

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.

It is an interesting hypothesis. However, the author is requested to revisit the hypothesis described in the manuscript again to further improve it with adequate examples. Extracellular proteins are born as intracellular proteins, which, at a later stage, become extracellular proteins based on functional requirements or the cellular signaling of the organisms. Moreover, the cytosol works as an amino acid buffer (both essential and non-essential), and the synthesis of proteins for an organism is governed by its genomic make-up. Therefore, it is unclear how the extracellular protein hypothesis is relevant in the context of essential amino acids. It is also not clear whether the author categorizes "fibrous proteins" as extracellular proteins and "globular proteins" as intracellular proteins.

A few additional points are noted below.

1. It is indicated in the manuscript that "the Extracellular Protein Hypothesis posits that non-essential amino acids are crucial for the synthesis of extracellular proteins, suggesting a new paradigm in understanding amino acid essentiality."
2. "While all proteins can serve as valuable amino acid resources when broken down, these proteins will not easily be recycled back into the cell or repurposed as resources for new proteins as intracellular proteins."

In the context of the above two points, the author should further elaborate on the hypothesis in the context of "insulin" or "hemoglobin."

1. It is also stated that "there are consistent differences in amino acid composition between extracellular and intracellular proteins."

The author is requested to include some statistical data or sequence comparison data for a few important extracellular and intracellular proteins (of human origin) having similar and dissimilar structures. How about the functional differences?

1. Page 6, last paragraph, "which are comparatively" - the statement is incomplete.