Editorial Commentary

The optimal amino acid pattern for humans and its implications for nutrition of cancer patients

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Amino acids (AAs) are organic molecules containing both an amino group (-NH_2) and an acid group [e.g., carboxylic (-COOH) or sulfonic acid (-SO_3H)] (1). AAs occur in nature both freely and bound in peptides or proteins. The simplest AA—glycine—was detected in the coma of the comets 81P/Wild 2 (2) and 67P/Churyumov-Gerasimenko (3), and many more AAs have been found in meteorites (4). Laboratory experiments have shown that AAs, and even whole peptides, can form under conditions resembling those of the cold interstellar medium (5), supporting the notion that these building blocks of life were present on Earth at its very formation. All organisms on Earth, including the most primordial ones, use a ubiquitous genetically encoded set of 20 AAs to synthesize proteins and peptides. These 20 so-called "canonical proteinogenic AAs" (1) appear to have been optimized for building a broad variety of proteins, because they occupy the possible ranges of the three fundamental AA properties size, charge and hydrophobicity more evenly and broadly than other possible AA combinations (6). However, the relative amount of each of these 20 AAs that an individual organism requires for optimizing its physiological functions is species-specific and its estimation relies on approximate empirical methods—until recently, as we will explain in this editorial.

To synthesize a protein, eukaryotic cells first transcribe the corresponding protein-coding DNA region to a pre-mRNA molecule which subsequently undergoes splicing during which specific regions of the mRNA transcript, the introns, are cut out and only the protein-coding regions, the exons, are retained and pasted together (7). The resulting mature mRNA is translocated to the cytosol into ribosomes and translated into protein in a multistep process (1). The totality of exons is known as the exome, which accounts for approximately 1–2% of the eukaryotic DNA, depending on the species.

An organism's exome thus contains information about the relative proportion with which individual AAs are translated into proteins, providing a logical basis for deducing individual AA requirements for a given species. This has first been tested in a seminal study published in 2017, in which Piper *et al.* fed fruit flies with an "exome-matched" AA composition (8). This composition was derived *in silico* as the average relative proportion of each AA based on its prevalence in the entire exome; it differed significantly from the AA composition in natural or laboratory proteins (9). Piper *et al.* demonstrated that the exome-matched AA diet decreased uric acid production, was more satiating, enhanced growth and increased reproduction compared to a diet containing a non-matched AA composition (8). They also were able to predict which of the so-called essential or indispensable AAs is limiting in a given dietary protein by comparing each of the essential AA's relative concentration

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in the dietary protein to the one in the exome-matched protein.

In a recent study published in the *Journal of Agricultural and Food Chemistry*, a team led by Quingping Wu and Yizhen Xie from the Guangdong Academy of Sciences, China, now derived the exome-matched AA pattern for humans and for the first time tested its application in cancer treatment by using tumor-bearing mice fed with their species-specific exome-matched AA composition (10). Based on approximately 123,000 protein sequences translated from the exome regions for humans and 87,000 for mice, the authors first computed the relative AA composition requirements for each species. The resulting essential and conditionally essential AA pattern for humans was shown to approximately match that recommended by the World Health Organization. A further comparison with soy protein and whey protein isolate—two dietary proteins known to contain all essential AAs for humans—showed that soy protein had limiting amounts of the essential AAs methionine and leucine, while whey protein contained all essential AAs in adequate proportions, thus confirming the superior protein quality of whey protein isolate compared to soy protein and the general possibility to utilize exome-matched AA proportions to evaluate protein quality (10).

The major focus of this study, however, was on the effect of feeding a diet aligned with the exome-matched AA composition to mice inoculated with highly metastatic 4T1 murine breast cancer cells. Mice were divided into four different groups of which all received paclitaxel chemotherapy, but which differed in protein supplementation: one group received a nutritional supplement designed for cancer patients at a dose of 18 g/kg/day; one group received the same supplement at 18 g/kg/day, but adjusted by adding the underrepresented AAs serine and glycine to closely match the AA pattern predicted from the murine exome translation data; one group received the unadjusted supplement but at double dosage (36 g/kg/day); and one group received no nutritional supplement in addition to the standard diet.

