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AMINO ACIDS: SENSING AND IMPLICATION INTO AGING

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Abstract. An ability to sense and respond to nutrient availability is an important requisite for life. Nutrient limitation is among main factors to influence the evolution of most cellular processes. Different pathways that sense intracellular and extracellular levels of carbohydtrates, amino acids, lipids, and intermediate metabolites are integrated and coordinated at the organismal level through neuronal and humoral signals. During food abundance, nutrient-sensing pathways engage anabolism and storage, whereas limitation triggers the mechanisms, such as the mobilization of internal stores including through autophagy. These processes are affected during aging and are themselves important regulators of longevity, stress resistance, and age-related complications.

Keywords: Aging, Amino acids, Macronutrients, Sensing.

1. INTRODUCTION

Macronutrients are organic compounds that undergo biochemical reactions to produce energy or plastic materials of the cell. Glucose and related carbohydrates, amino acids and lipids are main cellular nutrients, and distinct mechanisms to sense their availability operate in the cell. Essentiality is not necessarily a hallmark of nutrients; for certain amino acids essentiality is context dependent. In healthy organism, the *de novo* synthesis of these amino acids from different precursors meets organismal requirements. However, under particular metabolic needs, such as during rapid growth they must be obtained from the environment [37, 52]. Nutrient deficiency is a strong pressure for selecting efficient mechanisms of nutrient sensing in all species. Taking into account the importance of nutrient homeostasis for all living organisms it is surprising that we know relatively little about direct nutrient-sensing mechanisms. Direct binding of the molecules to their sensors or indirect mechanisms relying on the detection of intermediate molecule that reflects nutrient abundance are principal mechanisms of sensing of a particular nutrient. Regardless of the manner in which nutrient sensing occurs, for a protein to be considered as a sensor, its affinity must be within the range of physiological fluctuations of the nutrient concentration or its surrogate.

Unicellular organisms are directly exposed to environmental fluctuations of nutrients. They sense intracellular and environmental nutrient levels. In multicellular eukaryotes most cells are not directly exposed to changes in environmental nutrients, and homeostatic responses aim to control circulating nutrient levels within a narrow range. Nevertheless, internal nutrient levels fluctuate, and hence intracellular and extracellular nutrient-sensing mechanisms are also present in multicellular organisms.

In these organisms, nutrients also trigger release of hormones. They act as long-range signals with non-cell-autonomous effects, to coordinate proper responses in the organism.

In this Review, I discuss intracellular and extracellular sensing mechanisms of amino acids and their implication in aging, stress resistance and age-related disturbances.

2. SENSING OF AMINO ACIDS

Amino acids are the building blocks for proteins, critically most important molecules of living organisms. Protein biosynthesis is energetically expensive and complex. The cell senses extracellular and intracellular amino acid levels to couple their abundance and organism needs. When amino acids are limited, internal reserves may be used due to protein degradation by proteolylis for example via proteasome-mediated hydrolysis and autophagy. Amino acids are subsequently recycled and allocated for the biosynthesis of specific proteins required under nutrient limitation. Additionally, during periods of prolonged starvation and hypoglycaemia, amino acids are used for the production of other cellular constituents such as glucose and ketone bodies to fuel the particular needs of certain organs such as brain. Hence, the accurate sensing of amino acid levels is a key for proper homeostasis of proteins and amino acids, and in some cases their use as energy sources.

