Unraveling the Nutritional Significance of Essential Amino Acids through Synthesis Cost and Cellular Allocation

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Abstract

In human clinical nutrition, it is broadly accepted that essential amino acids are critical for muscle and other body protein synthesis. However, the connection between humans' loss (or cessation) of biosynthesis for these amino acids and their nutritional significance remains largely unexplained. Interestingly, observations in plants—which can produce all 20 proteinogenic amino acids—indicate that supplementation with amino acids deemed essential to humans inhibits plant growth, whereas most nonessential amino acids do not. More precisely, this growth-inhibitory effect corresponded solely to amino acids that are 'high-cost' in terms of biosynthesis.

These findings formed a key basis for the hypothesis developed here. By integrating them with prior research on "Economical Evolution" in bacteria and my subsequently proposed "Differential Recycling Efficacy Framework," I present an additional inference: high-cost amino acids tend to be more abundant in cytoplasms where resource recovery is easier, and this cellular allocation drives their role as triggers for cytoplasmic protein synthesis. This hypothesis speculates that the reason plant growth is inhibited by high-cost amino acids is that, although plants need to break down nutrients stored during the day at night for their growth, externally supplied high-cost amino acids may suppress the plant's protein degradation process.

This new hypothesis, termed the **Allocation-Derived Significance Hypothesis**, posits that an amino acid's biosynthetic cost determines its nutritional role via its cellular and subcellular allocation. Since this cellular-allocation-based concept of nutrition is novel, it may offer a fresh perspective in the life sciences and provide new insights for clinical nutrition.

Keywords: Essential amino acids, Amino acid synthesis cost, Economical Evolution, Differential Recycle Efficacy Framework, Allocation-Derived Significance Hypothesis

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Introduction

In human clinical nutrition, it is broadly accepted that essential amino acids are critical for muscle and other body protein synthesis [1]. Among these essential amino acids, branched-chain amino acids (BCAAs) in particular are often recommended for their recognized ability to promote muscle growth [2]. In contrast, nonessential amino acids are rarely considered to have comparable nutritional value. Indeed, in standard formulas for assessing dietary protein quality based on amino acid composition, only the content of essential amino acids is factored into the calculation, while nonessential amino acids remain excluded [3].

However, the causal connection between the nutritional importance assigned to certain amino acids and their essentiality—regarded here as the evolutionary loss of their biosynthetic pathways—remains poorly understood. For instance, leucine is well known in mammals as a potent activator of protein synthesis via the mTORC1 pathway, yet comparable leucine-dependent activation of TOR signaling is also observed in other eukaryotes—including *Saccharomyces cerevisiae*, which retains the full biosynthetic capacity for all 20 proteinogenic amino acids [4]. These observations suggest that leucine's nutritional significance cannot be explained solely by the secondary loss of its biosynthetic pathway and may instead reflect other evolutionary pressures.

On the other hand, among the 20 proteinogenic amino acids, there are notable differences in their synthesis cost—i.e., the resources and energy required for their biosynthesis [5,6]. The disparity between the least and most expensive amino acids can exceed sixfold, implying that such cost differences are unlikely to be biologically negligible [5,6]. In my previous work, I proposed the **DRE Framework**, positing that this disparity in amino acid synthetic costs could underlie both the compositional gap between intra- and extracellular proteomes and the essential–nonessential distinction observed in animals [7]. In this paper, I extend my reasoning in a new direction by introducing the **Allocation-Derived Significance Hypothesis**, which proposes that differences in amino acid synthesis cost may also explain the nutritional significance of essential amino acids.

