

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

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This is an intriguing review paper about a hypothesis to explain the occurrence of essential amino acids that is based on ideas of intracellular protein pools as the main source of amino acids for protein synthesis in cells, and extracellular protein pools containing fewer essential amino acids than intracellular pools. This review paper is well-written and comprehensive. The manuscript may be further improved with the following suggestions:

- The topic of amino acid metabolism has been extensively studied for decades, and there are many papers and books published about the topic. I recommend leveraging that and extending the list of literature to cover most of the essential literature, especially that published in the recent 5 years.
- Suggest discussing the aspects of amino acid-derived compounds that are involved in cellular metabolism - for instance, monoamines and polyamines, which are amino acid derivatives that can be utilized by living systems as carbon and nitrogen sources if the amino acid pool is not sufficient.
- Generally, although amino acid metabolism is conserved among different groups of organisms, suggest narrowing down the topic to a certain group of organisms, e.g., eukaryotes/animals, plants, or bacteria, instead of spreading out and touching all organisms, which currently seems to be the aim of the current version of this paper.
- Many organisms are able to regulate the extracellular availability of amino acids and their breakdown by excretion of specific enzymes; I suggest discussing this topic in the frame of this paper as well. Examples are chitinases, e.g., in soil bacteria.
- Suggest discussing the aspect of involvement of the microbiome in human and animal cell amino acid metabolism. The gut microbiome has been proved to have a huge impact on the nutrient supply in human and animal metabolism.
- If the paper aims to analyze the topic generally in all kingdoms of life, I also suggest discovering the aspect of symbiotic organisms and their influence on amino acid synthesis and metabolism - e.g., nitrogen-fixing bacteria and their supply of nitrogen to plants as a precursor for amino acid synthesis.