-NH_2 and one C=O will remain.

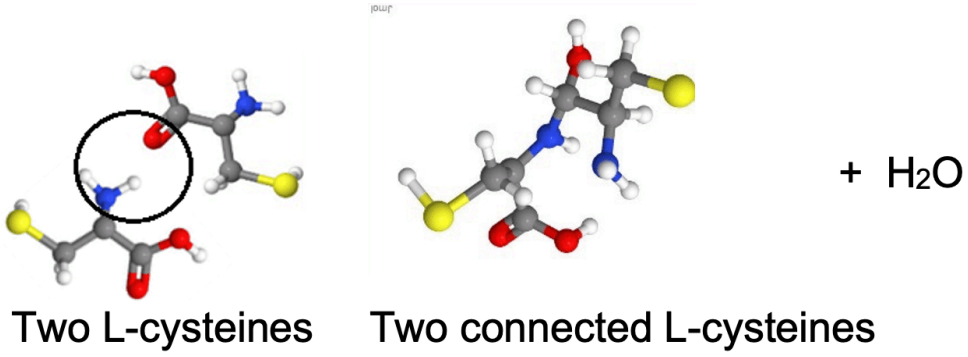

Illustration 3. Connection of two L-cysteines

The properties of oxygen, sulfur, and iron allow the oxygen and sulfur atoms to swap places in the Fe-S cluster. The exchange is mediated by the electron flow facilitated by the nearby molecules.

Fe-S clusters, the Fe^{3+} - Fe^{2+} change.

Fe-S clusters are the essential structures of the electron transfer chain. The central part of all Fe-S molecules is [Fe_2-S_2]. The Fe atom may have three or two electrons. In the [Fe_2-S_2] cluster, both Fe atoms bind two cys-S components (HOOC-CH(-NH_2)-CH_2-S-R) (Illustration 4)[2][3].

Two probable structures for [Fe_2S_2] are presented in Illustration 4.

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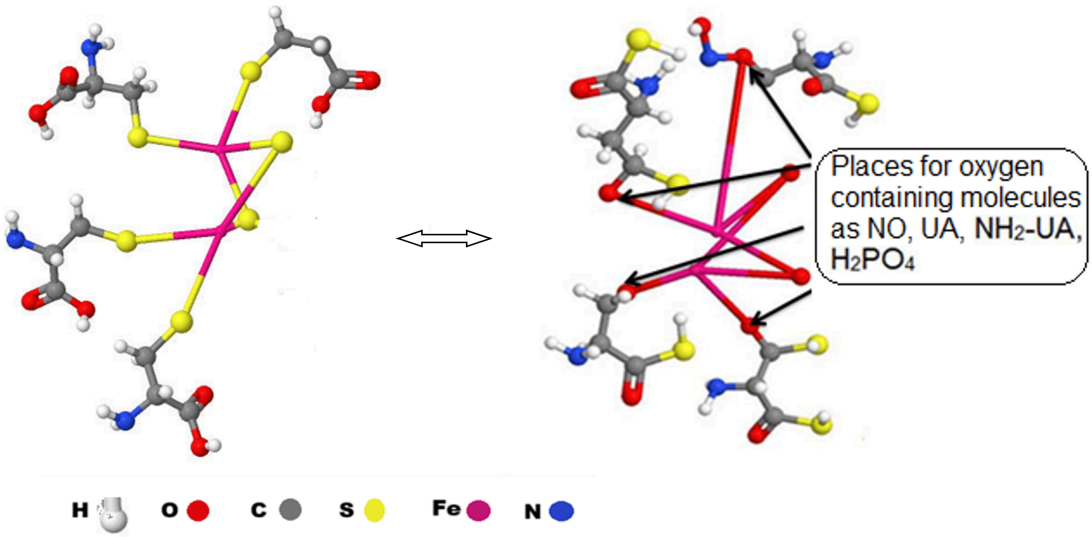

Illustration 4. Two probable structures for $Fe_2S_2[SH\text{-}CH_2\text{-}CH(\text{-}NH_2)\text{-}COOH]_4^{e2-}$ and their density functional theory optimised structures.

Energy transformation

Evolution of the Energetic system in the living world

The maintenance of life requires a continuous flow of electrons. Eukaryote cells provide this through continuous glycolysis. In cells, two glucose are converted into an adenosine triphosphate (ATP) molecule, two CO_2, one acetic acid one Pyruvate molecule and energy.

Vitamin C and ATP are the activators and initiators of energy transformation.

Sulphur – Oxygen change

Kinga Linowiecka et al. stated that L 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 5)[4].

Binding OH by Fe^{3+} results in two electrons (Fe^{2+}) as two H^+ will leave the molecule, creating the membrane potential[4]. Later in the Fe-S cluster, Fe^{2+} will become Fe^{3+} by hydrogen atoms.

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$$2\ Fe^{3+} + AA = 2\ Fe^{2+} + DHA + 4H^{+}$$

$$2\ Fe^{2+} + DHA + 4H^{+} = 2\ Fe^{3+} + AA$$

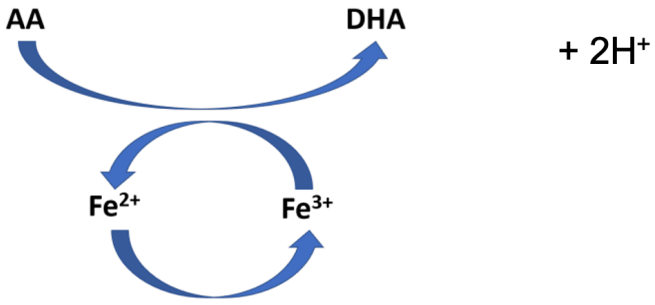

Illustration 5. The role of Vitamin C in the Fe^{3+} - Fe^{2+} transformation[4].

Abbreviations: AA: L-ascorbic acid; DHA: dehydroascorbic acid.

AA and the two OHs on the ribose of an ATP molecule can change the S to OH in the Fe-S clusters. First, ATP and AA activate the Fe-S clusters by two OH, resulting in energy transfer. After this, the cluster is ready for function.

The sulfur–oxygen exchange caused by AA is demonstrated in Illustration 6.

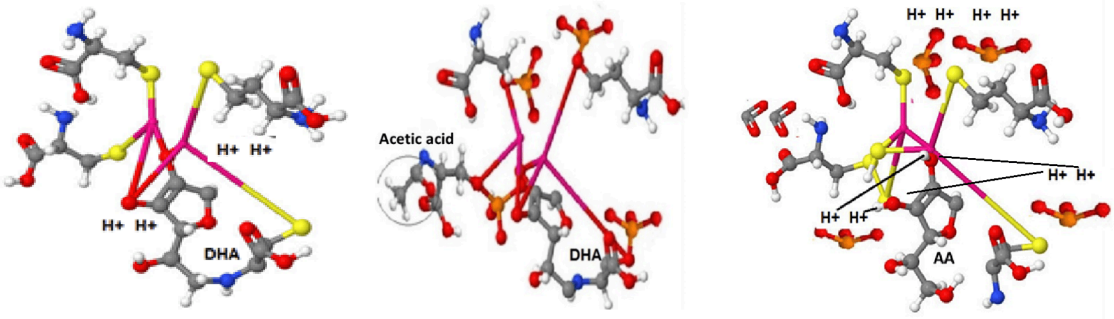

Illustration 6. Ascorbic acid results sulfur – sulfur-oxygen change in Fe-S clusters.

Abbreviations: DHA: dehydroascorbic acid; AA: L-ascorbic acid

Mitochondria contain vitamin C

Korth et al. supposed that two L-vitamin C molecules are in the NADPH pocket, presumably near the adenine binding site in the inner membrane of the mitochondria[5]. Their conclusion is based on molecular mechanistic docking computations.

ATP-uric acid-ATP cycle

The view that uric acid (UA) is the end-product of ATP metabolism is generally accepted. Gounaris et al. described that the hypoxanthine molecule could develop as an effective capture of inorganic nitrogen species. These authors have also reported that

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hypoxanthine, the biochemical precursor of adenine and guanine, captured nitrite ions and was reductively transformed into adenine[6]. A similar reaction may occur by UA amination. We predict that UA is not an end-product but one element of an ATP – adenosine – inosine – hypoxanthine – xanthine – UA – NH_2UA – adenosine – ADP - ATP cycle (Illustration 7).