Reevaluation of Previous Findings

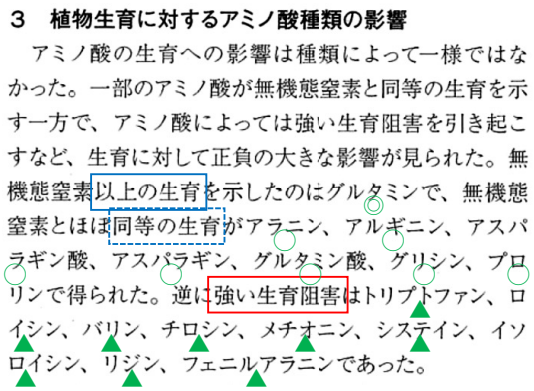
This section presents and evaluates two figures that combine data from previously published papers, thereby providing the background for the hypothesis proposed in this study.

Figure 1 pairs a textual summary (on the left) with a corresponding graph (on the right). The text on the left, written in Japanese, consolidates findings on the growth responses of five crop species when each amino acid is supplied as a fertilizer [8]. Glutamine (Gln), which exhibited particularly strong growth, is marked with a "◎"; amino acids considered comparable to inorganic fertilizers are marked with a "○"; and those that inhibited plant growth are marked with a "▲." On the right is a bar graph from a recently published preprint [6], which displays each amino acid in order of its

calculated synthesis cost—i.e., the sum of the required substrate materials and energy needed for biosynthesis. Additionally, the growth-response marks (“◎,” “○,” “▲”) corresponding to each amino acid on the left have been added to the respective amino acids in the bar graph on the right.

In that bar graph, essential and nonessential amino acids generally separate into left and right sides, except for the notable exceptions of tyrosine (Tyr) and cysteine (Cys). Notably, “◎/○” and “▲” also aligned according to that essential–nonessential boundary, dividing into opposite sides. More precisely, “◎/○” and “▲” segregated according to whether the amino acids were low-cost or high-cost, respectively, indicating that higher-cost amino acids inhibited plant growth. This suggests a clear trend: the more expensive the amino acid is to synthesize, the greater the negative impact on plant growth.

Figure 1. Growth Responses to Amino Acids and Their Synthesis Cost in Crop Species



３　植物生育に対するアミノ酸種類の影響

アミノ酸の生育への影響は種類によって一様ではなかった。一部のアミノ酸が無機態窒素と同等の生育を示す一方で、アミノ酸によっては強い生育阻害を引き起こすなど、生育に対して正負の大きな影響が見られた。無機態窒素以上の生育を示したのはグルタミンで、無機態窒素とほぼ同等の生育がアラニン、アルギニン、アスパラギン酸、アスパラギン、グルタミン酸、グリシン、プロリンで得られた。逆に強い生育阻害はトリプトファン、ロイシン、バリン、チロシン、メチオニン、システイン、イソロイシン、リジン、フェニルアラニンであった。

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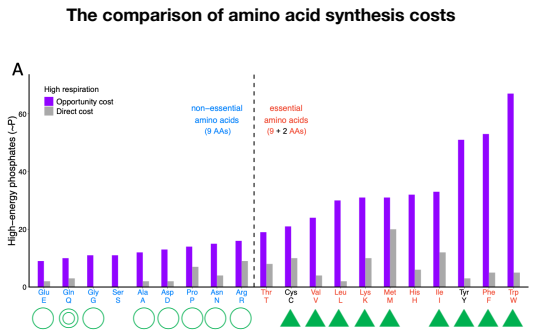