First, it is important to mention that additional protein supplementation, independent of composition and dose, did not promote tumor growth compared to the group receiving no protein supplement. However, mice receiving additional protein had higher body mass during the third and final week of the experiment. This justifies clinical guidelines according to which cancer patients should aim at protein intakes in the higher range of 1.5–2 g/kg/day in order to compensate for systemic inflammation and tumor-induced muscle protein degradation, without having to fear that additional AAs could "feed the tumor" (11). In fact, cancer cells are quite independent from dietary AA consumption, because they frequently utilize glutamine as an energetic fuel whose plasma levels are hardly influenced by diet (12); or they cannibalize their host by using a process called macropinocytosis in which whole peptides and proteins are internalized into the cell and subsequently broken down into AAs in order to supply anabolic and catabolic (energy-generating) substrates (13).

A second important observation was that mice receiving the AA-adjusted protein supplement could increase their grip strength significantly more than the mice receiving either no or the unadjusted, glycine- and serine-deficient protein supplement. However, the group receiving the latter at double dosage could increase their grip strength to a similar degree as the mice receiving the adjusted protein formula. Follow-up analyses of the transcriptome profile of skeletal muscle tissue revealed significant differences between the groups receiving the unadjusted and adjusted protein supplement regarding the expression of genes related to immune system modulation within the skeletal muscle microenvironment. In particular, expression of the protein complement 3 (C3) was significantly upregulated in muscle cells from mice having received the adjusted protein supplement. C3 is the central activator of the complement system and has been shown to facilitate muscle regeneration (14). There was also a statistically significant decrease in B cells and increase in monocytes in the skeletal muscle microenvironment of mice receiving the adjusted protein formula, which suggests a link between immune system modulation and increased grip strength development in these mice mediated by receiving an optimal AA pattern.

A third interesting result of the study was that protein supplementation counteracted the paclitaxel-induced gut dysbiosis which consisted in an increased *Firmicutes*-to-*Bacteroidetes* ratio in stool samples. Interestingly, mice receiving a double dose of the unadjusted protein supplement had the lowest *Firmicutes*-to-*Bacteroidetes* ratio, suggesting that the quantity of AAs may be more important for restoring chemotherapy-induced dysbiosis than AA quality. However, there appeared to be some additional benefits of AA adjustment towards the exome-based AA pattern since the adjusted supplement group had a significantly higher relative abundance of bacteria from the genus *Alistipes* than the unadjusted supplement group; these bacteria were previously shown to be more prevalent