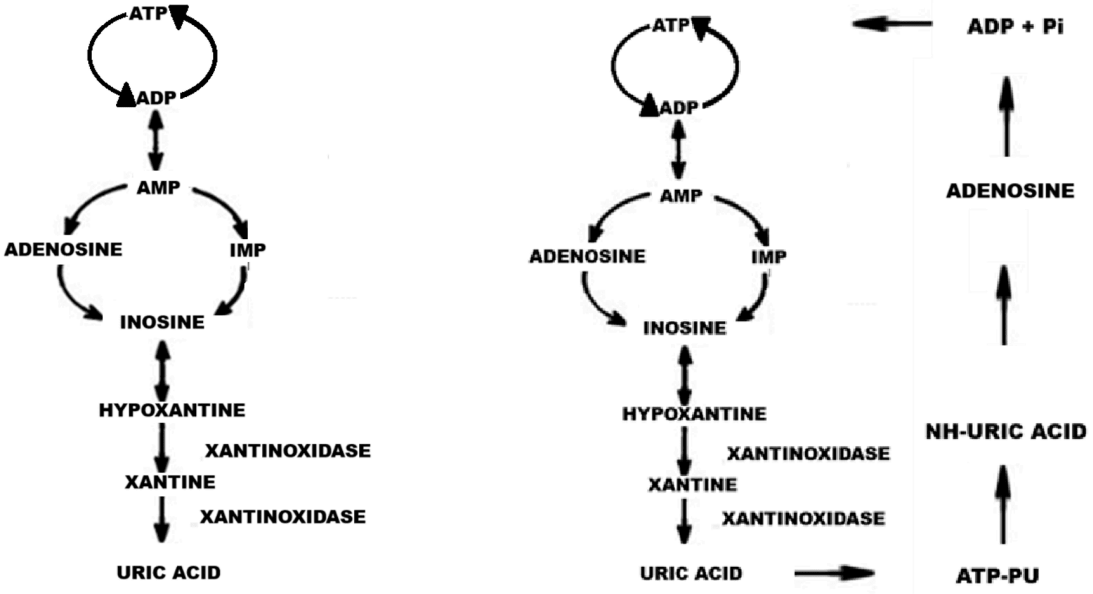

Illustration 7. The hypothetical ATP-uric acid-ATP cycle.

Left: Uric acid is the end-product of ATP metabolism[6]. Right: ATP – Uric acid – ATP cycle

Abbreviation: IMP: inosine monophosphate; ATP-PU: ATP Producing Unit; Pi: PO_3^{3-}

Amination of uric acid

Nitrogen monoxide

Nitrogen monoxide (NO) is an important neurotransmitter in the mammalian body. It can also occur in the cells of bacteria, plants, fungi and animals, and has an important regulatory role in processes such as ATP production and cellular respiration, apoptosis, photosynthesis, phagocytosis, and cell movement.

Recent progress in NO biology shows that NO is generated within distinct cell compartments, including specific plasma membrane regions, mitochondria, chloroplasts, peroxisomes, the Golgi complex and intracellular membrane systems[7].

We suppose, that $[Fe_8S_7(SCH_2CH_3)_6]^{e2-}$ clusters of nitrogenase take up oxygen atoms from the C1 position of UA molecules. At the same time, nitrogen will be offered by the same $[Fe_8S_7(SCH_2CH_3)_6]^{e2-}$ clusters of nitrogenase. Thus, UA will be nitrified with the help of the aminotransferase enzyme, producing an aminated UA, and 4 CO_2 molecules.

$4UA + 4NO + 2 \text{ acidic acids} = 4\ NH_2\text{-}UA^{e-} + 4\ CO_2$

The reaction is mediated by aminotransferase and $[Fe_8S_7(SCH_2CH_3)_6]^{e2-}$ cluster.

The Evolution of Mitochondria

Energy production may have taken place in primitive cells in the cell membrane. Later, a structure specialised in this area. The mitochondrion is an organelle found in the cells of most eukaryotes, such as animals, plants and fungi. Lynn Margulis (1938-2011) suggested that the ancestor of eukaryotic cells avoided being destroyed by oxygen by entering into a symbiotic relationship with an aerobic bacterium. This gave rise to the mitochondria of eukaryotes (Illustration 8)[8][9]. Thus, eukaryotes have genetic material from both cells and can live in hypoxic and normoxic environments using SET-AG of the ancestor cell and SET-OP of the mitochondrion. All eukaryotic cell has mitochondria.

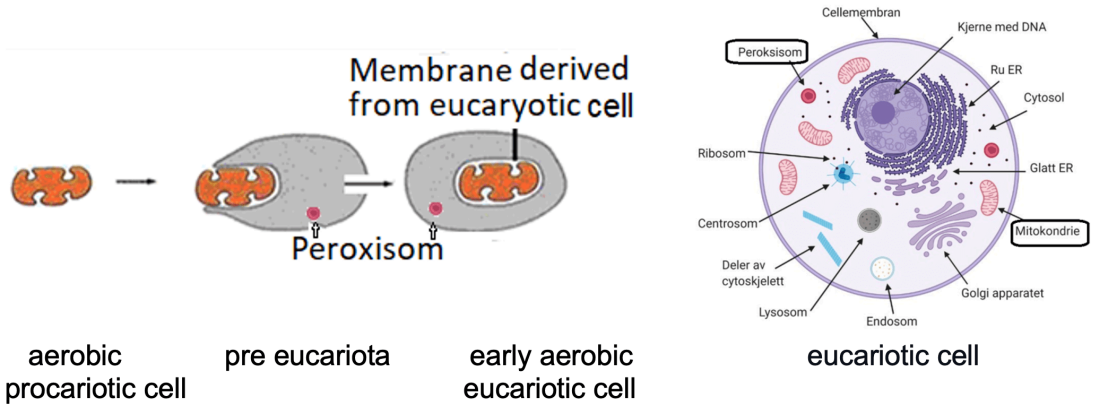

Illustration 8. The evolution of mitochondria according to the theory of endosymbiosis

Electron transport chain

An electron transport chain (ETC) is a series of membrane-bound protein complexes (Complex I, Complex II, Complex III and Complex IV) 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. In the mitochondrion, four Fe_2-S_2, one Fe_3-S_4, and seven Fe_4-S_4 clusters offer the proper function of Complex I, Complex II, and Complex III, as described by Austin et al (Illustration 9)[10].

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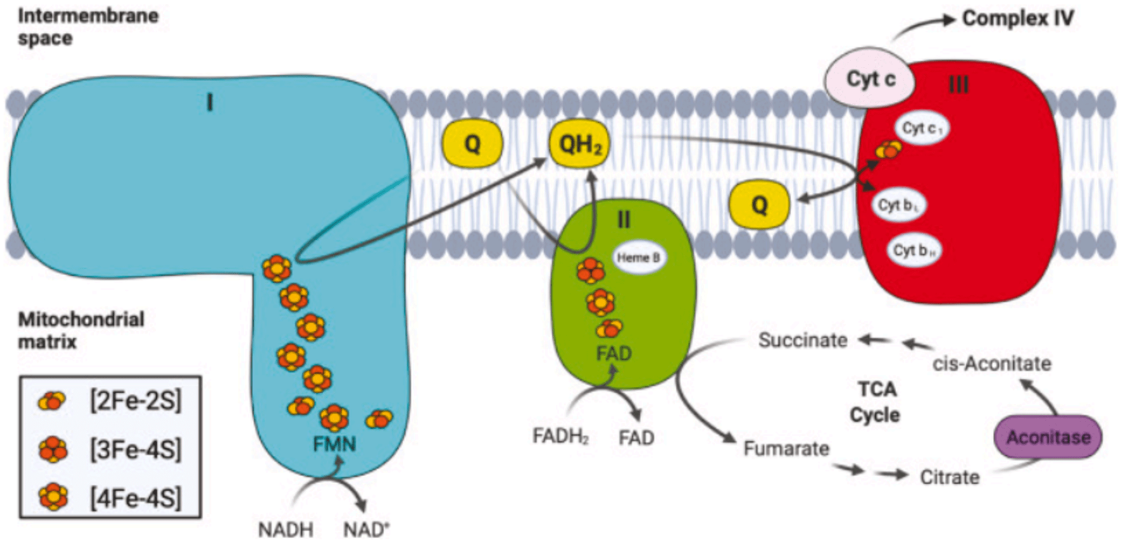

Illustration 9. A simplified version of the mitochondrial ETC showing complexes I (blue), II (green) and III (red)[10]

The hypothesis of the structure for energy transformation

We suppose that in the NH_2-UA molecules, C2 and C8 are the electrons' entering points, and N10 is the electrons' leaving point (Illustration 10).