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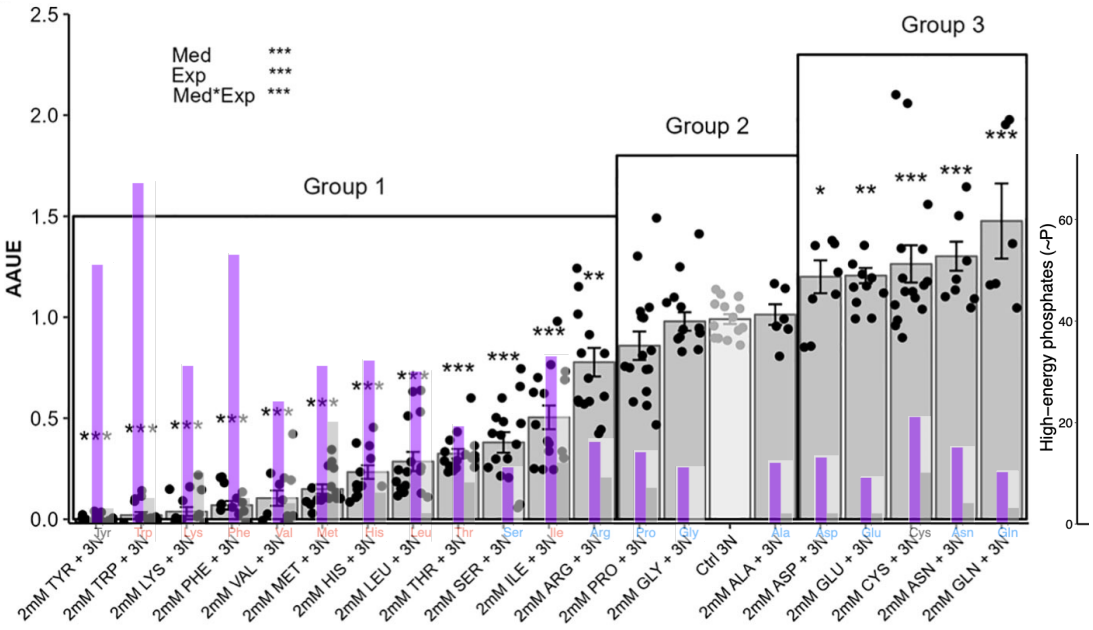
On the left, a Japanese textual summary consolidates results from five crop species grown with each amino acid as a fertilizer [8]. Amino acids marked “◎” showed notably strong growth (e.g., glutamine), while those marked “○” exhibited growth comparable to inorganic fertilizers, and those marked “▲” inhibited growth. On the right, a bar graph (adapted from a recently published preprint [6]) orders each amino acid by its synthesis cost—the total substrates and energy required for biosynthesis. The same growth-response marks (“◎,” “○,” “▲”) are overlaid on each bar. Essential and nonessential amino acids generally segregate to opposite ends of the cost scale, with tyrosine (Tyr) and cysteine (Cys) as exceptions. Notably, high-cost amino acids (“▲”) tended to inhibit plant growth, whereas lower-cost amino acids (“◎/○”) supported neutral or enhanced growth. This trend underscores a potential link between higher biosynthetic cost and greater inhibitory effects on plant growth.

Figure 2 shows results from a study in *Arabidopsis thaliana*, where an ample supply of inorganic nitrogen is provided, and additional amino acids are then supplied as nutrients [9]. In the graph, amino acids placed farther to the right indicate better growth (as measured by AAUE), while those on the left indicate poorer growth. Overlaid on these positions are the same amino acid synthesis cost data used in Figure 1 [6]. The results reveal a strong negative correlation (r = –0.75) between amino acid synthesis cost and the plant's growth index (AAUE, calculated as log(x+1)).

Figure 2. Amino Acid Synthesis Cost and Growth Index (AAUE) in *Arabidopsis thaliana*



This figure presents data from *Arabidopsis thaliana* experiments in which sufficient inorganic nitrogen was supplied, followed by additional supplementation with various amino acids [9]. Amino acids plotted farther to the right indicate better growth (higher AAUE), whereas those to the left show poorer growth. The same synthesis cost data used in Figure 1 are overlaid on the x-axis [6], revealing a strong negative correlation (r = –0.75) between amino acid synthesis cost and the plant's growth index (AAUE, calculated as log(x+1)). These findings suggest that higher-cost amino acids are associated with reduced growth performance under these experimental conditions.

