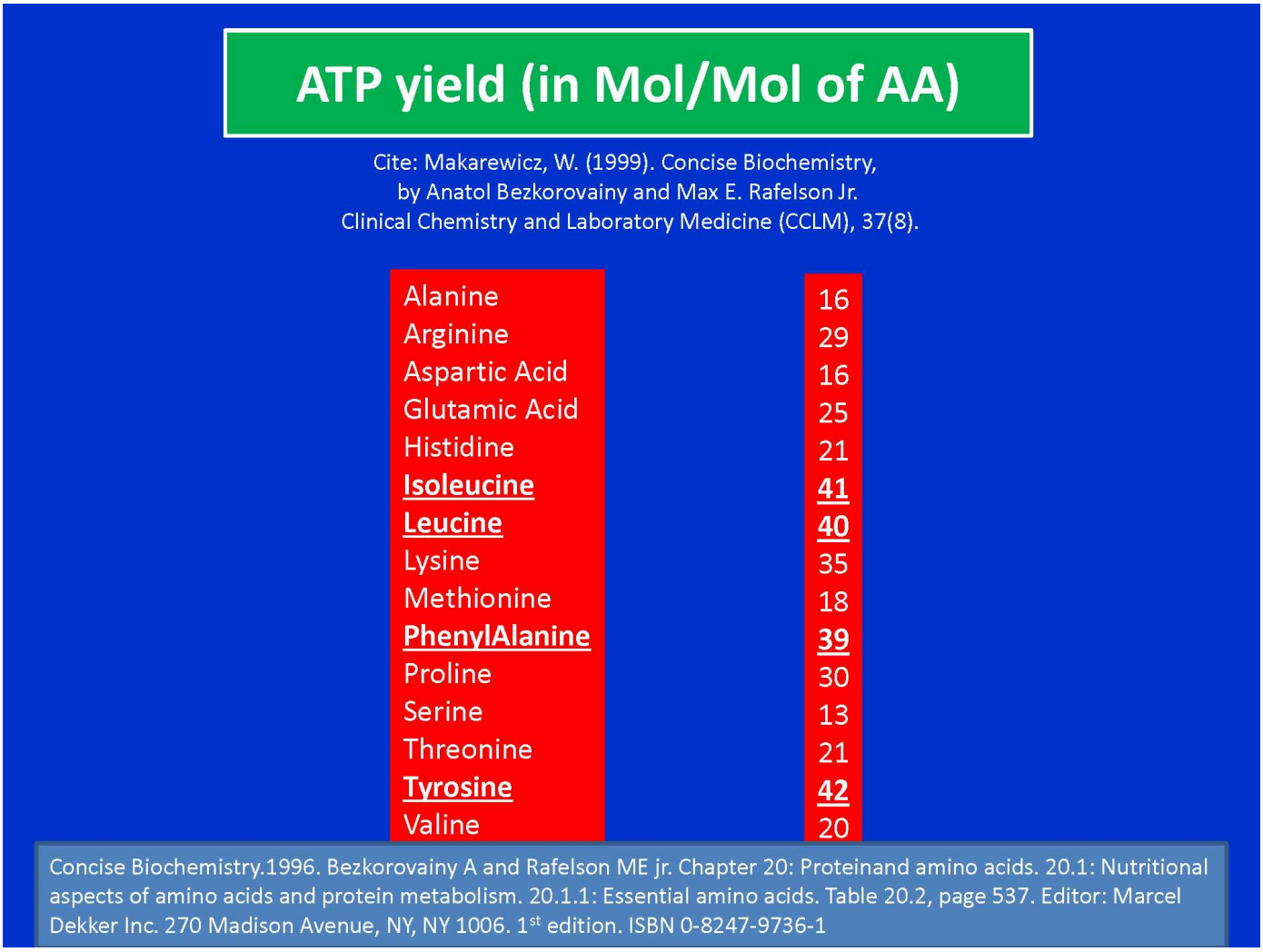
Review of: "Why We Stop Synthesizing Essential Amino Acids: The Extracellular Protein Hypothesis"

Francesco Dioguardi

Potential competing interests: No potential competing interests to declare.