Illustration 10. The leaving and entering points of electrons in an aminated uric acid molecule

We have created a hypothetical structure responsible for ATP production that provides the cell energy[11]. The hypothesis is based on known data such as the oxidative pentose pathway, the electron transport system in mitochondria[12], the biochemical nature of $H_2PO_4^-$, the results of Turecek and Chen about the nature of adenine[1], and the oxidative experimental results supported by stoichiometric calculations suggesting that there are two vitamin C molecules in the NADPH pocket of the mitochondrion[5]. The JSME Editor, courtesy of Peter Ertl and Bruno Bienfait, helped to calculate the 3D structures of the hypothesised vision of Structure for Energy Transformation (SET)[13].

The first hypothesis was further developed[11][14][15][16][17][18][19]. The present paper represents the final hypothesis.

Our hypothetical SET consists of a modified version of the well-known complexes I, II, III, IV and V (Illustration 8). SET is the engine of the five multienzyme complexes in the peroxisomes and the mitochondria. Thus, the concept of SET helps to understand the energetics of eukaryotic cells.

We believe that SETs provide the cell with new ATP molecules, and afford energy supply and H^+ in eukaryotes. Units of SETs are made up of the same building blocks.

The constituent elements of the structures of energy transformation

ATP synthase

ATP synthase forms rows of dimers in cristae membranes. The mitochondrial F1 and FO regions of ATP synthase are the most conspicuous protein complexes in the mitochondrial cristae. ATP synthase is an ancient nanomachine. It uses the electrochemical proton gradient across the inner mitochondrial membrane to produce ATP by rotator catalysis[20][21][22]. Carrier molecules take ADP in the nanomachine, where, with help from chemical energy in food, phosphate can be added to it, producing more ATP[23]. The origin of ADP, Pi and energy is not detailed while the present hypothesis answers these points.

Pyruvate dehydrogenase

Pyruvate dehydrogenase complex (PDC) is a complex of three enzymes that converts pyruvate into acetyl-CoA by pyruvate decarboxylation (Illustration 11). Acetyl-CoA may then be used in the citric acid cycle to carry out cellular respiration, and this complex links the glycolysis metabolic pathway to the citric acid cycle. Pyruvate decarboxylation is also known as the "pyruvate dehydrogenase reaction" because it involves pyruvate oxidation[24].

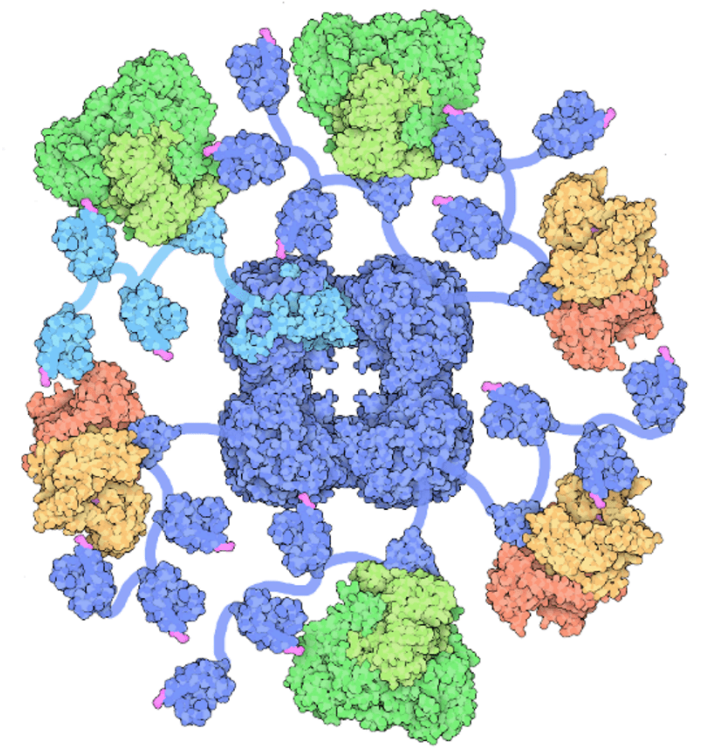

Illustration 11. Pyruvate dehydrogenase complex

Building molecules of the electron transfer chain

The energy supply structures contain the mitochondrial multienzyme complexes (Illustration 9). They are made up of permanent components, forming a nest waiting for the source molecules. Fe-S clusters, Flavine, and nicotinamide are the most important constituent elements of the nest. This structure arranges the mitochondrial multienzyme complexes into functional units. ATP,

CO_2, and membrane potential (H^+) are formed from the source molecules (D-glucose, UA, NO, $H_2PO_4^-$) entering the structure while new ATP molecules are formed and CO_2 + energy is liberated.

The supposed structures for energy transformation

Electron Transfer Chain

Austin et al described that four [Fe_2-S_2], one [Fe_3-S_4], and seven [Fe_4-$S_4(SCH_2CH_3)_4]^{e2-}$ clusters offer the proper function of Complex I, Complex II, and Complex III (Illustration 9)[10]. We suppose that instead of the seven [Fe_4-$S_4(SCH_2CH_3)_4]^{e2-}$ clusters, one [Fe_3-$S_4(SCH_2CH_3)_4]^{e2-}$, one [Fe_4-$S_4(SCH_2CH_3)_4]^{e2-}$ + four [Fe_8S_7 $(SCH_2CH_3)_6]^{e2-}$ clusters form the electron transfer chain. We calculate with [Fe_8S_7], as it helps the amination of the uric acids.

We suppose that the four [Fe_8S_7 $(SCH_2CH_3)_6$] clusters of nitrogenase and four [Fe_2-S_2] clusters form a ring connected to the [Fe_3-S_4] and [Fe_4-S_4] clusters. The Fe_3S_4 cluster bounds two [Fe_8S_7] clusters and the Fe_4S_4 clusters the other two [Fe_8S_7] clusters. The connection of the ten Fe-S clusters forms the **electron transfer chain.**

Multiplex electron transfer chain

The [Fe_3-S_4] and [Fe_4-S_4] clusters bind neighbouring ETCs. They form a **multiplex electron transfer chain with six ETCs** (METC).

ATP-producing unit (ATP-PU) / structure of energy transformation for aerobic glycolysis (SET-AG).

The ATP synthase enzymes and the METC form the ATP-producing unit (ATP-PU) / structure of energy transformation for aerobic glycolysis (SET-AG).

Energy transformation of oxidative phosphorylation (SET-OP).

SET-AG + pyruvate dehydrogenise complexes form the structure of energy transformation for oxidative phosphorylation (SET-OP).

The SET-AG is in the peroxisomes, while SET-OP is in the mitochondria.

The clusters must be activated by ATP and initiated by AA before starting the electron transfer.

The [Fe_8S_7 $(SCH_2CH_3)_6]^{e2-}$ clusters obtain six cys parts. Thus, it offers places for six oxygen-containing molecules. The cluster bounds one UA by the C6 positioned oxygen, one aminated UA by the C2 or C8 positioned oxygen, one NO molecule and two H_2PO_4 molecules, by the double bounded oxygen of the molecules (Illustration 12).

Four aminated uric acid molecules connected to Nicotinamide and Flavine molecules link the four [Fe_8S_7 $(SCH_2CH_3)_6]^{e2-}$ clusters of nitrogenase (Illustration 12). The four No, four UA, eight D-glucose and the 32 $H_2PO_4^-$ molecules are not presented.

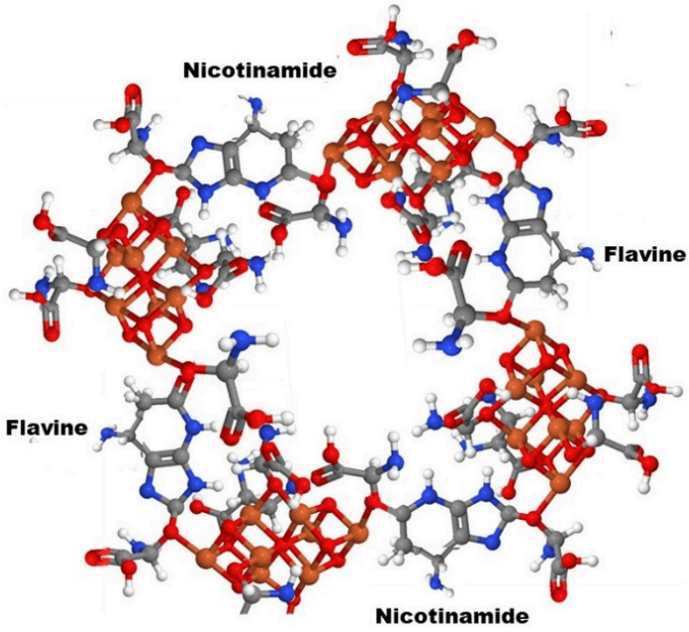

Illustration 12. Four aminated uric acid molecules connected to nicotinamide and Flavine molecules link the four $[Fe_8S_7(SCH_2CH_3)_6]^{e2-}$ clusters of nitrogenase.