Interestingly, although plants are capable of synthesizing all 20 proteinogenic amino acids and, therefore, in principle, are not constrained by the essential–nonessential amino acid boundary, the data in both **Figure 1** and **Figure 2** show growth responses that appear to parallel the division between essential and nonessential amino acids in humans. Moreover, closer examination indicates that the inhibitory effect correlates more strongly with the "synthesis cost" of amino acids—encompassing both the substrate and the energy required for biosynthesis—than with their essential or nonessential classification.

Additional Background

This section summarizes existing information relevant to the current hypothesis on how amino acid synthesis cost affects amino acid utilization in living organisms, as well as what is currently known about amino acid sensing at the cellular level.

A key insight into the relationship between amino acid synthesis cost and amino acid usage emerged from studies estimating the biosynthetic costs of amino acids in bacteria, which culminated in the milestone paper “Economical Evolution” [10]. Economical Evolution demonstrated that bacteria tend to use low-cost amino acids in the proteins they secrete extracellularly, resulting in the extracellular proteome having a lower overall synthesis cost compared to the intracellular proteome.

Building on this concept, I proposed the **Differential Recycling Efficacy (DRE) Framework**, arguing—based on statistical analyses of publicly available data from various organisms—that the idea of Economical Evolution may also apply to multicellular eukaryotes [7]. The DRE Framework posits that, within the compartments formed over the course of biological evolution, there are inherent differences in how easily resources can be recovered. These differences likely influence the distribution of amino acids according to their synthesis cost, causing high-cost amino acids to predominate in compartments where resource recovery is relatively easy, and low-cost amino acids to be allocated where recovery is more difficult. Originally, the DRE Framework was intended to explain how the disparity in amino acid composition between intracellular and extracellular proteomes in animals might have driven the classification of amino acids into essential and nonessential categories.

Another key factor involves the Target of Rapamycin (TOR) system, a nutrient-sensing pathway common to eukaryotes. In organisms such as animals and yeast, amino acids like leucine and arginine are known to activate TORC, triggering intracellular protein synthesis and simultaneously suppressing autophagy, an intracellular degradation pathway [4]. Recent findings indicate that, in plants, branched-chain amino acids (BCAAs)—including leucine—also activate TORC, eliciting anabolic reactions similar to those in animals and yeast [11]. Viewed in isolation, this suggests that high-cost BCAAs could also serve as factors promoting protein synthesis in plants.

However, as shown in the previous section, plants exhibit a correlation between the biosynthetic cost of amino acids and their nutritional effects, such that higher-cost amino acids inhibit plant growth. Because this correlation has not been previously noted, no hypothesis has been proposed to explain its underlying cause. In the following section, I will integrate the information presented thus far and examine the differences between animals and plants, thereby constructing a hypothesis that elucidates the background behind these observations.

Hypothesis Formulation

This section presents a formulation of a hypothesis that integrates the findings discussed so far.

In animals, essential amino acids are believed to act as triggers for growth [12]. However, as shown in Figures 1 and 2, high-cost essential amino acids appear to inhibit growth in plants. Thus, it would seem that the growth effects of high-cost versus low-cost amino acids are completely reversed between animals and plants. Nevertheless, BCAAs also exhibit similar effects at the cellular level [11], suggesting that this reversal may stem from fundamental differences between these types of multicellular organisms (i.e., animals and plants).

Animal bodies typically contain a greater proportion of protein (by weight) than plant bodies. Consequently, increases in animal body mass inherently involve large amounts of protein synthesis. In contrast, plant growth is thought to depend more heavily on extracellular cellulose production and vacuolar expansion, making protein synthesis a comparatively smaller contributor to overall biomass increase. Additionally, it has been proposed that plants store nutrients produced via photosynthesis during the day and break them down at night to drive growth; in this process, autophagy is believed to play a vital role [13].

Autophagy is a cellular function shared by all eukaryotes—including animals, plants, and yeast—and leucine, which is high-cost and essential in humans, has been reported to suppress autophagy in these organisms. Accordingly, continuous supplementation of such amino acids would likely trigger protein synthesis in plants while inhibiting autophagic protein degradation. Because plants must rely on stored nutrients at night, a steady external supply of leucine would oppose this autophagic process. Therefore, I hypothesized that the divergence in strategies for amino acid utilization in body composition between plants and animals could be a key factor behind the contrasting nutritional effects of amino acids in these organisms.