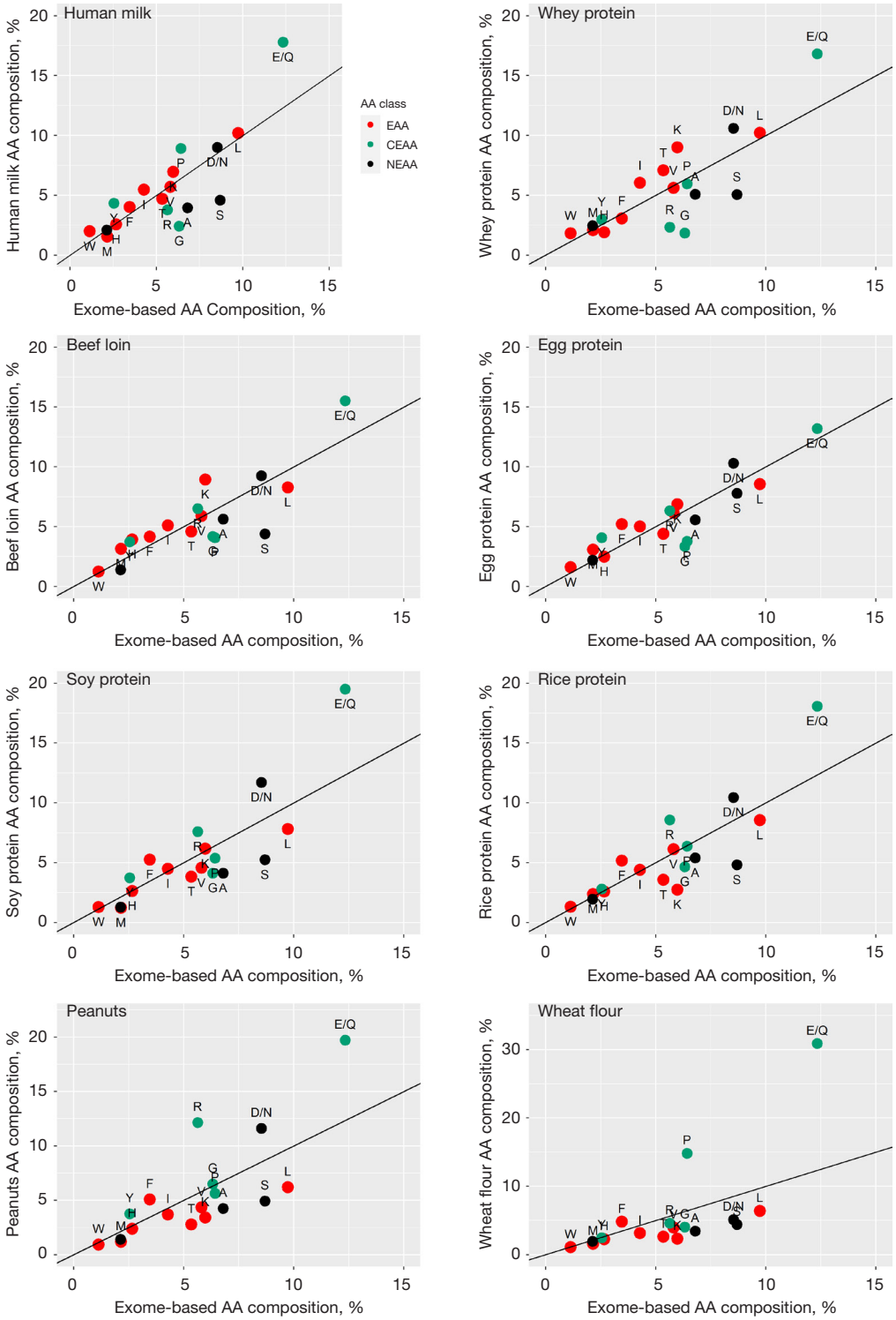

Figure 1 A comparison between the human exome-based AA pattern (x-axis) and several animal- and plant-based protein compositions (y-axis). The AA pattern for whey and soy protein were taken from Morifuji *et al.* (19), the pattern for human milk from *Tab. 8* in Zhang *et al.* (20), and the other profiles from Wu (1). AA, amino acid; EAA, essential amino acid; CEAA, conditionally essential amino acid; NEAA, non-essential amino acid; E/Q, glutamic acid/glutamine; D/N, aspartic acid/asparagine; A, alanine; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; P, proline; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

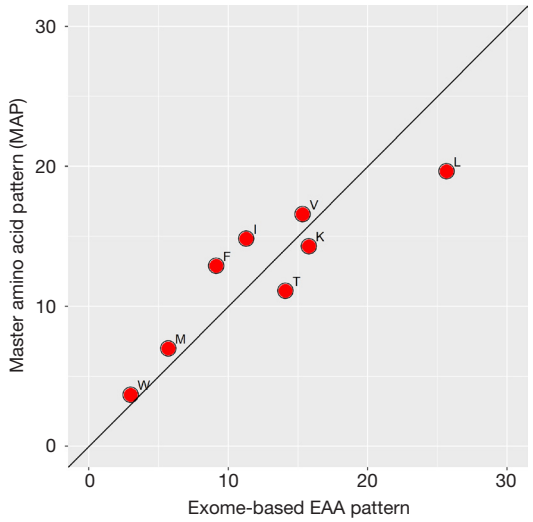

Figure 2 A comparison between the relative AA concentration in the "master amino acid pattern" (MAP) supplement and the exome-based AA pattern when restricted to the eight essential AAs present in MAP. AA, amino acid; EAA, essential amino acid; F, phenylalanine; I, isoleucine; K, lysine; L, leucine; M, methionine; T, threonine; V, valine; W, tryptophan.

in elderly humans who are physically fit (15), suggesting that protein quality may affect muscle functioning also by modulating the gut microbiome. However, the broader translational implication of this finding is unclear, since currently 13 species of *Alistipes* are known and some of them may also behave pathogenic in certain contexts (16).