Activation and initiation of the multiplex electron transfer chain.

We suppose that the ATP-producing unit (ATP-PU) forms new ATP molecules. The amination of UA, the ribose binding to the UA-originated adenine, and the three Pi bounds all need energy (Illustration 13), provided by five ATP and carbon oxidation.

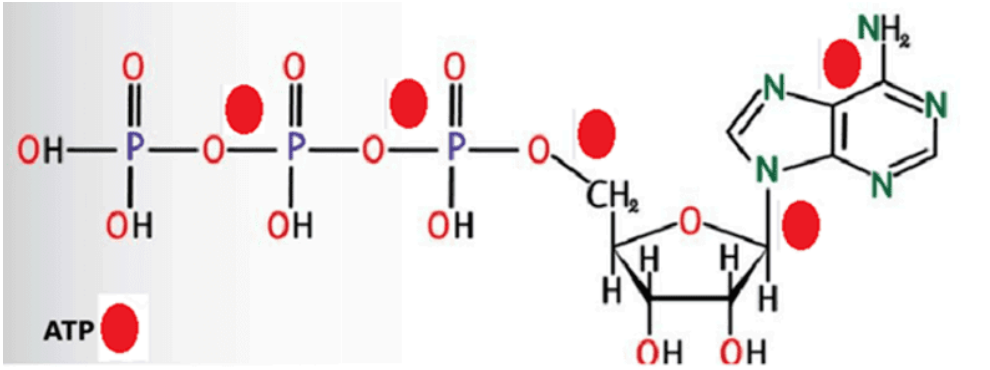

Illustration 13. Five ATP are needed for the making a new ATP

The energy transformation in one ETC results in four new ATP molecules. The construction of four ATP needs the energy of 4X5 ATP (Illustration 13) + energy of 20 carbon oxidation. Thus 20 ATP must enter the ETC. 2 X four ATP activates the second and third $[Fe_8S_7]$, 2 X three ATP is used for the activation of the first and fourth $[Fe_8S_7]$, and six ATP are needed for the activation of the four $[Fe_2S_2]$, the $[Fe_3S_4]$ and the $[Fe_4S_4]$ clusters. Three AAs bind to the first and second $[Fe_8S_7]$ and to the $[Fe_4S_4]$ clusters initiating the electron transfer (Illustration 14), Table I.

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Source molecules of the energy-producing units

The activation of the ETC changes the sulfur atoms to oxygen-containing molecules, such as H_2PO_4, NO, UA, and NH_2-UA. In addition, D-glucose and acetic acid molecules will be bonded to the connecting cys part of the Fe-S clusters (Table II, Illustration 14, 15).

The ETC of the ADP-producing unit is presented in illustration 14. The eight D-glucose are not illustrated. The chain consists of twenty-four connecting points. Sixteen connecting points are between the four $[Fe_8S_7\ (SCH_2CH_3)_6]^{e2-}$ and four $[Fe_2\text{-}S_2(SCH_2CH_3)_4]^{e2-}$ clusters (1-16); two connecting points (17, 18) are between two [8Fe-7S] and $[Fe_4\text{-}S_4]$ clusters and further two (19, 20) between the $[Fe_3\text{-}S_4]$ and two $[Fe_8S_7]$ clusters. The remaining 4 cys and the $[Fe_3S_4]$ and $[Fe_4S_4]$ clusters connect the neighbour ETC clusters to form the METC, containing 6 ETC (ME1, ME2, ME3, ME4, Illustration 14, 15).

Each $[Fe_8\text{-}S_7]$ clusters have four places for activation, each $[Fe_2\text{-}S_2]$ cluster and the $[Fe_3\text{-}S_4]$ have one while the $[Fe_4\text{-}S_4]$ cluster has two activation points. In the $[Fe_8\text{-}S_7]1$, $[Fe_8\text{-}S_7]$ 2 and $[Fe_4\text{-}S_4]$ clusters one AA is responsible for the activation. (Table I, Illustration 15).

Fe-S Cluster	ATP	AA
$[Fe_8\text{-}S_7]1$	3	1
$[Fe_8\text{-}S_7]2$	3	1
$[Fe_8\text{-}S_7]3$	4	
$[Fe_8\text{-}S_7]4$	4	
$[Fe_2\text{-}S_2]1$	1	
$[Fe_2\text{-}S_2]2$	1	
$[Fe_2\text{-}S_2]3$	1	
$[Fe_2\text{-}S_2]4$	1	
$[Fe_3\text{-}S_4]$	1	
$[Fe_4\text{-}S_4]$	1	1
	20	3

Table I. Activation points of the Fe-S clusters

Twenty ATP molecules activate the ETC while three AAs initiate the reaction. Two OH of the ribose on the ATP bound to two Fe atoms of the $[Fe_8S_7\ (SCH_2CH_3)_6]^{e2-}$, while the NH_2 part of the ATP's adenine will be bound to the C=O part of the connecting point (Illustration 15). In that way, the 20 ATP molecules will bind 20 C=O of the connected cys.

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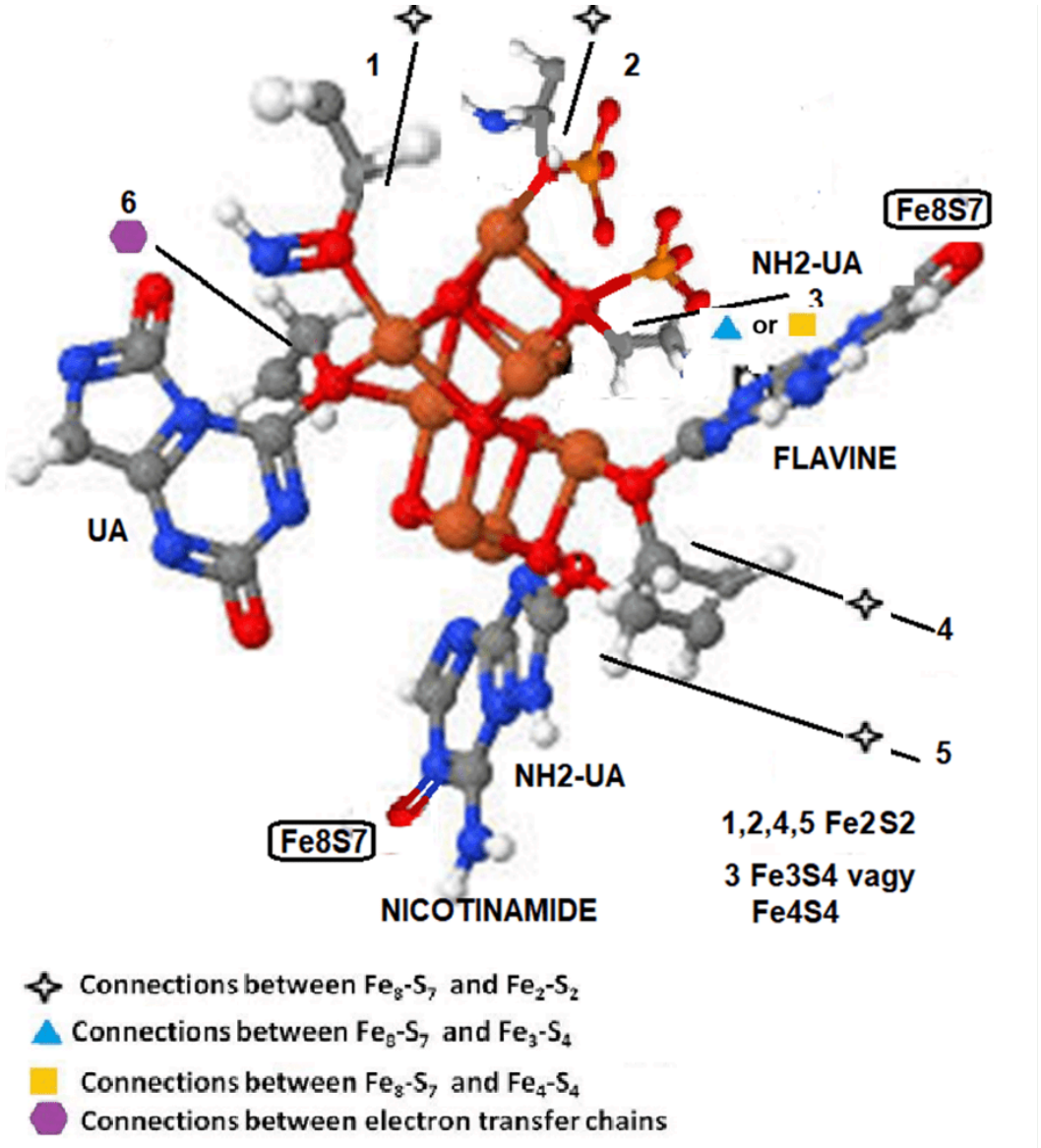

Illustration 14. The connecting points of the Fe_8S_7 cluster.