From this perspective, the gap between high-cost and low-cost amino acids may drive differences in each amino acid's nutritional significance within the cell, based on the following three background factors:

1. **Synthesis Cost Disparities**
   Each of the 20 proteinogenic amino acids has a specific synthesis cost, and the gap between the least and most expensive is estimated to exceed sixfold [5,6].

2. **Subcellular Distribution Imbalances**
   These cost disparities appear to create imbalances in amino acid allocation across subcellular compartments. The cytoplasm, where protein synthesis occurs, can be regarded as a compartment with relatively easy resource recovery. However, plants allocate amino acids differently than animals do; for instance, the extracellular matrices of animals are largely protein-based, whereas plants store substantial quantities of free amino acids in the vacuole. These stored amino acids are often highly hydrophilic and low in cost. Within the DRE

Framework, the vacuole can be viewed as an “extracellular-like” compartment within the cell that preferentially sequesters low-cost amino acids [7].

3. **Triggering Cytoplasmic Protein Synthesis**
   If plant cells initiate cytoplasmic protein synthesis in response to some external signal—possibly associated with de novo amino acid synthesis during photosynthesis—and the cytoplasm already contains a high fraction of high-cost amino acids, then it is more logical for these high-cost amino acids to serve as the trigger rather than low-cost ones. Depending solely on low-cost amino acids as the trigger could lead to a relative shortage of high-cost amino acids once protein synthesis begins.

Based on these three considerations, it can be inferred that differences in amino acid synthesis cost lead to subcellular compositional disparities, thereby causing each amino acid to differ in its “nutritional trigger” role.

Allocation-Derived Significance Hypothesis

Building on the reasoning outlined in previous sections, I propose the **Allocation-Derived Significance Hypothesis**, which aims to clarify why the cost of amino acid synthesis imparts a distinct nutritional role to each amino acid. Specifically, the hypothesis posits that disparities in amino acid synthesis cost drive differences in their allocation across subcellular compartments, resulting in corresponding variations in each amino acid’s function as a “nutritional trigger.”

This hypothesis originally arose from the observation that in plants—where the distinction between essential and nonessential amino acids should presumably be irrelevant—the nutritional effects of these amino acids appear reversed compared to those in animals, yet they neatly divide in accordance with the essential–nonessential boundary.

From a broader perspective, the hypothesis suggests that in cellular organisms—whether animal or plant—cells universally rely on intracellularly abundant, high-cost amino acids to trigger intracellular protein synthesis, and that these high-cost amino acids happen to be the ones classified as “essential.”

Accordingly, this paper proposes that phenomena traditionally viewed as reflecting a nutritional divide between essential and nonessential amino acids in living organisms may not hinge on the loss of biosynthetic capability itself. Rather, they may arise from cost-driven disparities in amino acid composition across biological compartments (including the cytoplasm, extracellular matrices, and vacuoles), which ultimately shape each amino acid’s distinct nutritional role.

Discussion

A long-standing question in human clinical nutrition has been why essential amino acids—those that humans have lost the ability to synthesize—hold special nutritional significance. While analyzing plant-based data, I found that amino acids appear to diverge in their nutritional effects—either promoting or inhibiting growth—both in accordance with the essential–nonessential classification and, more precisely, based on their respective synthesis costs. This phenomenon has not been documented previously and thus has never been explained.

However, with these seemingly paradoxical findings, a path toward resolving the mystery of essential amino acids' nutritional significance has begun to emerge. Building on these insights, I integrated the concepts of Economical Evolution and the DRE Framework—both of which demonstrated cost-based amino acid allocation—with existing knowledge to date. This line of reasoning led to the **Allocation-Derived Significance Hypothesis**, which posits that differences in synthesis cost drive subcellular amino acid allocation, and that this allocation in turn determines whether a particular amino acid functions as a trigger for intracellular protein synthesis.