2.1. GENERAL CONTROL NONDEREPRESSIBLE 2 PROTEIN

In protein biosynthesis, no amino acid compensates for the absence of another. The cell must be able to efficiently detect the lack of any amino acid to prevent potential failures in peptide biosynthesis. Ribosome incorporates amino acids into a peptide with the help of specific transfer RNA in the form of aminoacyl-tRNA. The enzymes catalyzing formation of aminoacyl-tRNA, amino-acid-specific aminoacyl tRNA synthetases, execute the loading of amino acids to their cognate tRNAs [19] and uncharged tRNAs accumulate during low levels of free amino acids. Failure to complete a peptide chain under amino acid limitation is inefficient due to which cells recognize this situation and prevent translation initiation. Single protein is able to detect any uncharged tRNA independent of its amino acid specificity. This allows detection of low levels of any amino acid in the context of an abundance of the other ones. This protein is general control nonderepressible 2 (GCN2) protein that possesses high affinity to all uncharged tRNAs (Fig. 1a), and represents an elegant example of amino acid sensing by the indirect detection. Under low intracellular amino acid levels, the binding of GCN2 to a certain uncharged tRNA triggers a conformational change resulting in kinase activation and inhibition of phosphorylation of a key early activator of translation initiation – eukaryotic translation initiator factor 2α (eIF2α) [4]. Mouse models have proven the importance of GCN2 and eIF2α in mammalian responses to transient decrease in amino acids [43, 55]. This amino acid-sensing pathway seems to play a key role in the central nervous system for the detection of imbalances in amino-acid composition in food [16].

Inhibition of protein synthesis by GCN2 and eIF2α occurs in concert with other cellular responses to amino acid depletion such as the inhibition of the mechanistic target of rapamycin (mTOR) pathway. This restricts translation to those messenger RNAs that encode proteins required for cellular adaptation to nutrient starvation and suppressing biosynthesis of most other proteins [48].

2.2. MTORC1

The mTOR kinase as part of mTOR complex 1 (mTORC1) controls cellular energetic processes by inducing numerous anabolic processes including biosynthesis of proteins and lipids [22]. Growth factors activate mTORC1 through a well-studied signal transduction cascade initiated by the binding of a receptor at the membrane resulting in the activation of the Rheb GTPase. Rheb binds mTORC1 and activates its kinase in a growth-factor-dependent manner [13, 47, 55]. In addition to hormones, intracellular amino acids also activate mTORC1. In this way complex integrates information on both systemic and cellular nutrient levels. However, being highly responsive to changes in amino acid levels mTORC is not an amino acid sensor. Indeed, mTORC1 activation is an example of a key sensing signaling process, the actual nutrient sensor remain unidentified (Fig. 1b). mTORC1 is not equally

sensitive to all amino acids: for example, leucine is particularly important for its activation [17]. One can speculate on the selective importance of leucine levels for mTORC1 activation. It is one of the most reliable amino acid in proteins and probably is limiting during protein synthesis. Interestingly, GCN2-knockout mice fed a leucine-deficient diet have a more severe phenotype than the same animals fed diets lacking tryptophan or glycine [55]. Thus, leucine seems to be crucial for the organismal sensing of amino acid sufficiency and deprivation by different pathways. Molecular characterization of the amino acid-dependent activation of mTORC1 started with identification of the Rag GTPase family [39], which regulates mTORC1 through a mechanism distinct to that of growth factors. The growth factors regulate kinase activity of mTORC1 and the Rag GTPases recruit mTORC1 to the lysosomal surface to activate it [38].

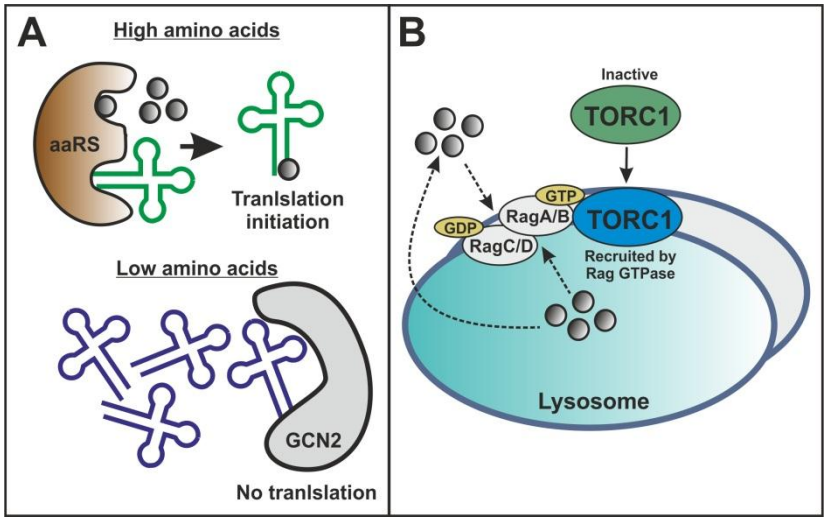

Fig. 1. Mechanisms of amino acid sensing by GCN2 protein (A) and TORC1 recruitment to the lysosomal membrane by Rag GTPases (B).