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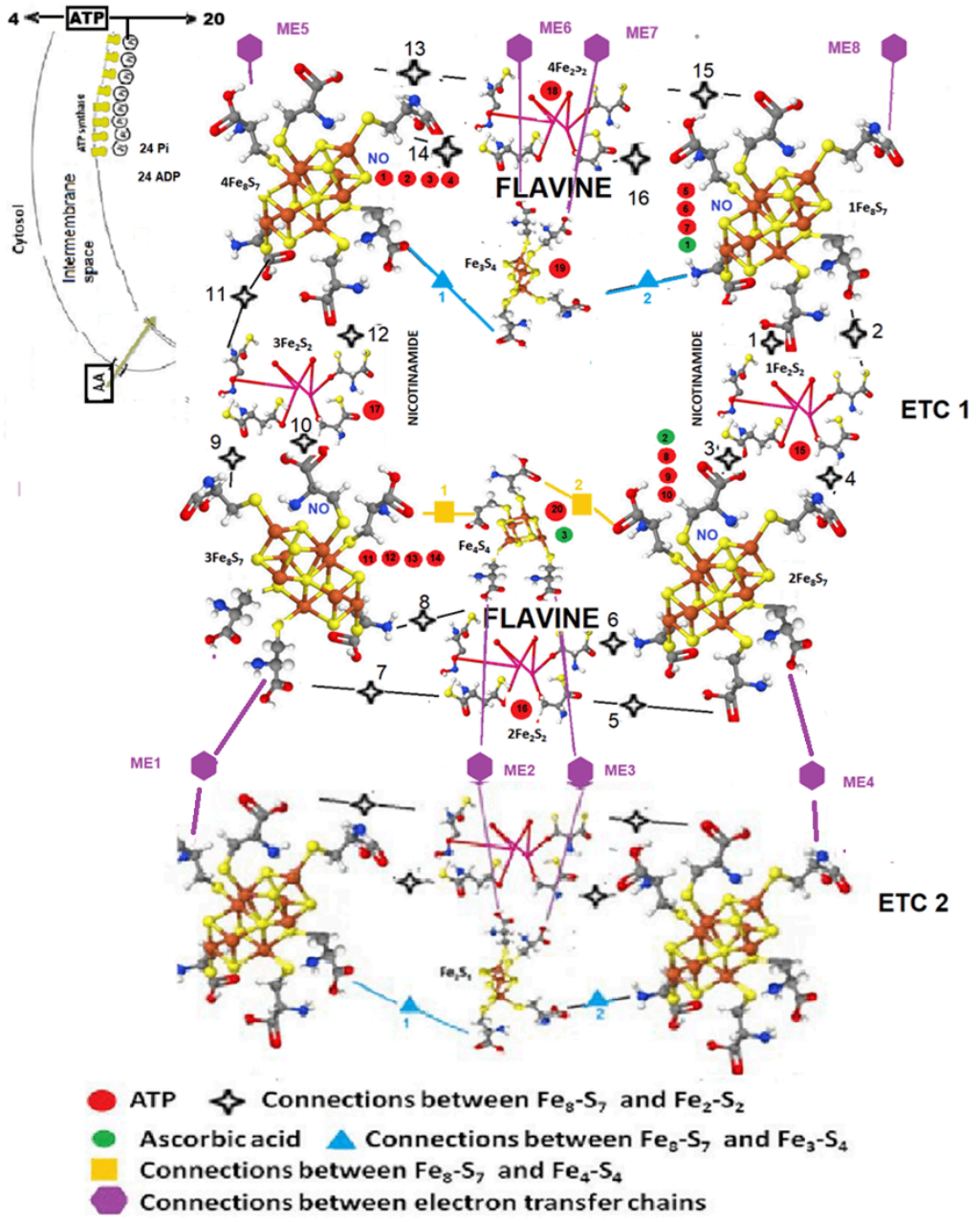

Illustration 15. The electron transfer chain of the ADP-producing unit; The eight D-glucose, and thirty-two H_2PO_4 molecules are not illustrated.

The twenty C-NH_2 structures of the connecting points bound eight D-glucose, eight acetic acids, two flavine, two nicotinamide and two AA molecules. (Table II Illustration 16)

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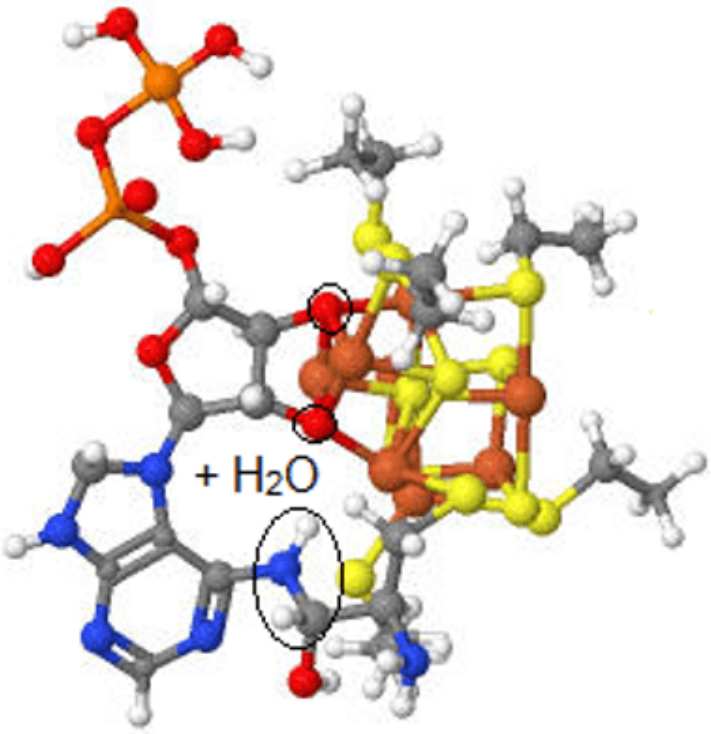

Illustration 16. The connection of ATP molecule to one connecting point.

The connecting points of the electron transfer chain

The predicted molecules of the connecting points are listed in Table II.

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	Connecting point	binding point		binding point
		molecule C=O	cys-cys	molecule C-NH_2
1	$Fe_8S_7$1a	ATP15	$Fe_2S_2$1a	**AA1**
2	$Fe_8S_7$1b	ATP7	$Fe_2S_2$1b	Nicotinamide
3	$Fe_8S_7$5a	ATP8	$Fe_2S_2$2a	**AA2**
4	$Fe_8S_7$5b	ATP9	$Fe_2S_2$2b	acac1
5	$Fe_8S_7$2a	ATP10	$Fe_2S_2$3a	D-GL1
6	$Fe_8S_7$2b	ATP16	$Fe_2S_2$3b	Flavine
7	$Fe_8S_7$6a	ATP11	$Fe_2S_2$4a	D-GL2
8	$Fe_8S_7$6b	ATP12	$Fe_2S_2$4b	acac2
9	$Fe_8S_7$3a	ATP13	$Fe_2S_2$1a	acac3
10	$Fe_8S_7$3b	ATP14	$Fe_2S_2$1b	D-GL3
11	$Fe_8S_7$7a	ATP1	$Fe_2S_2$2a	D-GL4
12	$Fe_8S_7$7b	ATP2	$Fe_2S_2$2b	Nicotinamide
13	$Fe_8S_7$4a	ATP3	$Fe_2S_2$1a	Flavine
14	$Fe_8S_7$4b	ATP4	$Fe_2S_2$1b	D-GL5
15	$Fe_8S_7$8a	ATP5	$Fe_2S_2$2a	D-GL6
16	$Fe_8S_7$8b	ATP6	$Fe_2S_2$2b	acac4
Fe_3S_4 and Fe_4S_4 clusters				
Fe_3 1	$Fe_8$1	ATP 17	$F_3$1	acac5
Fe_3 2	$Fe_8$2	ATP 18	$F_3$2	D-GL7
Fe_4 1	$Fe_8$3	ATP19	$F_4$1	D-GL8
Fe_4 2	$Fe_8$4	ATP20	$F_4$2	acac6

Table II. Connecting points of the electron transfer chain.

