
Interplay Between Nutrient-Sensing Molecules During Aging and Longevity

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Introduction

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Several types of nutrient-sensing molecules have been recognized, and in mammals, the major nutrient-sensing molecules include mTOR, GCN2, AMPK, and sirtuins. Most of these pathways are conserved in eukaryotes. In addition to nutrient sensing, these pathways are regulated by varied hormones [1]. Interestingly, different mechanisms are employed by the mammalian cells to sense the various types of macronutrients (glucose, amino acids, and lipids). When the availability of food is high, the nutrient-sensing pathway triggers anabolism and storage, whereas, during nutrient scarcity, it engages in energy-producing catabolic pathways to ensure diverse homeostatic mechanisms. The different sensors that detect macronutrient can be either direct or indirect [2]. Deregulation of nutrient-sensing pathways represents one of the hallmarks of aging [3].

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Amino Acid Sensing

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The most studied nutrient-sensing strategy involves the sensing of amino acids. mTORC1 (mammalian/mechanistic target of rapamycin complex 1) plays a key role in detecting abundance of amino acids, although the mechanism is indirect and indistinct. Scarcity of amino acids is directly detected by GCN2, a kinase that binds to the uncharged tRNA molecule [1]. The synthesis of protein is energetically demanding; hence, the cells are equipped to sense the changes in amino acid availability precisely. During extreme nutrient deprivation, proteins are degraded through proteasome-mediated process or through autophagy to generate amino acid stores.

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26 These amino acids are further recycled to generate glucose or ketone bodies to meet
27 the different energy requirements of the body, particularly the brain [2]. Besides its
28 importance for protein synthesis, amino acids are essential for other processes such
29 as tryptophan (precursor for NAD⁺ and serotonin biosynthesis), methionine (plays a
30 role in one-carbon transfer reactions), glutamate (neurotransmitter), and many others
31 that are intermediate metabolites in several cellular processes. Lower organisms
32 can synthesize all the amino acids from carbon skeleton; however, higher organisms
33 require the essential amino acids in their diets [4].

34 GCN2 Senses Amino Acid Starvation

35 The deficiency of any of the 20 amino acids cannot be compensated by the others;
36 thereby the cells are capable of detecting the lack of any of the amino acids. This is
37 mediated through the presence of the enzyme GCN2 (kinase general control nonde-
38 repressible 2) [5]. During protein synthesis, the amino acids are added to the grow-
39 ing peptide chain by the ribosome through the binding of specific transfer RNAs
40 (tRNAs) that is covalently linked to its respective amino acid [6]. Uncharged tRNA
41 acts as a surrogate marker for low levels of amino acids. Under nutrient scarcity, the
42 low levels of amino acids increase the accumulation of uncharged tRNAs in the cell.
43 Thus, this leads to inefficient translation, and the cells prevent this process by trig-
44 gering adaptive responses that lead to inhibition of translation initiation. In bacteria,
45 there is a direct control on transcription, whereas in eukaryotes uncharged tRNAs
46 activate a signal transduction pathway through the direct interaction with GCN2 [4,
47 7]. This protein has a HisRS (histidyl-tRNA synthetase) domain that binds to all
48 uncharged tRNAs irrespective of its amino acid specificity. GCN2 on binding to the
49 uncharged tRNA undergoes a conformational change that leads to its kinase activa-
50 tion through homodimerization and autophosphorylation [8, 9]. Besides its autoac-
51 tivation, the only other protein that GCN2 target through phosphorylation is the
52 eukaryotic initiation factor 2 alpha (eIF2 α), a key early activator of translation ini-
53 tiation. The phosphorylation of eIF2 α inhibits the efficient initiation of translation
54 at the methionine start codon, thereby preventing global protein synthesis [7, 10].
55 However, there is a selective translation of certain mRNA having specific regulatory
56 elements in their 5'-UTRs (untranslated regions), a phenomenon known as transla-
57 tional derepression. An example of a derepressed mRNA is the one that codes for
58 GCN4 transcription factor. The GAAC (general amino acid control) pathway acts
59 through GCN4 to regulate the activation of transcription of amino acid biosynthetic
60 and transport genes [11, 12].

61 In mammals, depletion of essential amino acids including leucine, histidine,
62 tryptophan, or lysine in the diet leads to a rapid activation of GCN2 [13]. Additionally,
63 GCN2 can be activated due to depletion of amino acids caused by other non-dietary-
64 related mechanisms such as during acute stress caused by trauma or sepsis, which
65 can lead to increased production of nitric oxide catalyzed by nitric oxide synthase
66 leading to decreased level of arginine [14, 15]. GCN2 can be activated by the deple-
67 tion of amino acids caused via dietary limitation and enzymatic action or through