Because mTORC1 kinase activation by Rheb occurs at the outer lysosomal surface, it is only possible to follow recruitment of mTORC1 (Fig. 1b). Hence, amino acid abundance and the consequent recruitment of mTORC1 is a prerequisite for the activation of mTORC1 by growth factors. Cell-based biochemical studies have identified the proteins responsible for tethering the Rag proteins to the lysosomal surface [38] like guanine exchange factors and GTPase-activating proteins, as well as other regulatory proteins operating upstream of the Rag GTPases [3, 34, 35, 49].

The lysosomal-centered mechanism of mTORC1 activation is puzzling, but some pieces of evidence suggest that the lysosome has a key role in amino acid homeostasis. The yeast vacuole, an organelle similar to the mammalian lysosome, accumulates nutrients including amino acids (Kitamoto et al., 1988), and mTORC1 recruitment is conserved in yeast [5]. In addition, high intraluminal concentrations of certain amino acids have also been shown in lysosomes [18]. Protists such as Dictyostelium *discoideum* obtain energy through phagocytosis and lysosomal degradation [33] that is followed by a transient increase in intralysosomal nutrient levels. The lysosome and vacuole are the organelles in which amino acids and other nutrients are scavenged through the catabolic process of autophagy. Thus, high levels of amino acids within the lysosome or vacuole system seem to partially reflect cellular amino acid abundance and it is reasonable to couple its sensing with recruitment and activation of mTORC1. Germline and sporadic mutations in genes involved in the signal transduction of nutrient levels upstream of the Rag GTPases have been found in human syndromes with growth defects, neurological disorders, tumorogenesis and immunological problems [11, 49].

2.3. Amino Acid-Sensing Taste Receptors

Living organisms have to obtain energy and nutrients from external sources. Predicting the nutritional value of food before digestion allows for the accurate selection of food sources and for the

anticipation of increased nutrient abundance. Few mechanisms act synergistically, including experience and social interactions, but a fundamental nutrient-sensing event occurs at the level of the taste. Nutrient sensing by taste receptors is not only a means of sensing of extracellular nutrients, but also is a mechanism of extra-organismal sensing that allows the inquiry of prospective food sources. In humans, five test categories are present including sweet, umami, bitter, sour and salty. In taste-sensitive cells the taste receptors are exposed in the apical membrane oriented towards the environment [2].

Taste receptors T1R and T2R families belong to G-protein-coupled receptors with seven transmembrane domains with an extracellular N-terminus and an intracellular C-terminus. The T2R family is involved in the detection of bitter molecules as potentially toxic compounds. Two T1R family members are responsible to sense the presence of amino acids. Although other taste receptors also exist [2] and the genetic studies using heterologous expression experiments showed that the T1R1–T1R3 heterodimer senses amino acids. Human amino acid taste receptors have particularly high affinity to glutamate, but other L-amino acids also may be bound to them, whereas D-amino acids do not [32]. Amino acid binding to a taste receptor triggers signal transduction through the plasma membrane via activation of G-protein cascade to induce the release of neurotransmitter [8], which is then integrated with other neurotransmission events at the level of the central nervous system. Additionally, taste receptors also presented in endocrine cells of the gut [53]. Intestinal taste receptors operate through G-protein in a similar manner to that of the oral epithelium. This binding is followed by the cascade elicited by enteral taste receptors leading to release of incretins into the blood circulation. That serves as an anticipatory signal for the imminent digestion of nutrients.

Interestingly, extracellular amino-acid sensing by taste receptors can modulate mTORC1 activation without affecting intracellular amino acid levels [50], a meaningful cross-talk that evolves an anabolic machinery of the cell in anticipation of an elevation in intracellular amino acid levels.