Abbreviations: AA: ascorbic acid; D-DL: D glucose; acac: acidic acid

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Illustration of the connecting points

ATP and acetic acid in the connecting points 4, 8, 9, 16, Fe_3S_4 1 and Fe_4S_4 1 – (illustration 17)

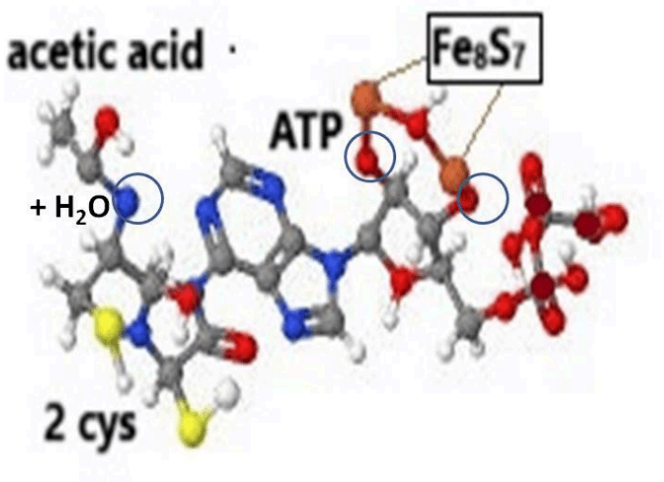

Illustration 17. ADP and acetic acid in the connecting points 4, 8, 9, 16, Fe_3S_4 1 and Fe_4S_4 1.

ATP and D-glucose in the connecting points 1, 7, 10, 11, 14, 15, Fe_3S_4 2 and Fe_4S_4 2 (Illustration 18)

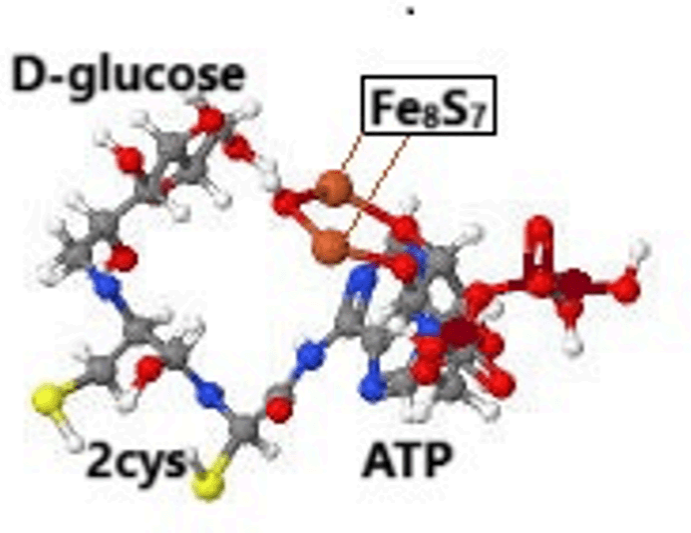

Illustration 18. ATP and D-glucose in the 1, 7, 10, 11, 14, 15, Fe_3S_4 2 and Fe_4S_4 2 connecting points.

Connecting points of the multiplex electron transfer chain

One METC contains six ETC. The connecting points of the METC are demonstrated in Table III. Neighbor Electron chains are connected by Fe_4S_4 and Fe_3-S_4 clusters (Illustration 18). The calibration of the METC: 3 x 30,3 Angstrom: 3,14 = 28,94 Angstrom (Illustration 19).

	Connecting point	binding point	cys-cys	binding point
		molecule C=O		molecule C-NH_2
ME1	Fe_8 3 (ETC1)		Fe_8 4 (ETC2)	
ME2	Fe_4S_4 (ETC1)		Fe_3S_4 (ETC2)	acac7
ME3	Fe_4S_4 (ETC1)		Fe_3S_4 (ETC2)	AA3
ME4	Fe_8 2 (ETC1)		Fe_8 3 (ETC2)	
ME5	Fe_8 4 (ETC1)		Fe_8 3 (ETC6)	
ME6	Fe_4S_4 (ETC1)		Fe_3S_4 (ETC6)	
ME7	Fe_4S_4 (ETC1)		Fe_3S_4 (ETC6)	acac8
ME8	Fe_8 1 (ETC1)		Fe_8 2 (ETC6)	

Table III. Connecting points between two electron transfer chains.

ME: connecting point between electron transfer chains.

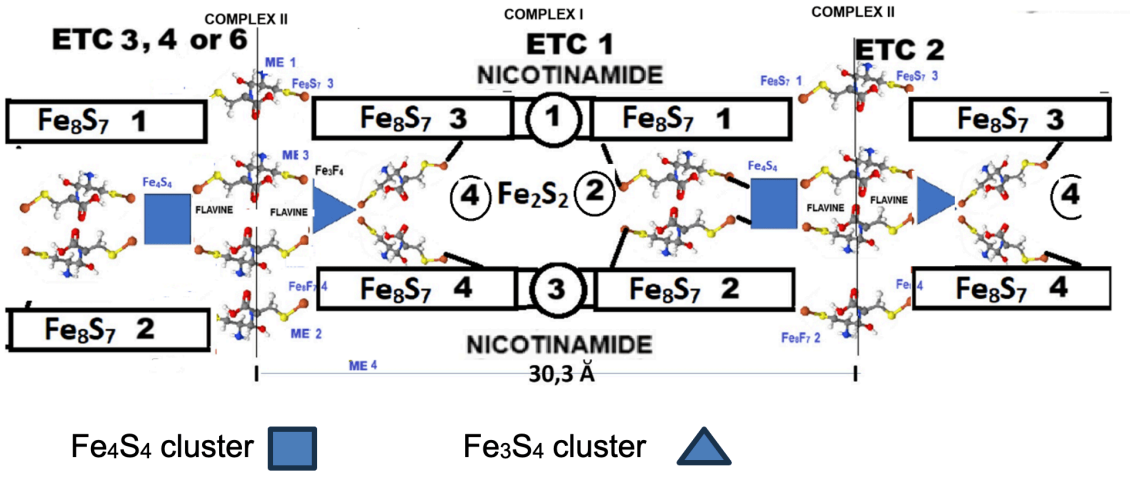

Illustration 19. Connection of 2 electron transfer chains

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Multiplex electron transfer chain

METC consists of 6 ETCs. ETC1, ETC2 and ATC3 form a ring (METCa) which is bound to the METCb, containing the ETC4, ETS5 and ETC6 units (Illustration 20)