Reflecting from this new perspective, I began to consider that the conventional understanding that "essential amino acids stimulate protein synthesis" might not be entirely accurate. Nearly a century has passed since human essential amino acids were identified and reported, during which time the concept that "the content and balance of essential amino acids are crucial in assessing nutritional value in nutrition science" has become firmly established [14]. While this appears to hold true clinically, in reality, recent studies indicate that tyrosine—traditionally classified as nonessential—behaves more like an essential amino acid in *Drosophila* experiments [15]. In fact, among the 20 proteinogenic amino acids, tyrosine ranks third in terms of synthesis cost. If a so-called "nonessential" but high-cost amino acid such as tyrosine shares the same nutritional significance as essential amino acids, this finding supports the present hypothesis: that the determinant of nutritional roles lies not in whether an organism has retained or lost the biosynthetic pathway, but rather in the synthesis cost of each amino acid. The DRE Framework, cited as background for the current hypothesis, was originally constructed to explain the origin of essential amino acids. It proposed that the boundary between essential and nonessential amino acids in humans and animals originated from disparities in amino acid composition between intracellular and extracellular environments, as dictated by this framework. However, in this paper, I have proposed that this same DRE Framework also generates amino acid disparities between the cytoplasm and other cellular compartments, and that this forms the basis for determining the significance of amino acid nutrition. Ultimately, if both the essential–nonessential boundary and the factors defining the significance of amino acid nutrition are considered to arise from disparities in amino acid composition across biological compartments and cellular allocations—themselves stemming from the same differences in amino acid synthesis cost—then it seems inevitable that these two boundaries would largely coincide.

One might then ask whether nonessential amino acids truly lack nutritional value. We know that animal bodies contain a large fraction of extracellular proteins, primarily collagens, which are almost

entirely composed of low-cost (nonessential) amino acids, consistent with predictions from the DRE Framework. If high-cost amino acids act as triggers for intracellular protein synthesis, it is plausible that low-cost amino acids play a similar role in extracellular protein formation. Indeed, a double-blind clinical trial reported that supplementation with a mixture of low-cost, nonessential amino acids can alleviate joint discomfort, suggesting broader, previously unrecognized functions for these amino acids [16].

A recent study also showed that in human pediatric growth, essential amino acids act as triggers for growth hormone secretion, and that this triggering effect was observed even without an actual supply of essential amino acids [17]. Although an organism's overall growth may not necessarily reflect cellular-level nutritional behaviors, the fact that these high-cost amino acids serve as significant nutritional triggers on a macroscale level paradoxically underscores the importance of the hypothesis presented here.

In this paper, I proposed the **Allocation-Derived Significance Hypothesis** to explain why essential amino acids hold special nutritional significance. As is common with hypothesis-driven papers, evaluating the validity of this hypothesis is critical; however, traits acquired over the course of evolution are notoriously difficult to verify experimentally. Likewise, the observed correlation between amino acid cost and nutritional significance is shaped by evolutionary processes, making experimental proof inherently challenging. In any event, evolution is rarely driven by a single causal factor, and the phenotypes we see today almost certainly result from multiple interacting influences. Under these circumstances, I offer one possible strand of reasoning in this paper—this newly conceived hypothesis—for further consideration.

Conclusion

In this paper, I have proposed that high-cost amino acids (including essential amino acids) derive their distinctive nutritional significance from cost-driven allocation patterns between the cytoplasm and other cellular or extracellular compartments. This perspective helps elucidate why essential amino acids hold a uniquely important status in nutrition. By considering amino acid synthesis cost and its influence on subcellular allocation, we can gain a more expansive view of the nutritional behavior of amino acids—one that moves beyond the traditional dichotomy of "essential versus nonessential" classification.

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