3. Effects of Dietary Proteins and Amino Acids on Aging

Since proteins and their constituents the amino acids are major constituents of living organisms, many studies show that dietary proteins generally act as lifespan-regulating factors (Fig. 2). For example, deprivation of certain essential amino acids extends the lifespan of several model organisms, including Drosophila and mice.

3.1. Contribution of Dietary Proteins to Animal Aging

Studies with various model animals indicate a general negative correlation between the amounts of dietary proteins and lifespan. Many studies compared the effects dietary proteins and carbohydrates on aging by changing the dietary protein:carbohydrate (P:C) ratio. Investigation with Drosophila *melanogaster* show that a low-protein/high-carbohydrate diet is associated with longer lifespan [25, 28], whereas overall caloric intake had minimal effects on lifespan [29]. Similarly, low-protein/high-carbohydrate diets are linked to health and longevity in mice [44]. In fruit fly Drosophila, insulin-like peptides (dILPs) seem mediate the effects of the P:C ratio on lifespan regulating expression of target of brain insulin gene, which encodes an α-glucosidase [6]. Reduced protein intake also appears to extend lifespan by inhibiting the insulin/IGF-1 or TOR signaling pathways [20]. Additionally, it may reduce the levels of proteins with oxidative damage [6, 42].

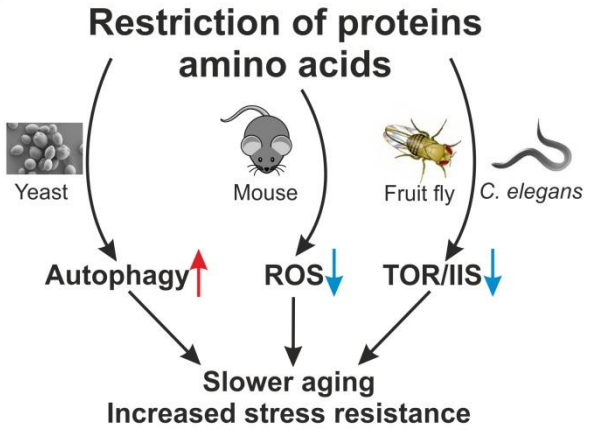

Fig. 2. Lifespan regulation by protein and amino acid restriction in varied organisms is mediated by TOR/IIS signaling, ROS and authophagy.

Despite a lack of direct evidences linking protein intake to longevity, the source of dietary protein may affect human health. A study performed on human, indicates that high animal-protein intake positively correlates with the risk of developing of urothelial cell carcinoma. Oppositely, high plant-protein intake negatively correlates with this risk [1]. This work also suggests that IGF-1 is a risk factor for the development of urothelial cell carcinoma in the setting of high animal-protein intake. A study of aged population (50-65 years) shows that subjects that consumed high amount of protein had a 75% increase in overall mortality and fourfold increase in cancer-related death risk [26]. Interestingly, plant-derived protein diet did not show this harmful effect. Further, a nutritional investigation study demonstrates that a plant-based, low-calorie diet significantly reduces total serum cholesterol and body fat percentage in obese people compared with those achieved with a traditional, low-calorie diet [27]. However, the underlying mechanisms remain undiscovered. These studies reveal potential health benefits from diet that is enriched with plant proteins. Comparably, plant proteins contain significantly lower methionine content than animal proteins [30] and this specific peculiarity may underlie the beneficial effects of dietary plant proteins.

3.2. Role of Specific Amino Acids in Longevity

Many studies have determined the effects of specific dietary amino acids on lifespan. Under low amino acid status, particularly methionine restriction, lifespan increases lifespan in Drosophila by down regulating TOR signaling [24]. Restriction in methionine extends lifespan in a variety of rat strains with different pathologies, suggesting that methionine deficiency alters the rate of aging rather than fixing a specific pathological defect [57]. Amino acid restriction significantly extends the mean and maximum lifespans of mice [31, 45]. Mice, restricted in methionine, displays reduced levels of insulin, IGF-1 and glucose, similar to calorie-restricted mice. Gene expression profiles of methionine-restricted and calorie-restricted mice were significantly different. Thus, these two dietary regimens may affect longevity through partly independent pathways. Methionine restriction also increases the lifespan of male Wistar rats and decreases the production of mitochondrial reactive oxygen species and DNA damage [40, 41].