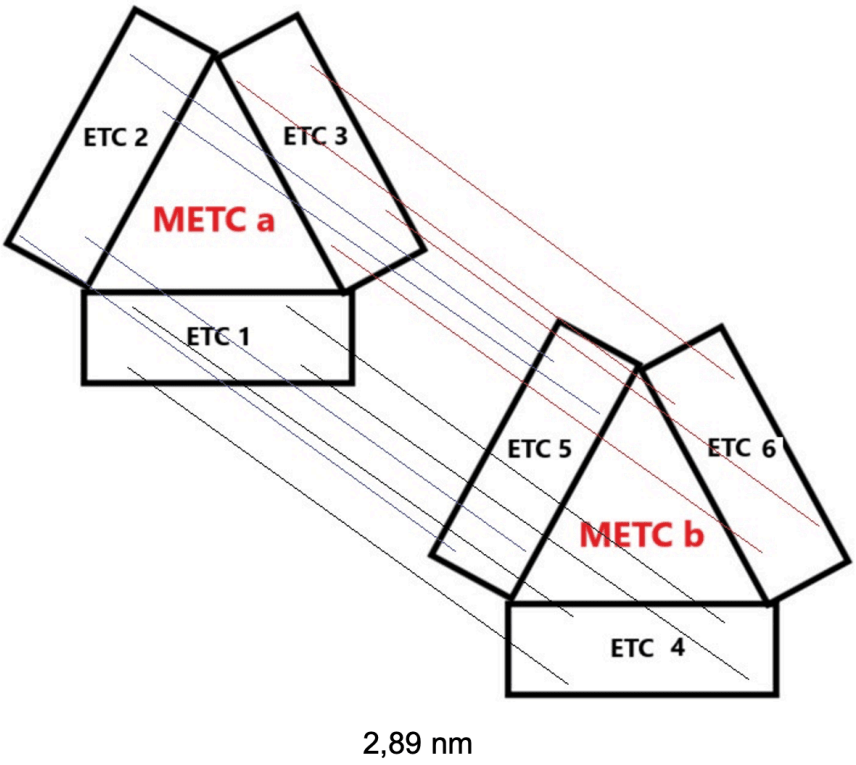

Illustration 20. The calculated sizes of the multiplex electron transfer chains

Oxygen binding points of multiplex electron transfer chain

Oxygen-containing molecules will replace the sulfur atoms after the ETC is initiated. Table IV demonstrates the source and structure molecules of the ETC. The ETC has 48 cys structures. The four 8Fe8-7S7 clusters hold 6x4=24, the four [Fe_2-S_2], the [Fe_3-S_4], and the [Fe_4-S_4] clusters contain 6x4 cys, offering 48 oxygen binding points (Table IV).

Each $[Fe_8S_7\,(SCH_2CH_3)_6]^{e2-}$ clusters obtain six cys parts. Thus, it offers places for six oxygen-containing molecules. The cluster bounds one UA by the C6 positioned oxygen, one aminated UA by the C2 or C8 positioned oxygen, one NO molecule and two H_2PO_4 molecules, by the double bounded oxygen of the molecules. Each Fe_2-S_2, Fe_4-S_4 and Fe_3-S_4 cluster bound four H_2PO_4 molecules, by the double-bounded oxygen.

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structure molecules	Source molecules				O binding point
	UA	NH_2-UA	H_2PO_4	NO	
4 Fe_8-S_7	4	4 x 2	8	4	6x4 =24
4 Fe_2-S_2			16		4x4=16
1 Fe_4-S_4			4		1x4=4
1 Fe_3-S_4			4		1X4=4
ETC	4	4x2=8	32	4	48
2 Flavine					
2 Nicotinamide					

Table IV. Source and structure molecules of electron transferring.

Abbreviation: UA: uric acid; NH_2-UA: nitrified UA; D-GL: D glucose; ETC: electron transfer chain.

The 20 connecting points offer 20 NH_2 and 20 C=O places. The C=O places will be connected by the NH_2 of the adenosine in the ATP, while the twenty NH_2 places will bound eight D-glucose, six acetic acid, two Flavine, two nicotinamide and two AA molecules (Table V). One further AA, connected to the ME3 connecting point, will activate the Fe_4-S_4 cluster (Table III).

	Flavine	nicotinamide	D-GL	acetic acid	AA	
4 8Fe-7S	2	2	8	2	2	
4 2Fe-2S				4		
1 4Fe-4S				1	1	
1 4Fe-3S				1		
ETC	2	2	8	8	3	23

Table V. Molecules bounded by C=O parts of the connecting points

Results of the energy-producing units

Table VI summarises the relation of the oxygen binding points to the oxygen-containing molecules and the results of ETC. The participating molecules are UA, NH_2-UA, H_2PO_4, and NO.

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	NH_2-UA	adenosine	Pi	H	CO_2	ribose	acetic acid	Pyruvate	new ADP	ATP
4 8Fe-7S	4	4	8	16	12	4	4	4	4	new 4
4 2Fe-2S			16	32	8					ADP-ATP 20
1 4Fe-4S			4	8	2					
1 4Fe-3S			4	8	2					
ETC	4	4	32	64	24	4	4	4	4	24

Table VI. Results of structures of energy transformations in the electron transferring

Abbreviation: NH_2-UA: nitrified UA; Pi: PO_3^{3-}

Continuous electron and ATP production, the two steps of ATP production

The process of energy conversion begins in the ETC. The first step produces aminated uric acid PO_3^{3-} and ADP molecules. Finally, ATP synthase produces ATP from ADP + PO_3^{3-}.

The SET-AG = ADP-Pu contains six ETCs + ATP synthase.

SET-OP = SET-AG + Pyruvate dehydrogenase complexes.

The ADP-producing unit (ADP-PU) is the smallest unit of energy transformation. The SET of Aerobe Glycolysis (SET-AG) consists of one ADP-Pus, placed in the peroxisomes.

SET of oxidative Phosphorylation (SET-OP) has SET-AG + Pyruvate dehydrogenase. SET-OP is located in the mitochondria.

Energy and CO_2 production in the energy-producing units

The creation of four new ATP molecules needs 20 ATPs, resulting in 20 ADP + energy used up by the process. The transformation results in the oxidation of 20 carbon atoms (Table VI). The energy obtained by the oxidation will provide energy for the twenty ADP-ATP transformations and the four new ATP.

Hypothesis Explanation

Glucose and ATP are the cells' most essential energy carriers. During glucose transformation, ATP might be formed in specific cell structures. Eukaryote cells have the SET-AG and the SET-OP. Accordingly, they can survive in hypoxic–anoxic conditions.

The Fe-S clusters might be connected by cys-S bounds, forming one METC, where the transformation is completed. We suppose, that instead of the seven [Fe_4-S_4] clusters suggested by Austin et al.[10] four [Fe_8-S_7] clusters of nitrogenase, one [Fe_4-S_4] and one [Fe_3-S_4] are in the ETC, forming the Adenosine Triphosphate Producing Unit (ATP-PU).

One [Fe_4-S_4] cluster four [Fe_2-S_2] clusters, one [Fe_3-S_4] cluster and four 8Fe-7S [Fe_8-S_7] clusters might be responsible for Pi production (Table VI).

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Six ETCs and the ATP synthase enzymes might form the METC, the SET-AG, which produces four ATP, 48 O^{2-}, 48 H^{+} and 24 CO_2 (Table VI). The 48 O^{2-} must react with 24 carbons, producing 24 CO_2. The carbon atom of the CO_2 originates from the eight carbon atoms of the eight glucose and 8 acetic acid molecules. ATP synthetase and many other specific enzymes are responsible for the proper function of the METC. The reaction of the SET starts when all segments of the chain are connected. AA plays a determinant role in creating continuity. The energy investment results in 20 ADP molecules. They will be regenerated in the ATP synthesises, using the energy obtained from the oxidation of 24 carbon atoms, before ending the transformation.

The summary of the hypothesis:

SET-AG:

4 UA + 4 NH_2-UA + 4 NHO + 32 H_2PO_4 + 8 D-glucose + 8 acetic acid = 4 ATP + 4 NH_2-UA + 4 Pyruvate + 4 acetic acid + 24 CO_2 + energy

SET-OP:

4 UA + 4 NH_2-UA + 4 NHO + 32 H_2PO_4 + 8 D-glucose + 8 acetic acid = 4 ATP + 4 NH_2-UA + 4 acetic acid + 24 CO_2 + [3x4=12 CO_2 by pyruvate dehydrogenase] + ENERGY

Energetic of the transformation

The creation of new ATP molecules needs energy. Twenty ATP starts the reaction, resulting in 20 ADP. During the transformation, 24 carbon atoms are oxidised, resulting in energy. This energy creates four new ATP and regenerates the 20 ADP molecules.

Discussion

The similarity between the hypothetic ETC compared to known structures.