The study by Gong *et al.* (10) elegantly connects the topic of species-specific AA requirements with translational breast cancer research. It also confirms the notion that protein quality is at least as important as protein quantity, which should be considered when discussing optimal diets for cancer patients. For the first time, the optimal AA pattern for humans has been deduced in a logical way from genomic information rather than measured. The empirical estimation of AA requirements is a difficult task, is not possible for all canonical AAs simultaneously and yields different results, depending on the method (17). This is also reflected in different protein quality metrics, which also vary according to the AA pattern they are compared against (18). In contrast, the exome-based AA pattern calculated by Gong *et al.* could serve as a new reference against which the quality of different food proteins can be evaluated. This is exemplarily shown in *Figure 1*, where I have plotted the relative AA composition of various food protein sources against the exome-based AA composition. The quality of a food protein source could be scaled according to the number and extent of indispensable (essential) AAs which fall below the diagonal line in a plot such as the ones displayed in *Figure 1*. For example, one could use the relative concentration of each essential AA in a given food and in the exome-based AA pattern whose minimum defines the first limiting essential AA (8). *Figure 1* shows that proteins of animal origin have less limiting essential AAs than plant proteins, and the deviations of most conditionally essential or nonessential AAs from the ideal AA concentration (the solid line with slope 1) are also smaller. With the exception of soy, most plant proteins are limiting in more than one essential AA and therefore have significantly lower quality than proteins of animal origin. In addition, many edible plants contain phytochemicals known as antinutrients which further reduce protein quality by inhibiting the activity of intestinal proteases and peptidases and thus attenuate the hydrolysis of proteins into absorbable peptides and AAs (21,22). The question of protein quality is highly relevant for cancer patients who often require a higher-than-normal AA supply in order to compensate for AA consumption by their tumors and tumor-induced muscle protein degradation (11). Hence, translating the findings of Gong *et al.* into clinical practice, it is expected that animal proteins will benefit cancer patients' skeletal muscle tissue and its immune environment more than equal amounts of plant proteins.

Other clinical innovations that could advance from this study include the provision of exome-based AA supplements to cancer patients or to adjust their dietary proteins to approximately match the exome-based AA pattern by using single AAs. A popular supplement originally called the "master amino acid pattern" (MAP) is available in many countries worldwide and we have used it together with a ketogenic diet in a clinical study of breast cancer patients (23). MAP is only composed of eight essential crystalline AAs (*Figure 2*) and according to a study by its inventor, Prof. Lucà-Moretti, could be used as the sole dietary protein source with a net nitrogen utilization close to 100% (24). However, while theoretically all nonessential AAs could be synthesized *de novo* from essential AAs, it has also been shown that in the longer term, diets composed of only the essential AAs are suboptimal for growth, muscle mass acquisition and reproduction (25). In contrast, exactly these traits were shown to be optimized with complete and optimal species-specific AA patterns (8,10,26), so that it would be interesting to compare an exome-based AA supplement

against MAP or similar supplements in the future.

What future studies should also investigate is the effect of aligning the dietary AA pattern of patients or healthy subjects with the human exome-based AA pattern. Outcomes of interest would include the effects on muscle strength and transcriptional profiles, immune cells and their cytokines, the microbiome and detoxification pathways, since it would be expected that an optimal AA pattern minimizes the amount of AAs being catabolized and producing nitrogen waste which needs to be detoxified. It would also be interesting to conduct dose-response studies with exome-based AA formulas and find out whether and how gender, age and lifestyle factors such as exercise would affect the intensity of protein transcription, which changes the need for certain AAs, but is not taken into account by the exome-based proportioning of AAs. It is now time to expand the preclinical research on exome-based AA optimization and translate the findings into the clinic.

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Footnote

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