Evaluation of "Why We Stop Synthesizing Essential Amino Acids: The Extracellular Protein Hypothesis" by Genshiro Esumi was extremely demanding. Esumi's Extracellular Protein Hypothesis (EPH) is worth reading, since he obliges us to think or re-think about the roots of life and its evolution. Esumi's paper is brilliant and stimulating. The observation that the most abundant proteins of the body, i.e., collagens, have a very poor content in essential amino acids (EAA), and that a similar excess in non-essential amino acids (NEAA) may characterize extracellular proteins, is wise and new. But the imbalance in the EAA/NEAA ratio (EAA/NEAA < or <<0,9) is present in any protein of the body, peculiarly in muscles, and some extracellular proteins, such as serum albumin, the most abundant

circulating protein, although EAA/NEAA <0,9, EAA is significantly present (https://www.uniprot.org/uniprotkb/A0A0C4DGB6/entry). It is of great interest that if stoichiometric ratios are calculated, the amino acid composition of the alimentary reference protein in humans, ovalbumin, shows that the number of molecules of 2 NEAA, alanine and glycine, is far more abundant (near +25%) than the number of molecules of all 5 EAA matching 75% of nitrogen needs in humans (leucine, isoleucine, valine, histidine, and lysine). Similar results may be found analysing actin or myosin in cells of muscles, the largest organ of the body in healthy humans. My concern, thus, is not about the possible bias provided by the lack of complete data on protein composition, but on the cause-effect relationship on which EPH is based. As very correctly indicated by the wise author, “the underlying reasons for this enigmatic pattern of individual and independent losses of similar amino acid synthesis capabilities in different eukaryotic lineages remain elusive and still unexplained,” still this very good paper indirectly suggests an important point: extracellular and intracellular proteins in mammals are based prevalently on EAA/NEAA < 0.9 since the content in EAA is lower than that in NEAA in any edible protein, and this is an evolutionary solution to reduce EAA intake dependency. It should be noticed, also, that very small amounts of synthetic capacity of quite any EAA have been shown also in humans, poorly sufficient to match only sudden and small requests by metabolism. Also, the inclusion of tyrosine in the area of conditionally EAA is noticeable; as already proposed by other authors, hydroxylation of phenylalanine to tyrosine is available only in liver cells, thus tyrosine is essential for any other cell of the body, explaining some of the results discussed by Esumi. Also, the rapid access to proteolysis when increased energy needs dominate metabolism and diet is not sufficient to match needs, seems to be further taken into account by Esumi. I would enclose a PDF with references indicating how efficient ATP production is by consuming amino acids for energy. The most efficient energy production by some amino acids does not spare the many less efficient ones to be wasted in emergency settings. Of notice, some pathological conditions appear to target selectively some tissues, as cancer does by affecting peculiarly collagens' integrity. Why some living beings at a certain point omitted the expensive paths driving to syntheses of those that we now call EAA and transmitted through evolution still remains unknown, in my opinion. Energy availability rules life or death, and the expensive synthesis of proteins by increasing ATP to AMP, in turn, rules MTORC inhibition by activation of AMPK and activation of autophagy, thus recycling of the less abundant EAA necessary to survive. Also, changes in amino acid concentrations have been proposed to rule protein synthetic drive, and lowest concentrations of EAA would promote a most significant modification by even small amounts of EAA provided by foods than the same amount if plasma concentrations were elevated, and this hypothesis explains why we can survive reduced protein intakes.

On the contrary, since EAAs promote and maintain protein synthesis, more or less 4 ATP is required for any peptidic bond, and summing intake and synthesis, if synthesis had not been deleted by evolution, would have been a threat to cell survival, altering energy needs and autophagy balance. A role for excess EAAs in most substrate- and energy-demanding cells, for protein duplication, including cancer cells, in triggering autophagy-driven apoptosis has been repeatedly reported.

These observations are not in contrast, but in consequence of Genshiro Esumi's wise thoughts. It was a burden, but also a privilege, to evaluate this very interesting and weighty paper.