Similarity and difference between the hypothetic ETC and the model of Austin[10]:

a. The four ADPs originate from two Flavin Adenosine Dinucleotides (FADs) and two Nicotinamide Adenosine Dinucleotides (NADs) (Illustration 21)

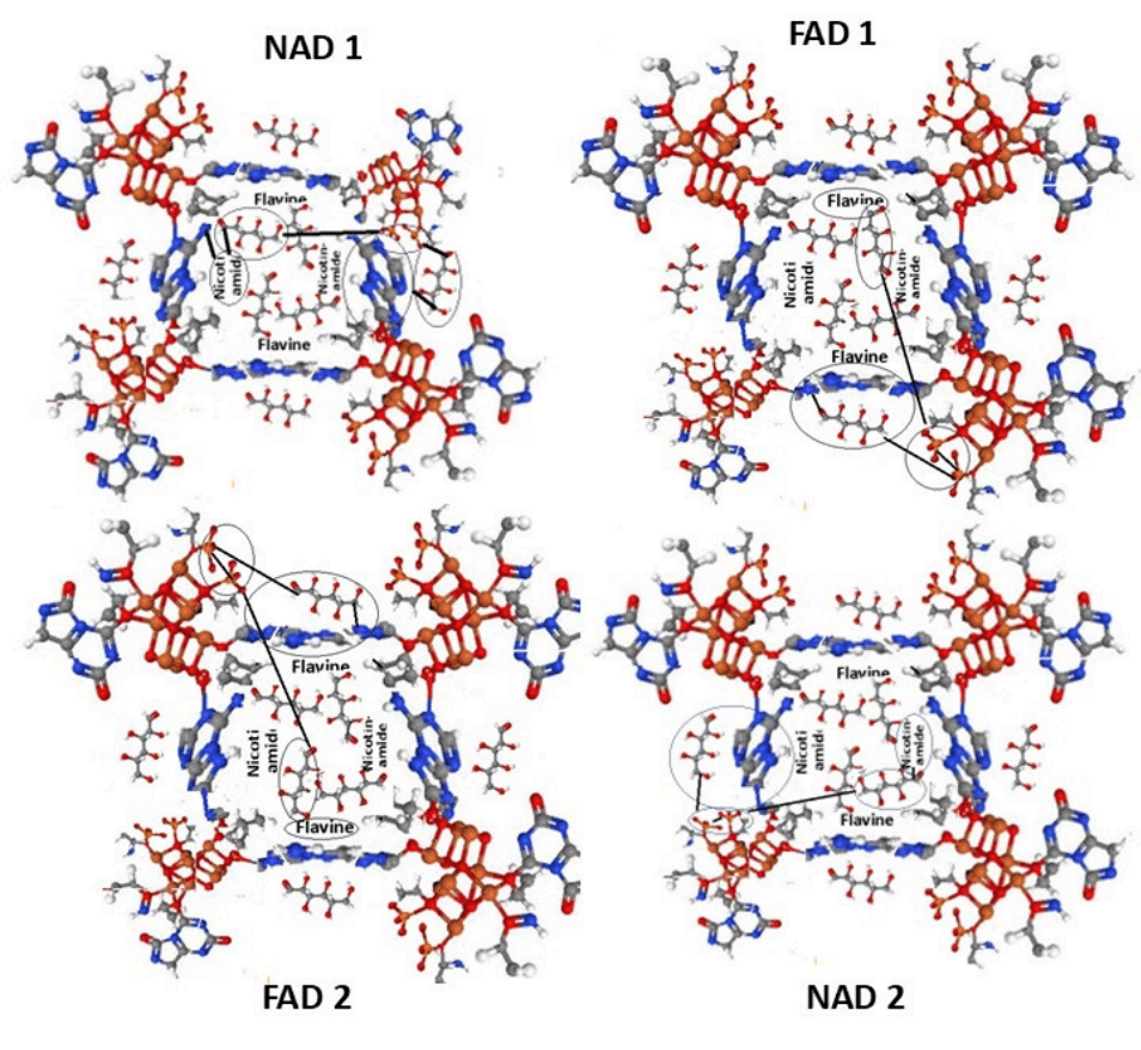

Illustration 21. Two FAD and two NAD molecules are in the ADP-producing unit.

b. We suppose that in complex I instead of the six Fe_4S_4 four Fe_8S_7 clusters are (Illustration 22).

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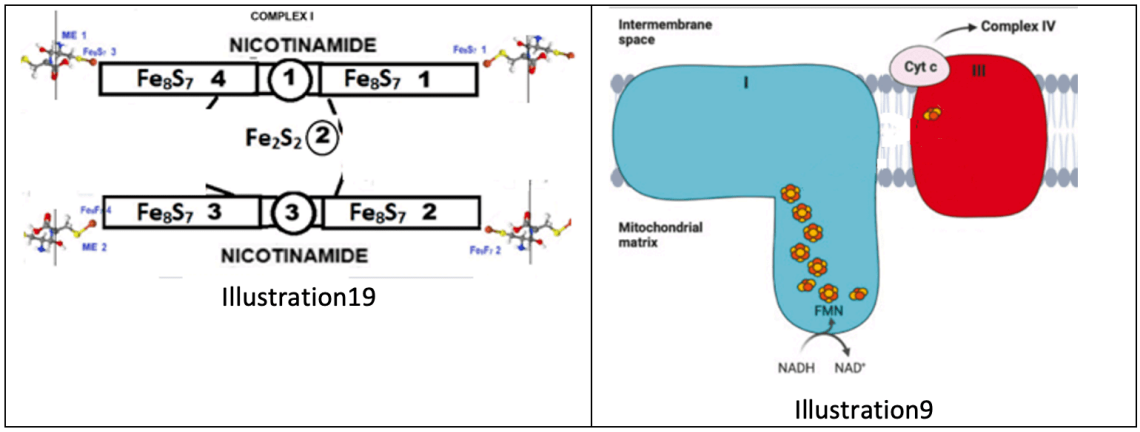

Illustration 22. The ETC contains 4 Fe_8S_7 clusters instead of the six Fe_4S_4 clusters.

c. We suppose the Fe-S clusters are connected to form the continuous METC. The Fe4S4 cluster bounds the neighbour ETC through Fe3S4; thus, it corresponds to complex II (Illustration 23).

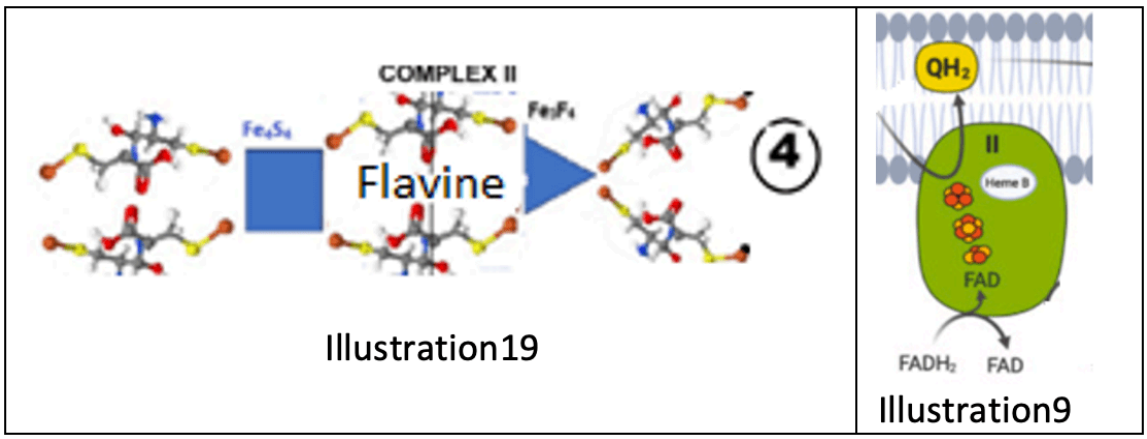

Illustration 23. The Fe_3S_4 clusters bound with the Fe_4S_4 clusters form the multiplex electron chain.

Korth et all supposed that two L-vitamin C molecules are in the NADPH pocket, presumably near the adenine binding site in the inner membrane of the mitochondria, based on molecular mechanistic docking computations[5].

In our hypothesis, two AAs are between the first and second Fe_8F_7 clusters, thus near the adenine binding site and one of the nicotinamide molecules in the inner membrane of the mitochondria (Illustration 14).

The hypothesis predicts that AA initiates the energy transformation, where new ATP, CO_2, H^+, acetic acid Pyruvate molecules and energy are produced from D-glucose molecules. The building of the four new ATP molecules needs the energy from twenty ATP molecules. Finally, the 24 ADP molecules will be converted to 24 ATP using the energy obtained from the oxidation of 24 carbon atoms (eight acetic acids and eight carbon of the glycose–ribose conversion). The process of transformation results in all METC producing 48 O^{2-}; they might destroy the cell if the glucose molecules are not available in the cell. The hypothesis opens the way to a successful intravenous vitamin C treatment of cancer.

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