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 author introduces us to a topic largely known within the life sciences and yet, largely not understood within the community. The author, by introducing his concept of “The Extracellular Protein Hypothesis,” sought to, from his perception, correct the understanding that the non-essential amino acids are dubbed so because they can be synthesized. He argues that nutrition, which is one of the bases for making such classifications as essential vs. non-essential, cannot be solely depended on as a yardstick for classification. This is because (and reasonably so) it is essentially hard to argue that the nutritional constituents of various widely differing species are so similar as to account for very close similarities of the essential amino acids across these species. The second is the cost analysis of the EAA vs. the NEAA.

One of the reviewers has tackled some of the concerns, for example, the need for a bountiful supply of animal proteins to have the levels of EAAs required for the proper functioning of the organism. This fact is true. For example, the malaria parasite, the Anopheles spp., is intracellularly bound in vertebrates such as man, where it digests hemoglobin (in the blood) that supplies it with its EAAs. So, despite the variations in species, nutritional requirements from the food chains are very much similar since the organisms feed on themselves within the food web. However, it is reasonable to argue that probably, nutrition might not be all that there is to it.

Agreed, this is a challenging topic. Yet, the author has tackled it courageously. However, I believe that the author can still tie up some loose, "flailing" ends. For example, the author rightly tied up the NEAA with both syntheses and functions such as with the elastins and collagens, etc., in the extracellular matrix. These proteins serve very important structural purposes or functions. However, for the EAA, he suggests that they act to serve as amino acid buffers for the de novo synthesis of amino acids (which would then be the NEAA). I don't believe that this is even the primary function of the EAAs. This is because the proteins in the extracellular matrix can still be broken down and recycled backwards into the cell even at a high cost of amination (thus, essentially making the EAA “essential”). Therefore, even though *in vivo* pH buffering and amino acid building blocks are some of the functions of the EAA, the EAA is the reason for the hydrophobicity of membrane proteins that define cell homeostasis; viz, transport, catalysis, drug-protein interactions, the ribosomal structures responsible for the entire amino acid synthetic machinery, to mention a few. This functional fact could be one of the reasons why the EAA is intracellularly located (remember, the author did show in Fig. 1 the higher hydrophobicity of the EAAs) and **might** be a contributory fact to the selective synthesis of the extracellular proteins to maintain organisms' amino acid balance.

Suggestively, besides nutrition and synthesis cost, the core functions of the NEAAs and the EAAs are of importance in this regard. The points above are somethings to keep in mind (and incorporate if you want) since the depictions of the EAAs' role (by the author) are too simplistic or passing in my view.

However, this is a beautiful concept that would serve as a “healthy digest” for the life sciences community. Despite its limitations, even as agreed upon by the author, it would serve to introduce other possibilities to ponder upon as regards this topic and maybe stir research in an entirely new, or not previously explored, direction.