Review of: "Why We Stop Synthesizing Essential Amino Acids: The Extracellular Protein Hypothesis"

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Potential competing interests: No potential competing interests to declare.

The paper of Genshiro Esumi tries to provide an explanation as to why organisms can maintain their amino acid balance by solely synthesizing amino acids that are more abundant in extracellular proteins compared to intracellular proteins. He calls his hypothesis the Extracellular Protein Hypothesis.

The topic is interesting, as the proposed hypothesis represents a step towards the attempt to understand a phenomenon that is not easy to explain. As highlighted by the author, some important limitations remain due above all to the lack of studies on this topic; nevertheless, the hypothesis advanced seems plausible and is certainly worthy of attention to develop further studies.

I invite the author to consider some points listed below that, in my opinion, could improve the understanding of the results.

1. The term “amino acids” is used many times in the text. Therefore, the text could be lightened, and the generic acronym AA could be used. For the essentials, EAA; for non-essential, NEAA.
2. Similarly, with "Extracellular Protein Hypothesis” (EPH).
3. Pag 3. “*This suggests a potential simple correlation between the acquisition of feeding capabilities and the consequential loss of amino acid synthesis abilities*.” If this were true, since all food proteins always contain a large excess of non-essential AAs, organisms should have lost the ability to synthesize these and not the essential ones. The fact that EAAs are scarce in food proteins means that to satisfy their demand, it is necessary for the body to consume a large quantity of exogenous proteins, and therefore many NEAAs. These, if not used, must be deaminated and converted into energy in the Krebs cycle. From this perspective, the difficulty in obtaining EAA supplies and the inability to synthesize them seems more like a mechanism aimed at limiting survival.
4. Pag 4. “… *synthesis cost in units of high-energy phosphate bonds*..”, do they refer to those of ATP and GTP?
5. Pag. 6. “*I found that the eigenvector of the first principal component*…” I suggest better defining what is meant by the first principal component (PC1).
6. “*Unexpectedly, I found …. (Figure 2b)*” In the text, the reference to the figures should be sequential (2a, 2b, etc.), therefore start with figure 2a. Please modify.
7. “*PCA, a statistical method for extracting trends from high-dimensional data in order of their statistical significance*.” I think it is better to place this sentence in the first lines of the paragraph.
8. In my opinion, a section dedicated to "methods" could make the text more streamlined and easier to understand.
9. Figures. Generally, there must not be bibliographical references in the figures as they are already present in the text.

10. Table 2 and Table 3. What does the acronym LN mean? It would be more understandable to specifically indicate what the red bar and the blue bar mean.
11. Reference 1. No uppercase name. Please correct.
12. Reference 22. No uppercase names. Please correct.