Lifespan extension in *C. elegans* due to treatment with metformin, a well-known antidiabetic drug, and mutations in metr-1/methionine synthase are associated with decreased levels of internal methionine [7]. Several studies suggest that methionine has a positive impact on longevity [14]. Additionally, methionine supplementation does not shorten long lifespan in Drosophila with DRs [15]. Supplementation with all kinds of amino acids or essential amino acids suppresses DR-promoted longevity. Methionine restriction also causes a slight decrease in the average lifespan without affecting reproductive fitness in Drosophila [54]. Thus, other amino acids have a role in lifespan regulation. In agreement with this concept, restriction of tryptophan increases mouse lifespan [9]. Dietary amino acid composition affects lifespan by regulating various nutrient-sensing signaling pathways. In yeast, GCN2, which binds to uncharged cognate transfer RNAs [10, 51], eIF2α kinase and TOR pathway

components mediate longevity by acting as cellular amino acid sensors [12]. At reduced levels of amino acids, TOR signaling is inhibited, whereas GCN2 is activated. This inhibits overall protein biosynthesis and increases the translation of specific proteins involved in longevity. In addition, restriction of dietary tryptophan protects mice from renal and hepatic ischemic injury and reduces inflammation in a Gcn2-dependent manner in association with reduced serum IGF-1 [36]. In yeast, longevity extension due to methionine restriction is mediated by TOR [23] and autophagy [46]. The anti-aging effects of calorie restriction are largely conserved from yeast and nematodes to primates. However, it is worth to investigate whether the mechanisms through which amino acid restriction promotes life- and healthspan.

4. Conclusions and Perspectives

Despite intensive research, our understanding of nutrient-sensing mechanisms is far from complete. For instance, the amino acid sensor upstream mTORC1 has not been indentified yet. It is possible that this sensor in some way is associated with the lysosome. Since it is widely believed that mTORC1 may potentially integrate hormone and nutrient signals, its interplay with other related pathways coordinating organisms' response to change in nutrient supplementation have to be disclosed. General picture will have to be provided to clarify interplay between regulatory pathways involved in nutrient sensing, but also incorporate regulation by other signaling events. Nutrient abundance not only affects development of metabolic disturbances, but also to some extent is associated with cancer development and the ageing process.

There are many remaining challenges ahead in our understanding of the role of specific macronutrients in lifespan regulation. Alteration of one nutrient can affect lifespan, changing nutrient intake or processing of other nutrients in the mixture. Some studies on the reduction of a single nutritional component may have been misinterpreted. Recent studies indicate that dietary balance among nutrients has bigger effects on aging than individual components. Also many studies show that protein/nonprotein nutrient ratio rather than amount of proteins or calories plays key roles in the regulation of lifespan. The genetic factors that mediate effects of nutritional components on aging are mostly focused on insulin/IGF-1 signaling, TOR and sirtuins, but it does not necessarily mean that these factors are the most important ones. Therefore, identification of genetic factors using unbiased methods and systems biology approaches may lead to better mechanistic insights. Additionally the studies on human subjects uncover the effects of dietary nutritional components on health and aging. It will be exciting to combine all available knowledge to translate discoveries from those done in model organisms into therapeutic applications.

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Здатність відчувати і адекватно реагувати на доступність поживних речовин є важливим фактором для життя. Обмеження доступності поживних речовон є одним з основних факторів, що впливає на еволюцію більшості клітинних процесів. Різні сигнальні механізми, що задіяні у детекції внутрішньо- і зовнішньоклітинного рівня вуглеводів, амінокислот, ліпідів, а також проміжних метаболітів, взаємодіють на рівні організму через нервову і гуморальну системи. При доступності поживних речовин сигнальні шляхи активують анаболічні процеси, а при їх обмеженні актвуються механізми мобілізації з внутрішніх резервів включаючи аутофагію. Протікання цих процесів змінюється з віком проте вони самі є важливими регуляторами тривалості життя, чутливості до стресів, а також розвитку порушень повязаних з віком.

Ключові слова: старіння, амінокислоти, поживні речовини, чутливість.