Review of: "The dual energetic supply of eukaryotic cells"

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In this review article the author attempts to describe the two pathways of energy production in eukaryotic cells and suggests an important event in evolution of eukaryotes leading to development of modern bioenergetics of eukaryotic cells based on symbiotic fusion of ancient anaerobically fermenting pre-eukaryotic microorganisms (with developed defense features against increasing concentration of O_2 in atmosphere) and ancient aerobically respiring procaryotic cells which acquired bioenergetic machinery resembling that of modern mitochondria. The author proposes the existence of the Structures for Energy Transformations, SET-AG and SET-OP. The author does not clearly explain what AG and OP stand for, but from the content of the article it seems that SET-AG is the structure running anaerobic fermentation and SET-OP is the structure running oxidative phosphorylation (OXPHOS). The role of Hypoxia-Induced Factor-1 alpha (HIF), mentioned in this article, is to modulate activities of anaerobic fermentation and aerobic OXPHOS. In an aerobic environment HIF is inactivated by O_2-induced proteolysis, but in the absence of O_2caused by the injury of blood capillaries HIF activates about 200 genes which promote activation of anaerobic fermentation to supply energy needed for angiogenesis. The author argues that the activation of HIF triggered by the tissue injury and by the subsequent lack of O_2, which induces anaerobic fermentation, is an evolutionary acquired innate ability of eukaryotic cells to support efficient tissue rejuvenation. The author also points out that HIF and the rejuvenation of damaged tissue increases chances of cancer development and malignancy, however this important point is not discussed in the article and no citation(s) is/are given to support this point.

Overall, the narrative of this review article does attract attention, however, this article must be extensively revised should the author plan to publish it in a reputable journal. Below we list the critiques of certain statements and clauses in the article which need to be properly addressed.

1. The title “The dual energetic supply of eukaryotic cells” needs to be changed to “The dualenergy supply of eukaryotic cells”. The words energetic and energy have different meanings, and the author needs to use word energy in this article.
2. “It is well known that the energy supply of cells is provided by glycolysis ($C_6H_{12}O_6$ = 6 CO_2 + 6 H_2O + 2880 kJ/mol). However, this is only partly true. In fact, ATP is also formed from sugar simultaneously when carbon dioxide is

formed." The above must be totally revised. Glycolysis of 1 mole of $C_6H_{12}O_6$ produces 2 moles of ATP along with 2 moles of NADH and 2 moles of pyruvate. The reaction $C_6H_{12}O_6$ = 6 CO_2 + 6 H_2O + 2880 kJ/mol is not balanced (6 moles of O_2 are missing on the reactants side) and its use in the context of energy supply in eukaryotic cells is not appropriate. ATP is produced from ADP and phosphate, but not from "sugar" and ATP is not formed "simultaneously when carbon dioxide is formed."

3. "Energy transformation is realized in unique structures such as Structure for Energy Transformation (SET)." The author does not give any information on what the SET is. The author gives a section on the Fe-S clusters, but the author does not make it clear if the Fe-S clusters are the moieties of the SET. If the Fe-S clusters are part of the SET, what is the protein skeleton that stabilizes the Fe-S clusters in space? Is the SET an assembly of glycolysis enzymes and/or electron transfer complexes in the inner mitochondrial membrane? We have never heard the term SET used in the context of glycolysis and/or mitochondrial energetics. Author needs to clarify what the SET is. Also, author needs to clarify what kind of energy transformation occurs in the SET.
4. "The contemporary cell is now known as a mitochondrion [2]." Mitochondrion is not a cell. It is a cellular organelle.
5. The title of Table 1 "The structure of the electron shell of oxygen, sulphur, and iron" should be changed. It should read "The electron configurations of Oxygen, Sulphur and Iron."
6. "The outermost electron shell of iron can contain two, three, or four electrons (Table 1)." The above statement is not correct. The atom of iron contains only 2 electrons in the outermost shell, which is the 4^{th} shell – $[Ar]3d^64s^2$. The most common oxidation states of iron are +2 and +3 in which iron has electron configurations $[Ar]3d^6$ and $[Ar]3d^5$ respectively with no electrons in the 4^{th} shell. The Fe-S clusters contain only oxidized iron ions which do not have any electrons in the 4^{th} shell.
7. "In the case of anoxia, ADP-PU produces ten CO_2, while in an oxygenated environment, SET-OP forms 9 X (ten + six CO_2)." What is a time scale in which CO_2 is produced? Without the time scale it is impossible to assess the rate of production. The author does not provide a source for the above data. It is unusual to assess the rate of energy production by amount of CO_2 produced. Normally it is assessed by the rate of ATP synthesis.
8. "The process produces four O^{e2-}, producing two CO_2 or four H_2O molecules. Other Fe-S clusters might have similar nature. Thus, the P-cluster of nitrogenase might make six O^{2e-} (illustration 2)." What does letter 'e' mean in "O^{e2-}" and in "O^{2e-}"? Does it mean oxide with oxidation state negative 2? If so, why is letter 'e' used here? How are two CO_2 or four H_2O molecules produced? What process is involved? The author needs to explain this.
9. "The participating molecules are four UA, four NH_2-UA (four UA + four NH_3), six D-glucose, two L-ascorbic acids, and twelve $H_2PO_4^{e-}$." Mysterious letter 'e' is used again in "$H_2PO_4^{e-}$". We think the author is showing an electron 'e-' in the $H_2PO_4^-$ anion. If so, this is unconventional way of writing the term $H_2PO_4^-$ and letter 'e' must be removed.
10. "In contrast, cells use aerobic glycolysis offered by the Structure for Energy Transformation (SET)-Aerobic Glycolysis (SET-AG) in an anoxic environment (Illustration 7). [1]" This clause does not make sense. Aerobic means a process in presence of O_2. Anoxic environment means environment in absence of O_2. How could aerobic glycolysis be offered in anoxic environment? Also, there is no such term as "aerobic glycolysis".
11. The illustration 3 is difficult to understand and illustrations 4a and 5 are too small for visualization. The illustrations 4a, 4b and 5 do not have proper legends. The table in the end of this article is not numbered and does not have a title. It

looks like that the author refers to this table as Table 2, but it should be numbered and have the title.

12. “In the ‘open’ state, ADP and phosphate enter Complex V; in Illustration 8, this is shown in white.” The author refers to illustration 8, but there is no illustration 8 in this article.
13. The dual energy supply concept in the article is largely based on the units SET-AG and SET-OP, but the structure and location of these units are not given. We understand that SET-AG is responsible for anaerobic fermentation and SET-OP for OXPHOS. The article spreads the idea that glycolysis and OXPHOS are independent processes, while they are interconnected. Glycolysis is also not the only source of ATP. The important assertions about structure and function of SET-AG and SET-OP should be explained in more details and supported by citations. We assume that SET-OP is in mitochondria, but where exactly in mitochondria: matric, IMM or intermembrane space? The author gives no information where the SET-AG is located. These concerns should be clarified in details. Should author provide more clarity about the structure, function and location of SET-AG and SET-OP, it will make easier for readers to understand the key concepts of this article.
14. The Lynn Margilus' hypothesis and the evidence for the concept of Endosymbiotic Conception should be supported by bibliographic references.
15. In the illustration 1 it is not clear which cell, aerobic prokaryotic cell or pre-eukaryotic cell shown, is able to defend itself against the dangerous effects of O_2. The author needs to clarify this.
16. The section “Ribose” is irrelevant to the content of this article and should be removed.

In conclusion, this article deserves the readers’ attention, but it has to be thoroughly revised to properly address the critique listed by us above.